Uniform Medical Plan Pre-authorization List

The Uniform Medical Plan (UMP) Pre-authorization List includes services and supplies that require pre-authorization or notification for UMP members.

How to submit a pre-authorization request or notification

Expedited requests

Use this process only when the member or his/her physician believes that waiting for a decision under the standard time frame could place the member's life, health or ability to regain maximum function in serious jeopardy.

- Availity Essentials: Read the information carefully to ensure your request meets the qualifications, then check the box on the form to attest that it is an expedited request.
- Via fax using the appropriate pre-authorization request form below

Online

- Submit an electronic pre-authorization request, and supporting clinical documentation through Availity Essentials>Patient Registration>Authorizations & Referrals>Authorizations
    - Learn more about submitting requests through Availity
- Sleep medicine: Sign in to the Carelon Medical Benefits Management (Carelon) Provider Portal
- Radiology program: Sign in to the Carelon Provider Portal or choose to be routed from Availity's electronic authorization tool via single sign-on.

Note: Check the status of your requests using the same platform you used to submit the request:

- Requests submitted through Carelon are updated on Carelon's portal: **ProviderPortal.com**.
- Requests submitted through Availity Essentials are updated in Availity: **availity.com**.

Fax

Submit the appropriate pre-authorization request form only if unable to submit online or if submitting an expedited request:

- Medical services (PDF)
- NICU/PICU Notification of Admission Form (PDF)
- Durable medical equipment (DME) (PDF)
- Skilled nursing facility (SNF), long term acute care (LTAC) and inpatient rehabilitation (PDF)
- Behavioral health facility submission forms. Tip: Download the form and then fill it out to avoid browser discrepancies.
    - Initial Request Form (PDF) (can be added to an Availity submission)
    - Concurrent Request Form (PDF)
    - Stepdown Request Form (PDF)
    - Discharge Notification Form (PDF)
- Applied Behavioral Analysis (ABA) Initial Request Form (PDF)
- Applied Behavioral Analysis (ABA) Concurrent Request Form (PDF)
- Transcranial Magnetic Stimulation (rTMS) Request Form (PDF) for initial and ongoing services

Direct clinical information reviews (MCG Health)

For select CPT codes, Availity's electronic authorization tool automatically routes you to MCG Health's website where you can document specific clinical criteria for your patient. If all criteria are met, you will see the approval on the Auth/Referral Dashboard soon after you click submit. Once all criteria are documented, you will then be routed back to Availity Essentials to attach supporting documentation and submit the request. Documenting complete and accurate clinical information for your patients helps to reduce the overall time it takes to review a request. View the services that may receive automated approval (PDF).

Type of service or request	Online	Phone	Fax (only if unable to submit online)
Skilled nursing facility only	Submit an electronic pre-authorization request through Availity Essentials	1 (844) 600-4376	1 (855) 848-8220
Long term acute care		1 (800) 423-6884	1 (855) 848-8220
Chemical dependency and mental health		1 (800) 780-7881	1 (888) 496-1540
Transplants		1 (800) 423-6884	1 (844) 679-7764

Professional services and DME		1 (800) 423-6884	1 (844) 679-7763
Expedited requests		1 (800) 423-6884	1 (844) 679-7764
Radiology program Codes requiring authorization are listed in the Radiology section below	Request pre-authorization from Carelon View workarounds for Carelon system outages	1 (877) 291-0509	
Sleep Medicine Codes requiring authorization are listed in the Sleep Medicine section below	Request pre-authorization from Carelon View workarounds for Carelon system outages	1 (877) 291-0509	
Inpatient concurrent review			
for: • Skilled nursing facilities (SNF) • Inpatient hospital continued stay • Inpatient rehabilitation (IPR) • Long-term acute care hospitalizations (LTACH) Notifications for: • Inpatient admissions for SNF/IPRL/LTACH/IP Hospital • Inpatient discharges for SNF/IPRL/LTACH/IP Hospital		1 (800) 423-6884	1 (855) 848-8220
Clinical Records for: • SNF stays • LTACH stays • IPR stays		1 (800) 423-6884	1 (844) 629-4404

Washington State Health Technology Clinical Committee (HTCC) Assessments

Under state law, the Uniform Medical Plans (UMP Achieve 1, UMP Achieve 2, UMP Classic, UMP Select, UMP CDHP, UMP High Deductible, UMP Plus – Puget Sound High Value Network, and UMP Plus – UW Medicine ACN) must comply with decisions made by the Health Technology Clinical Committee (HTCC). The HTCC is a committee of independent health care professionals that reviews selected health technologies (services) to determine the conditions, if any, under which the service will be included as a covered benefit and, if covered, the criteria the plan must use to decide whether the service is medically necessary. These services may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. In public meetings, the HTCC considers public comments and scientific evidence regarding the safety, medical effectiveness, and cost-effectiveness of the services in making its determination. Final decisions and ongoing reviews may be accessed on the HTCC website.

Criteria established by the HTCC supersede Regence Medical Policy.

Procedures that are subject to HTCC decision and require pre-authorization can be found on the UMP Pre-authorization List below.

Procedures denied due to an HTCC decision will be member responsibility.

Important pre-authorization reminders

1. Failure to pre-authorize services subject to pre-authorization requirements will result in an administrative denial, claim non-payment and provider and facility write-off. Members may not be balance billed.
2. Before requesting pre-authorization, please verify member eligibility and benefits via the Availity Portal as the member contract determines the covered benefits.
3. Verify that you are an in-network provider for each member to help reduce his or her out-of-pocket expense.
4. If services are to be rendered in a facility, the pre-authorization request submitted should designate the facility where the treatment will occur to ensure proper reconciliation with related inpatient claims.

5. HTCC Decisions, Medical policies, MCG and CMS criteria may be used as the basis for service coverage determinations, including length of stay and level of care. Visit MCG's website for information on purchasing their criteria, or contact us and we will be happy to provide you with a copy of guidelines for specific services.
6. Emergency services do not require pre-authorization, but are subject to hospital admission notification requirements (see below).
7. The member's contract language will apply.
8. Please note that a pre-authorization does not guarantee payment for requested services. (See #2 above). Our reimbursement policies may affect how claims are reimbursed. Payment of benefits is subject to pre-payment and/or post-payment review, and all plan provisions, including, but not limited to, eligibility for benefits and our Coding Toolkit clinical edits.
9. Investigational and cosmetic services and supplies are typically contract exclusions and are ineligible for payment. Unlisted codes may be used for potentially investigational services and are subject to review. Please refer to the Clinical Edits by Code list for additional information. View a sample non-covered member consent form (PDF).
10. Pre-authorization requirements are not dependent upon site of service. All CPT and HCPCS codes listed on our pre-authorization lists require pre-authorization. View list below for complete requirements.

Type of review	Timeframe	Additional time allowed for review if additional information is needed*:
Urgent/Expedited	Electronic submissions: 1 calendar day, excluding holidays Non-electronic submissions: 2 calendar days	Electronic submissions: 1 calendar day, excluding holidays Non-electronic submissions: 2 calendar days
Standard initial	Electronic submissions: 3 calendar days, excluding holidays Non-electronic submissions: 5 calendar days	Electronic submissions: 3 calendar days, excluding holidays Non-electronic submissions: 4 calendar days
Concurrent	24 hours	72 hours

	Must notify within 24 hours for newborn intensive care unit (NICU) or pediatric intensive care unit (PICU) admission. Exception: Maternity notifications are required on day 6.	

Pre-authorization review timeframes

If Pre-Authorization requests are received requesting urgent/expedited review timeframes and the documentation provided does not meet the urgent/expedited criteria, the review will be reclassified to a standard review and standard timeframes will apply.

Urgent/expedited criteria is defined as one or more of the following:

- The member's life, health or ability to regain maximum function is in serious jeopardy.
- The member's psychological state is putting the life, health or safety of the member or others is in serious jeopardy.
- The member will be subjected to severe pain that cannot be adequately managed without the service.

Payment implications for failure to pre-authorize services

Failure to secure approval for services subject to pre-authorization or concurrent review authorization will result in claim non-payment and provider write-off. Our members must be held harmless and cannot be balance billed.

Please note the following:

- Hospital claims for elective services that require pre-authorization will be reimbursed based upon the member's contract only when the physician or other health care professional has completed and received approval of the pre-authorization for the services. We therefore strongly suggest that facilities develop a method to ensure that required pre-authorization requests have been submitted by

the physician or other health care professional and approved prior to admission of the patient.

- If the physician or other health care professional follows the pre-authorization requirements outlined on our pre-authorization lists, they will not be subject to any pre-authorization penalties for failure of the facility to provide the required inpatient admission and discharge notification. Stays that extend beyond the pre-authorized number of days require admission notification and concurrent review. If a facility fails to receive authorization for additional days, the additional days will be provider liability.
- A pre-authorization does not guarantee payment for requested services. Health Plan reimbursement policies may affect how claims are reimbursed and payment of benefits is subject to all plan provisions, including eligibility for benefits. Services must always be covered benefits and medically necessary.
- If an elective service that requires pre-authorization needs to occur during the course of an inpatient admission, and that need could not be foreseen prior to admission, the facility or provider can request pre-authorization for the service while the member is inpatient (before the service occurs). If pre-authorization does not occur during the stay, services are subject to review post-service for medical necessity.

Pre-authorization exception

There may be exceptions to obtaining pre-authorization. The six situations listed below may apply as part of our Extenuating Circumstances Policy Criteria (PDF):

1. Member presented with an incorrect member ID card or member number or indicated they were self-pay, and that no coverage was in place at the time of treatment, or the participating provider or facility is unable to identify from which carrier or its designated or contracted representative to request a pre-authorization.
2. Natural disaster prevented the provider or facility from securing a pre-authorization or providing hospital admission notification.
3. Member is unable to communicate (e.g., unconscious) medical insurance coverage. Neither family nor collateral support present can provide coverage information.
4. Compelling evidence the provider attempted to obtain pre-authorization. The evidence shall support the provider followed our policy and that the required information was entered correctly by the provider office into the appropriate system.
5. A surgery which requires pre-authorization occurs in an urgent or emergent situation. Services are subject to review post-service for medical necessity.
6. A participating provider or facility is unable to anticipate the need for a pre-authorization before or while performing a service or surgery.

Learn how to notify us about an extenuating circumstance (PDF) prior to claim submission, or how to appeal a claim that has been administratively denied.

Inpatient admissions

See below for substance use disorder and mental health admissions.

Hospital admissions

- Pre-authorization is required for elective inpatient admissions.
- Notification of hospital admission and discharge required within 1 calendar day, regardless of federal holidays or day of the week.
- Elective early delivery, prior to 39 weeks gestation, is not a covered benefit (not applicable to emergency delivery or spontaneous labor).
- Notification is required via electronic medical record, when available. If electronic medical records are not available, notifications are required via fax or by calling 1 (800) 423-6884. Providers should not call Customer Service to notify of patient admissions or discharge. Learn more about this requirement in the Facility Guidelines section of our Administrative Manual.
- Concurrent medical necessity review is required and must include diagnosis and clinical information regarding the member's current inpatient stay. A census list, admission notice, diagnosis code alone or a face sheet without clinical information is not considered adequate for concurrent review. Failure to provide required records may result in a reduction in or denial of benefits.

Inpatient hospice

- Notification of admission or discharge is necessary within 24 hours of admission or discharge (or one business day, if the admission or discharge occurs on a weekend or a federal holiday). Notification of inpatient hospice admission and discharge required within 24 hours, regardless of federal holidays or day of the week.
- Notification is required via electronic medical record, when available. If electronic medical records are not available, notifications are required via fax. Learn more about this requirement.

Long-Term Acute Care Facility (LTAC)

- Pre-authorization is required prior to patient admission.

Rehabilitation

- Pre-authorization is required prior to patient admission.

Skilled Nursing Facility (SNF)

- Pre-authorization is required prior to patient admission.

Extracorporeal Circulation Membrane Oxygenation (ECMO) for the Treatment of Respiratory Failure in Adults (PDF)

- 33946, 33947, 33948, 33949, 33952, 33954, 33956, 33958, 33962, 33964, 33966, 33984, 33986, 33987, 33988, 33989
- Subject to review.

Substance use disorder and mental health

Pre-authorization is required for the services listed below. For select CPT codes, including transcranial magnetic stimulation services, Availity's electronic authorization tool automatically connects to MCG Health's website where specific clinical criteria can be documented for your patient. If all criteria are met, an approval will be received on the Auth/Referral Dashboard. **Emergency inpatient services do not require pre-authorization and are subject to admission notification requirements.**

- **Inpatient: Psychiatric or ASAM 4.0 detoxification**
  - Notification of admission must be received within 24 hours of admission or the next business day (whichever comes first). Medical necessity review will be conducted.
- **Sub-acute detoxification or ASAM level 3.7**
  - Notification of admission must be received within 24 hours of admission or the next business day (whichever comes first)
  - Initial assessment and initial treatment plan must be received within:
    - Two business days for inpatient or residential substance use disorder treatment services
    - Three business days for withdrawal management services
- **Residential treatment: substance use disorders or ASAM level 3.5**
  - Notification of admission must be received within 24 hours of admission or the next business day (whichever comes first)
  - Initial assessment and initial treatment plan must be received within:
    - Two business days for inpatient or residential substance use disorder treatment services
    - Three business days for withdrawal management services
- **Residential treatment: Psychiatric**
  - Requires pre-authorization before the member is admitted for services. Under certain circumstances, pre-authorization requests can be made within 24 hours of admission or the next business day.
- **Partial hospitalization: Psychiatric or ASAM level 2.5 for substance use disorders**
  - Request for authorization is required no later than the day of admission.
- **Intensive outpatient: Psychiatric or ASAM level 2.1 for substance use disorders**
  - Request for authorization is required no later than the day of admission.

Medical necessity for behavioral health services is determined by:

- Behavioral health medical policies
- The American Society of Addiction Medicine's (ASAM) criteria (PDF) for chemical dependency services

View our resources and forms for behavioral health facilities and our behavioral health medical policies.

Applied Behavior Analysis (ABA) Therapy

ABA Therapy is for the treatment of Autism Spectrum Disorders (ASD) when medically necessary.

- Procedure codes 0362T, 0373T, 97151, 97152, 97153, 97154, 97155, 97156, 97157, 97158
- Procedure codes 97151, 97152, and 0362T: Pre-authorization is not required when 97151, 97152, and 0362T are used for **initial** ABA assessments, but pre-authorization is required when 97151, 97152, and 0362T are used for ABA **reassessments**.
- Pre-authorization is only required for UMP members age 18 and older. Use the Availity Authorization tool if you are uncertain if pre-authorization is required for a member.

The following clinical providers, with expertise in using evidenced-based tools to establish or confirm the diagnosis of autism and experience in developing multidisciplinary autism treatment plans, can provide the diagnostic assessment, comprehensive evaluation report, and recommend treatment approach:

- Psychiatrist
- Neurologist
- Pediatric Neurologist
- Developmental Pediatrician
- Doctorate level psychologist
- Advanced registered nurse practitioner

Initial pre-authorizations must contain the following information; View specific details on what each of these below items need to contain (PDF)

- Pre-authorization request form (or equivalent information)
- Clinical evaluation, which includes confirmation of an ASD diagnosis, and recommended treatment approach from a clinician meeting the criteria above (clinical evaluation needs to have been completed within the 12 months prior to the initial pre-authorization request)
- Written Clinical Order, Directive, or Prescription for ABA Therapy services from a clinician meeting the criteria above
- ABA initial report that includes an ABA assessment treatment plan (to be completed by the Lead Behavior Therapist). This sample ABA assessment and treatment plan form (PDF) can be filled out and submitted or used as a reference tool.

A cover letter may be submitted; however, it is not required. A sample cover letter template (PDF) is provided for your reference. Other supporting documentation may be submitted.

View ABA therapy clinical considerations (PDF) for information about hours of service and documentation requirements.

Concurrent Review

The following document should be submitted within five business days prior to the end of a current authorization:

- Updated ABA assessment treatment plan (to be completed by the Lead Behavior Therapist). This sample ABA assessment and treatment plan form (PDF) can be filled out and submitted or used as a reference tool.
- A new Pre-authorization request form (PDF) (or equivalent information).

View ABA therapy clinical considerations (PDF) for information about hours of service and documentation requirements.

Following the submission of the concurrent review documentation, the plan may request additional information prepared and submitted by a clinician meeting the above clinical criteria. The plan will specify what must be included in this report which is intended to assess progress and prospective treatment in further detail and may include a written Clinical Order, Directive or Prescription for ABA Therapy services.

Initial Treatment Request

Procedure codes: 0362T, 0373T, 97151, 97152, 97153, 97154, 97155, 97156, 97157, 97158

- Procedure codes 97151, 97152, and 0362T: pre-authorization is not required when 97151, 97152, and 0362T are used for initial ABA assessments, but pre-authorization is required when 97151, 97152, and 0362T are used for ABA reassessments during course of treatment.
- Pre-authorization is only required for members age 18 and older. Use the Availity Authorization tool, availity.com, if you are uncertain if pre-authorization is required for a member.
- ABA therapy must be recommended or prescribed by a licensed provider experienced in the diagnosis and treatment of autism.

View documentation requirements in our Applied Behavior Analysis for the Treatment of Autism Spectrum Disorder (PDF) medical policy which should include:

- Clinical evaluation, which includes confirmation of an ASD diagnosis, and recommended treatment approach from a clinician meeting the criteria above.
- ABA initial report that includes an ABA assessment treatment plan (to be completed by the Lead Behavior Therapist).
- A cover letter may be submitted; however, it is not required. A sample cover letter template (PDF) is provided for your reference. Other supporting documentation may be submitted.

Concurrent Treatment Request (Reauthorization)

- Updated clinical documents should be submitted within 14 days of end of a current authorization.
- A new Pre-authorization request form (PDF) (or equivalent information).

- Following the submission of the concurrent review documentation, the plan may request additional information prepared and submitted by a clinician meeting the above clinical criteria. The plan will specify what must be included in this report which is intended to assess progress and prospective treatment in further detail and may include a written Clinical Order, Directive or Prescription for ABA Therapy services.

Allied health

Administrative Guidelines to Determine Dental vs Medical Services (PDF)

- 21245, 21246, 21248, 21249

Biofeedback (PDF)

- 90875, 90876, 90901, 90912, 90913, E0746
- We do not require pre-authorization for biofeedback for headache and migraine G43.xx, G44.201, G44.209 , G44.211, G44.219, G44.221, G44.229, R51

Durable medical equipment

Bone Growth Stimulation

- UMP is subject to HTCC Decision (PDF) – 20974, 20975, 20979, E0747, E0748, E0749, E0760

Continuous Glucose Monitoring

- For dates of service prior to January 1, 2022: UMP is subject to HTCC Decision (PDF): A9277, A9278, K0554, S1030, S1031
- Continuous Glucose Monitoring device coverage and preauthorization HTCC requirements will be managed under the UMP prescription drug benefit administered by the Washington State Rx Services

Definitive Lower Limb Prostheses (PDF)

- L5010, L5020, L5050, L5060, L5100, L5105, L5150, L5160, L5200, L5210, L5220, L5230, L5250, L5270, L5280, L5301, L5312, L5321, L5331, L5341, L5610, L5611, L5613, L5614, L5616, L5700, L5701, L5702, L5703, L5710, L5711, L5712, L5714, L5716, L5718. L5722, L5724, L5726, L5728, L5780, L5810, L5811, L5812, L5814, L5816, L5818, L5822, L5824, L5826, L5828, L5830, L5840, L5841, L5848, L5930, L5968, L5970, L5972, L5974, L5976, L5978, L5979, L5980, L5981, L5982, L5984. L5985, L5986, L5987

Implantable Drug Delivery System

- UMP is subject to HTCC Decision (PDF): C1772, C1889, C1891, C2626, E0782, E0783, E0785, E0786, 62350, 62351, 62360, 62361, 62362

Insulin Infusion Pumps, Automated Insulin Delivery and Artificial Pancreas Device Systems (PDF)

- S1034

Microprocessor-Controlled Lower Limb Prosthetics (PDF)

- UMP is subject to HTCC Decision (PDF)
- L5615, L5856, L5857, L5858
- Use Regence medical policy in addition to the HTCC to review requests regarding "functional level 2" and "experienced user exceptions".

Myoelectric Prosthetic and Orthotic Components for the Upper Limb (PDF)

- L6026, L6693, L6715, L6880, L6881, L6882, L6925, L6935, L6945, L6955, L6965, L6975, L7007, L7008, L7009, L7045, L7180, L7181, L7190, L7191

Noninvasive Ventilators in the Home Setting (PDF)

- E0466

Power Wheelchairs: Group 3 (PDF)

- K0848, K0849, K0850, K0851, K0852, K0853, K0854, K0855, K0856, K0857, K0858, K0859, K0860, K0861, K0862, K0863, K0864

Stents, Drug Coated or Drug-Eluting (DES)

- Refer to Cardiac Stenting in the Surgery section below.

Sleep Medicine

- View the Sleep Medicine Management Program for notification or authorization requirements.
- Review the codes requiring authorization or notification in the Sleep Medicine section.

Genetic testing

In compliance with WA HB 1689, guideline-recommended biomarker testing in patients with recurrent, relapsed, refractory, or metastatic cancer (including stage 3 or 4) will not require prior authorization for Washington members. This does not include non-specific molecular pathology codes (81400-81408).

Diagnosis codes Z800-Z803, Z8041 and Z8042 will no longer be exempted from pre-authorization for Washington members.

Genetic Testing for Alzheimer's Disease (PDF) - GT01

- 81401, 81405, 81406

Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome (PDF) - GT02

- 0235U, 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81307, 81308, 81321, 81322, 81323, 81404, 81405, 81406, 81432, 81433, 81351, 81352

Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease (PDF) - GT05

- 81401

Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes (PDF) - GT06

- 0238U, 81201, 81202, 81203, 81210, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, 81401, 81406

Genetic Testing for Cutaneous Malignant Melanoma (PDF) - GT08

- 81404

Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing (PDF) - GT10

- 81225, 81401, 81402, 81404, 81405, 81418, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U
- UMP is subject to HTCC Decision (PDF) for codes 81225, 81418, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U and 0076U.
- Codes 81225, 81418, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U and 0076U will deny as not a covered benefit when billed with the following diagnosis: depression, mood disorders, psychosis, anxiety, ADHD and substance use disorders.

Genetic Testing; Familial Hypercholesterolemia (PDF) - GT11

- 81401, 81405, 81406, 81407

KRAS, NRAS and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer (PDF) - GT13

- 81210, 81275,81276, 81311, 81403, 81404, 0111U

Preimplantation Genetic Testing of Embryos (PDF) - GT18

- 89290, 89291, 81228, 81229, 81349

Genetic Testing; IDH1 and IDH2 Genetic Testing for Conditions Other Than Myeloid Neoplasms or Leukemia (PDF) - GT19

- 81120, 81121

Genetic and Molecular Diagnostic Testing (PDF) - GT20

- 0232U, 0234U, 0235U, 0238U, 0244U, 81201, 81202, 81203, 81210, 81212, 81215, 81216, 81217, 81225, 81228, 81229, 81235, 81243, 81244, 81250, 81252, 81253, 81254, 81257, 81275, 81276, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81302, 81303, 81304, 81311, 81314, 81317, 81318, 81319, 81321, 81322, 81323, 81324, 81325, 81326, 81341, 81349, 81350, 81351, 81352, 81401,

81402, 81403, 81404, 81405, 81406, 81407, 81408, 81419, 81441, 81470, 81471, S3800, S3840, S3844, S3845, S3846, S3849, S3850, S3853, S3865, S3866
- UMP is subject to HTCC Decision (PDF) for code 81225.
- Code 81225 will deny as not a covered benefit when billed with the following diagnosis: depression, mood disorders, psychosis, anxiety, ADHD and substance use disorders

Genetic Testing for Biallelic RPE65 Variant-Associated Retinal Dystrophy (PDF) - GT21

- 81406

Gene Expression Profiling for Melanoma (PDF) - GT29

- 81552

BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy (PDF) - GT41

- 81210

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer (PDF) - GT42

- 81522
- UMP is subject to HTCC Decision (PDF) for codes 81518, 81519, 81520, 81521, 81523, 81541, 81542, 81551, S3854, 0262U, 0045U, 0047U, 0067U and 0009U
- Apply the Regence medical policy Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer (PDF) for conditions/treatments not addressed in the HTCC decision (e.g. BluePrint, and TargetPrint.)

Diagnostic Genetic Testing for Genetic Testing for FMR1 and AFF2 Variants (Including Fragile X and Fragile XE Syndromes) (PDF) - GT43

- 81243, 81244

Noninvasive Prenatal Testing to Determine Fetal Aneuploidies, Microdeletions, Single-Gene Disorders, and Twin Zygosity (PDF) - GT44

- 81408, 81243

Genetic Testing for CADASIL Syndrome (PDF) - GT51

- 81406

Diagnostic Genetic Testing for α-Thalassemia (PDF) - GT52

- 81257, 81258, 81259, 81269, 81404

Genetic Testing; Primary Mitochondrial Disorders (PDF) - GT54

- 0417U, 81401, 81403, 81404, 81405, 81440, 81460, 81465

Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC) (PDF) - GT56

- 0022U, 81210, 81235, 81275, 81276, 81404, 81405, 81406

Genomic Microarray Testing

- UMP is subject to HTCC Decision (PDF) for codes 81228, 81229, 81349, S3870, 0156U, 0209U, 0318U

Genetic Testing for Myeloid Neoplasms and Leukemia (PDF) - GT59

- 81120, 81121, 81351, 81352, 81401, 81402, 81403, 81450, 81451, 81455, 81456

Genetic Testing for PTEN Hamartoma Tumor Syndrome (PDF) - GT63

- 0235U, 81321, 81322, 81323

Genetic Testing for Evaluating the Utility of Genetic Panels (PDF) - GT64

- 81201, 81202, 81203, 81210, 81225, 81228, 81229, 81235, 81243, 81244, 81250, 81252, 81253, 81254, 81257, 81275, 81276, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81302, 81303, 81304, 81311, 81314, 81317, 81318, 81319, 81321, 81322, 81323, 81324, 81325, 81326, 81349, 81350, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81412, 81432, 81433, 81434, 81437, 81438, 81440, 81441, 81443, 81450, 81451, 81455, 81456, 81460, 81465, 81470, 81471
- UMP is subject to HTCC Decision (PDF) for code 81225
- Code 81225 will deny as not a covered benefit when billed with the following diagnosis: depression, mood disorders, psychosis, anxiety, ADHD and substance use disorders.

Genetic Testing for Methionine Metabolism Enzymes, including MTHFR (PDF) - GT65

- 81401, 81403, 81404, 81405, 81406

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies (PDF) - GT66

- 81403, 81404, 81405, 81406, 81324, 81325, 81326, 81448

Genetic Testing for Rett Syndrome (PDF) - GT68

- 0234U, 81302, 81303, 81304, 81404, 81405, 81406

Genetic Testing for Duchenne and Becker Muscular Dystrophy (PDF) - GT69

- 0218U, 81161, 81408

Fetal RHD Genotyping Using Maternal Plasma (PDF) - GT74

- 81403

Genetic Testing for Macular Degeneration (PDF) - GT75

- 81401, 81405, 81408

Whole Exome and Whole Genome Sequencing

- UMP is subject to HTCC Decision (PDF) for 0214U, 0215U, 81415, 81416, 81417

Genetic Testing for Heritable Disorders of Connective Tissue (PDF) - GT77

- 81405, 81408

Invasive Prenatal Fetal Diagnostic Testing for Chromosomal Abnormalities (PDF) - GT78

- 81228, 81229, 81349, 81405

Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss (PDF) - GT79

- 81228, 81229, 81349

Genetic Testing for Epilepsy (PDF) - GT80

- 0232U, 81188, 81189, 81190, 81401, 81403, 81404, 81405, 81406, 81407, 81419

Reproductive Carrier Screening for Genetic Diseases (PDF) - GT81

- 81161, 81243, 81244, 81250, 81252, 81253, 81254, 81257, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81412, 81434, 81443, S3844, S3845, S3846, S3849, S3850, S3853

Expanded Molecular Panel Testing of Cancers to Select Targeted Therapies (PDF) - GT83

- 0022U, 0037U, 0048U, 0211U, 0244U, 0250U, 0334U, 0379U, 0391U, 0444U, 81120, 81121, 81162, 81210, 81235, 81275, 81276, 81292, 81295, 81298, 81311, 81314, 81319, 81321, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81445, 81449, 81455, 81456, 81457, 81458, 81459

Genetic Testing for Neurofibromatosis Type 1 or 2 (PDF) - GT84

- 81405, 81406, 81408

ClonoSEQ® Testing for the Assessment of Measurable Residual Disease (MRD) (PDF) - GT88

- 0364U

Laboratory

Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers (PDF)

- 0239U, 0242U, 0326U, 0388U, 0409U, 0428U, 81462, 81463, 81464

Laboratory Tests for Organ Transplant Rejection (PDF)

- 81595

Measurement of Serum Antibiodies to Selected Biologic Agents (PDF)

- 80145, 80230, 80280

Maternity

Elective early delivery, prior to 39 weeks' gestation, is not a covered benefit (not applicable to emergency delivery or spontaneous labor).

Medicine

Bioengineered Skin and Soft Tissue Substitutes and Amniotic Products (PDF)

- A4100, A6460, A6461, Q4100, Q4101, Q4102, Q4105, Q4106, Q4107, Q4114, Q4116, Q4121, Q4122, Q4128, Q4132, Q4133, Q4151, Q4154, Q4159, Q4186, Q4187

Confocal Laser Endomicroscopy (PDF)

- 43206, 43252, 88375

Coverage of Treatments Provided in a Clinical Trial (PDF)

- S9990, S9991, S9988

Digital Therapeutic Products (PDF)

- 98978, A9291, A9292, E1905

Digital Therapeutic Products for Attention Deficit Hyperactivity Disorder (PDF)

- 98978, A9291

Digital Therapeutic Products for Chronic Low Back Pain (PDF)

- 98978, A9291, E1905

Digital Therapeutic Products for Post-traumatic Stress Disorder and Panic Disorder (PDF)

- A9291

Digital Therapeutic Products for Substance Use Disorders (PDF)

- 98978, A9291

Digital Therapeutic Products for Amblyopia (PDF)

- A9292

Hyperbaric Oxygen Therapy for Tissue Damage, Including Wound Care and Treatment of Central Nervous System Conditions (PDF)

- UMP is subject to HTCC Decision (PDF): 99183, G0277
- Regence medical policy is used only to determine units of treatment, criteria for diabetic "standard wound therapy" and to address any conditions not addressed in the HTCC decisions under the HTCC "limitations of coverage" or "non-covered indicators".

In Vivo Analysis of Colorectal Lesions(PDF)

- 88375

Intensity Modulated Radiotherapy (IMRT)

- UMP is subject to HTCC Decision (PDF): 77301, 77338, 77385, 77386, G6015, G6016

Laser Interstitial Thermal Therapy (PDF)

- 61736, 61737

Low-Level Laser Therapy (PDF)

- 97037

Neurofeedback (PDF)

- 90875, 90876. 90901

Orthopedic Applications of Stem-Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow (PDF)

- 38206, 38232, 38241

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia (PDF)

- 38205, 38206, 38240, 38241

Charged-Particle (Proton or Helium Ion) Radiotherapy

- UMP is subject to HTCC Decision (PDF) - 77520, 77522, 77523, 77525
    - Pre-authorization is not required for members under 21 years of age
- When the following codes are used for Charged-Particle (Proton or Helium Ion) Radiotherapy with SRS or SBRT, use HTCC Decision (PDF): 32701, 61796, 61797, 61798, 61799, 61800, 63620, 63621, 77301, 77338, 77371, 77372, 77373, 77432, 77435, G0339, G0340

Radioembolization, Transarterial Embolization (TAE) and Transarterial Chemoembolization (TACE) (PDF)

- 37243, 79445, C9797, S2095
- Note: Ovarian and Internal Iliac Vein Embolization as a Treatment of Pelvic Congestion Syndrome (PDF) is considered investigational.

Sleep Medicine

- View the Sleep Medicine Management Program for notification or authorization requirements.
- Review the codes requiring authorization or notification in the Sleep Medicine section.

Tinnitus: Non-invasive, non-pharmacologic treatments

- UMP is subject to HTCC Decision (PDF) for codes 0552T, 90832, 90833, 90834, 90836, 90837, 90838, 90867, 90868, 90869, 96156, 96158, 96159, 96160, 96161, 96164, 96165, 96167, 96168, 96170, 96171, S8948

- Pre-authorization is only required within tinnitus diagnosis codes: H93.11, H93.12, H93.13, H93.19, H93.A1, H93.A2, H93.A3, H93.A9
- Codes 0552T and S8948, when billed without a tinnitus diagnosis, will be denied as investigational based on Regence Medical Policy Low Level Laser Therapy
- Note: Codes 90867 and 90868, when billed with chronic migraine and chronic tension headaches, is not a covered benefit per HTCC Decision (PDF)

NOTE: For treatment of Tinnitus with transcranial magnetic stimulation (codes 90867, 90868, 90869) for members age 17 years and under, use Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders (PDF)

Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders (PDF)

- UMP is subject to HTCC Decision (PDF) for codes 90867, 90868, 90869
    - Per the HTCC, TMS for treatment resistant major depressive disorder (MDD) in UMP members age 18 or older is a covered benefit with conditions.
    - TMS for treatment resistant major depressive disorder (MDD) in UMP members age 17 and younger refer to Regence medical policy.
    - TMS for treatment of obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD) are not covered for all UMP members per the HTCC.
- Apply the Regence medical policy Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders (PDF) for code 0858T.

Gender Affirming Interventions for Gender Dysphoria (PDF)

- 15775, 15776, 17380, 55970, 55980
- Codes 55970 and 55980 are non-specific. The specific procedure code(s) must be requested in place of these non-specific codes.
- 11920, 11921, 15771, 15773, 15774, 15825, 15828, 15829, 17999, 19303, 19316, 19318, 19325, 19350, 21125, 21127, 21137, 21139, 21141, 21142, 21143, 21145, 21146, 21147, 21188, 21193, 21194, 21195, 21196, 21208, 53400, 53405, 53410, 53415, 53420, 53425, 53430, 54125, 54400, 54401, 54405, 54520, 54660, 54690, 55175, 55180, 56625, 56800, 56805, 57106, 57110, 57291, 57292, 57295, 57296, 57335, 57426, 58353, 58356, 58563, C1813, C2622, L8600
- Use code 17999 to request laser hair removal.
- Gender affirming surgical interventions for gender dysphoria require pre-authorization. Codes for specific procedures might also be listed as requiring pre-authorization in other medical policies, including but not limited to:
    - Abdominoplasty - 15830
    - Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast - 15771
    - Breast Reconstruction - 19316, 19318, 19325, 19350, L8600
    - Blepharoplasty and Brow Lift - 15820, 15821, 15822, 15823, 67900, 67901, 67902, 67903, 67904, 67906, 67908, 67909, 67950
    - Chin Implants - 21120, 21121, 21122, 21123, 21209
    - Collagen Injections - 11950, 11951, 11952, 11954

- Cosmetic and Reconstructive Procedures - 15771, 15773
- Endometrial Ablation - 58353, 58356, 58563
- Panniculectomy - 15830
- Reconstructive Breast Surgery, Mastopexy, and Management of Breast Implants - 15771
- Rhinoplasty - 30400, 30410, 30420, 30430, 30435, 30450

Pharmacy

UMP has a separate vendor – Washington State Rx Services – for their prescription drug benefit. Pre-authorization is necessary for certain injectable drugs that are not normally approved for self-administration when obtained through a retail pharmacy, a network mail-order pharmacy, or a network specialty pharmacy. These drugs are indicated on the UMP Preferred Drug List.

Drugs usually payable under the member's medical benefit and pre-authorized will continue with the same Regence process.

Hemophilia Clotting Factors

Hemophilia clotting factor codes J7170. J7201, J7202, J7203, J7204, J7205, J7207, J7208, J7210 require pre-authorization and if approved will be covered under the Medical benefits for the following groups. For all other groups please use the pharmacy link above.

- ATI Specialty Alloys and Components (group #10015713)
- WA State Health Care Authority (group # 10003948)
- Rin Tinto (grandfathered plan codes only) (groups #10021209 & 10019119)
- OTET (group #10007445)
- Northwest Evaluation Association (NWEA) (group #10002570)
- Utah Valley University (group #10042213)
- Encoder Products (group #10040552)
- Eagle Eye Produce Inc (group #10040165)

Infusion Drug Site of Care

Certain provider administered infusion medications covered on the medical benefit are subject to the Site of Care Program (dru408) medication policy (PDF). This policy does not apply to members covered under UMP Plus plans.

Radiology

Contact Regence for pre-authorization for the following codes:

Coronary Artery Calcium Scoring

- UMP is subject to HTCC Decision (PDF): S8092
- **Note**: 75571 for Cardiac Artery Calcium Scoring is not a covered benefit - reference HTCC Decision.

Wireless Capsule Endoscopy for Gastrointestinal (GI) Disorders (PDF)

- 0651T, 91110, 91111, 91113

Carelon Medical Benefits Management (Carelon)

We partner with Carelon to administer our Advanced Imaging Authorization radiology program.

- Login to Carelon's ProviderPortal
- Phone 1 (877) 291-0509

Note: If HTCC criteria is used for pre-authorization, see below links to that criteria. If there are no HTCC criteria or HTCC is out of scope for request, Carelon criteria will apply.

Contact Carelon to request pre-authorization for the following codes: 70336, 70480, 70481, 70482, 70490, 70491, 70492, 70496, 70498, 70544, 70545, 70546, 70547, 70548, 70549, 70551, 70552, 70553, 71250, 71260, 71270, 71271, 71275, 71550, 71551, 71552, 71555, 72125, 72126, 72127, 72128, 72129, 72130, 72131, 72132, 72133, 72141, 72142, 72146, 72147, 72148, 72149, 72156, 72157, 72158, 72159, 72191, 72192, 72193, 72194, 72195, 72196, 72197, 72198, 73200, 73201, 73202, 73206, 73218, 73219, 73220, 73221, 73222, 73223, 73225, 73700, 73701, 73702, 73706, 73718, 73719, 73720, 73721, 73722, 73723, 73725, 74150, 74160, 74170, 74174, 74175, 74176, 74177, 74178, 74181, 74182, 74183, 74185, 74712, 75559, 75563, 75572, 75573, 75574, 75580, 75635, 76391, 77078, 77084, 78012, 78013, 78014, 78015, 78016, 78018, 78070, 78071, 78072, 78075, 78102, 78103, 78104, 78185, 78195, 78201, 78202, 78215, 78216, 78226, 78227, 78230, 78231, 78232, 78258, 78261, 78262, 78264, 78265, 78266, 78278, 78290, 78291, 78300, 78305, 78306, 78315, 78429, 78430, 78431, 78432, 78433, 78445, 78451, 78452, 78453, 78454, 78456, 78457, 78458, 78459, 78466, 78468, 78469, 78472, 78473, 78579, 78580, 78481, 78582, 78483, 78491, 78492, 78494, 78597, 78598, 78600, 78601, 78605, 78606, 78610, 78630, 78635, 78645, 78650, 78660, 78700, 78701, 78707, 78708, 78709, 78725, 78740, 78761, 78800, 78801, 78802, 78803, 78804, 78830, 78831, 78832, 93303, 93304, 93306, 93307, 93308, 93312, 93313, 93314, 93315, 93316, 93317, 93350, 93351, 95782, 95783, 95805, 95807, 95808, 95810, 95811, E0470, E0471, E0561, E0562, E0601, 0042T, 0648T, 0649T

HTCC decisions administered by Carelon:

- Breast MRI
  - UMP is subject to HTCC Decision (PDF): 77046, 77047, 77048, 77049
  - HTCC criteria applies to all member requests regardless of gender
- Cardiac Magnetic Resonance Angiography (CMRA)
  - UMP is subject to HTCC Decision (PDF): 75557, 75561
- Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment
  - UMP is subject to HTCC Decision (PDF): 70554, 70555, 78608, 78609

    - Please see Carelon criteria for pre-authorization requirements for indications other than primary degenerative dementia or mild cognitive impairment
- Imaging for Rhinosinusitis
    - UMP is subject to HTCC Decision (PDF): 70450, 70460, 70470, 70486, 70487, 70488, 70540, 70542, 70543
    - Please see Carelon criteria for pre-authorization requirements for indications other than Rhinosinusitis
- Noninvasive Cardiac Imaging for Coronary Artery Disease
    - UMP is subject to HTCC Decision (PDF): 75574, 75580, 78429, 78430, 78431, 78432, 78433 78451, 78452, 78453, 78454, 78459, 78466, 78468, 78469, 78472, 78473, 78481, 78483, 78491, 78492, 78494, 93350, 93351
- Positron Emission Tomography (PET) Scans for Lymphoma
    - UMP is subject to HTCC Decision (PDF): 78811, 78812, 78813, 78814, 78815, 78816

Sleep Medicine

We partner with Carelon to administer our Sleep Medicine program.

- Login to Carelon's ProviderPortal
- Phone 1 (877) 291-0509
- View workarounds for Carelon system outages

Contact Carelon to request pre-authorization for the following codes: 95782, 95783, 95805, E0470, E0471

Carelon uses HTCC to pre-authorize sleep medicine diagnosis and equipment. Also refer to the Surgery section for additional information about pre-authorization requirements related to surgery for Sleep Apnea Diagnosis and Treatment.

HTCC decisions administered by Carelon:

- Sleep Apnea – Diagnosis and Equipment
    - UMP is subject to HTCC Decisions (PDF): 95807, 95808, 95810, 95811, E0561, E0562, E0601
    - Please see Carelon criteria for indications other than Sleep Apnea

Surgery

Ablation of Primary and Metastatic Liver Tumors (PDF)

- 47370, 47371, 47380, 47381. 47382, 47383

Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast (PDF)

- 15769, 15771, 15772, 11950, 11951, 11952, 11954

- Note: Codes 19380 and 19499 do not require pre-authorization but are considered, and will deny as, investigational when used for autologous fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions (PDF)

- J7330, S2112

Balloon Dilation of the Eustachian Tube (PDF)

- 69705, 69706

Balloon Ostial Dilation for Treatment of Sinusitis (PDF)

- 31295, 31296, 31297, 31298

Bariatric Surgery (PDF)

- 43771, 43848, 43860, 43886
- UMP is subject to HTCC Decision (PDF): 43644, 43772, 43773, 43774, 43775, 43820, 43845, 43846, 43887, 43888
- Bariatric surgery and HTCC guidelines apply, in order to establish eligibility for surgery and medical necessity.

Blepharoplasty, Repair of Blepharoptosis, and Brow Ptosis Repair (PDF)

- 15820, 15821, 15822, 15823, 67900, 67901, 67902, 67903, 67904, 67906, 67908, 67909, 67950

Bronchial Valves (PDF)

- 31647, 31648, 31649, 31651

Cardiac Stenting

- UMP is subject to HTCC Decision (PDF): 92928, 92933, 92937, 92941, 92943
- Pre-authorization is not required for members being treated for a condition other than stable angina

Carotid Artery Stenting

- UMP is subject to HTCC Decision (PDF): 37215, 37216, 37217, 37246, 37247, C7532

Catheter Ablation Procedures for Supraventricular Tachyarrhythmias (SVTA)

- UMP is subject to HTCC Decision (PDF): 93653, 93655, 93656, 93657

Cervical Fusion for Degenerative Disc Disease

- UMP is subject to HTCC Decision (PDF): 22551, 22552, 22554, 22853, 22854, 22859, 22600

Chemical Peels (PDF)

- 15788, 15789, 15792, 15793, 17360

Cochlear Implant (PDF)

- For Bilateral Cochlear Implants, UMP is subject to HTCC Decision.
  For Unilateral Cochlear Implants and replacement requests, UMP follows Regence Medical Policy.
- 69930, L8614, L8619, L8627, L8628

Cosmetic and Reconstructive Procedures (PDF)

- 11920, 11921, 11922, 11950, 11951, 11952, 11954, 15769, 15771, 15772, 15773, 15774, 17106, 17107, 17108, 19355, 21230, 21244, 21245, 21246, 21248, 21249, 21295, 21296, 41510, 49250, 54360, 67950, 69300, G0429
- Pre-authorization is required EXCEPT when services are rendered in association with breast reconstruction and nipple/areola reconstruction following mastectomy for breast cancer.
- Note: Codes 19380 and 19499 do not require pre-authorization but are considered, and will deny as, investigational when used for autologous fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast

Cryosurgical Ablation of Miscellaneous Solid Tumors Outside of the Liver (PDF)

- 31641, 32994, 50542

Deep Brain Stimulation (PDF)

- 61850, 61860, 61863, 61864, 61867, 61868, 61885, 61886, C1820, L8679, L8680, L8685, L8686, L8687, L8688, L8682, L8683
- Deep brain stimulation is not a covered benefit for treatment-resistant depression, per HTCC Decision (PDF).
- Note: HTCC decision applies to UMP members age 18 and older. Refer to Regence Medical Policy for UMP members age 17 and younger

Discography

- UMP is subject to HTCC Decision (PDF): 62290, 72295

Endometrial Ablation (PDF)

- 58353, 58356, 58563

Facet Neurotomy

- UMP is subject to HTCC Decision (PDF): 64633, 64634, 64635, 64636

Gastric Electrical Stimulation (PDF)

- 43647, 43881, 64590, 64595, E0765, C1767, L8679, L8680, L8685, L8686, L8687, L8688

Gastroesophageal Reflux Surgery (PDF)

- 43279, 43280, 43281, 43282, 43325, 43327, 43328, 43332, 43333, 43334, 43335, 43336, 43337

Hip Surgery for Femoroacetabular Impingement Syndrome (FAI)

- UMP is subject to HTCC Decision (PDF): 29914, 29915, 29916

Hypoglossal Nerve Stimulation (PDF)

- 64568, 64582, 64583, C1767

Implantable Peripheral Nerve Stimulation and Peripheral Subcutaneous Field Stimulation (PDF)

- 64585, 64590, 64595, 64596, 64597, 64598, L8679, L8680, L8683

Laser Treatment for Port Wine Stains (PDF)

- 17106, 17107, 17108

Leadless Cardiac Pacemakers (PDF)

- 0823T, 0825T, 33274

Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation (PDF)

- 33340

Lumbar Fusion for Degenerative Disc Disease

- UMP is subject to HTCC Decision (PDF): 22533, 22558, 22612, 22630, 22633, 22853, 22854, 22859
- Lumbar Fusion for degenerative disc disease uncomplicated by comorbidities is not a covered benefit per HTCC Decision; This includes diagnosis codes M51.35, M51.36, M51.37
  Note: This decision does not apply to patients with the following conditions: radiculopathy, spondylolisthesis (>grade 1), severe spinal stenosis, acute trauma or systemic disease affecting spine, e.g., malignancy
- UMP is subject to HTCC Decision (PDF) for Bone Morphogenic Protein
- Bone morphogenetic protein-7 (rhBMP-7) is not a covered benefit
- HTCC for bone morphogenetic protein does not apply to those under age 18

Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation (PDF)

- 0398T, 55880

Microwave Tumor Ablation (PDF)

- 32998, 50592

Negative Pressure Wound Therapy for Home Use (NPWT) (PDF)

- UMP is subject to HTCC Decision (PDF): 97605, 97606, 97607, 97608, A6550, E2402
- View the HTCC Decision: Definition of "Complete Wound Therapy Program" (PDF)
- View the NPWT FDA Safety Communication

Occipital Nerve Stimulation (PDF)

- 61885, 61886, 64553, 64568, 64569, 64585, 64590, 64596, 64597, 64598
- C1820, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688

- Occipital Nerve Stimulation is considered investigational for all indications, including but not limited to headaches
- Note: These codes may overlap with the codes in the Vagus Nerve Stimulation Medical Policy so to ensure proper adjudication of your claim, please call for pre-authorization on all of the above codes.

Orthognathic surgery (PDF)

- 21085, 21110, 21120, 21121, 21122, 21123, 21125, 21127, 21141, 21142, 21143, 21145, 21146, 21147, 21150, 21151, 21154, 21155, 21159, 21160, 21188, 21193, 21194, 21195, 21196, 21198, 21206, 21208, 21209, 21210, 21215, 21230, 21295, 21296
- Codes 21145, 21196, 21198 require pre-authorization EXCEPT when the procedure is performed for oral cancer diagnosis codes: C01, C02-C02.9, C03-C03.9, C04-C04.9, C05-C05.9, C06, C06.2, C06.9, C09-C09.9, C10-C10.0, C41-C41.1, C46.2, D00-D00.00, D10, D10.1-D10.9, D16.4-D16.5, D37-D37.0, D49-D49.0

Osteochondral Allograft/Autograft Transplantation (OAT)

- UMP is subject to HTCC Decision (PDF): 27415, 27416, 29866, 29867

Ovarian, Internal Iliac and Gonadal Vein Embolization, Ablation, and Sclerotherapy (PDF)

- 37241

Percutaneous Angioplasty and Stenting of Veins (PDF)

- 37238, 37239, 37248, 37249

Panniculectomy (PDF)

- 15830

Pectus Excavatum and Carinatum Surgery (PDF)

- 21740, 21742, 21743

Phrenic Nerve Stimulation for Central Sleep Apnea (PDF)

- C1823

Radiofrequency Ablation (RFA) of Tumors Other Than the Liver (PDF)

- 20982, 31641, 32998, 50542, 50592, 58580, 58674

Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants (PDF)

- 11920, 11921, 15769, 15771, 15772, 19316, 19318, 19325, 19328, 19330, 19340, 19342, 19350, 19355, 19370, 19371, L8600
- Pre-authorization is required EXCEPT when services are rendered in association with breast reconstruction and nipple/areola reconstruction following mastectomy for breast cancer. However, if autologous fat grafting with adipose-derived stem cell

enrichment is used for augmentation or reconstruction of the breast it would be considered investigational.
- Note: Codes 19380 and 19499 do not require pre-authorization but are considered, and will deny as, investigational when used for autologous fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast.

Reduction Mammaplasty (PDF)

- 19318

Responsive Neurostimulation (PDF)

- 61850, 61860, 61863, 61864, 61885, 61886, 61889, 61891, L8680, L8686, L8688

Rhinoplasty (PDF)

- 30120, 30400, 30410, 30420, 30430, 30435, 30450

Sacral Nerve Neuromodulation (Stimulation) for Pelvic Floor Dysfunction (PDF)

- 0786T, 0787T, 0788T, 0789T, 64561, 64581, 64585, 64590, 64595, 64596, 64597, 64598, C1767, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688
- Note: Please submit your pre-authorization request for the temporary trial period of sacral nerve neuromodulation AND the permanent placement at the same time, as these are treated as one combined episode.
- Treatment of chronic neuropathic pain is not a covered benefit, per HTCC Decision for codes 0786T, 0787T, 0788T, 0789T

Sacroiliac Joint Fusion (PDF)

- UMP is subject to HTCC Decision (PDF): 27278, 27280, 27279
- For indications not addressed in the HTCC, the Regence Medical Policy will apply

Spinal Cord and Dorsal Root Ganglion Stimulation (PDF)

- 0784T, 0785T, 0786T, 0787T, 0788T, 0789T, 63650, 63655, 63685, C1767, C1820, C1822, C1826, L8679, L8680, L8685, L8686, L8687, L8688
- Note: Please submit your pre-authorization request for the temporary trial AND the permanent placement at the same time.
- Spinal cord stimulation for the treatment of chronic neuropathic pain is not a covered benefit, per HTCC Decision for the following procedure and device codes; 0784T, 0785T, 0786T, 0787T, 0788T, 0789T, 63650, 63655, 63685, C1767, C1820, C1822, C1826, L8679, L8680, L8685, L8686, L8687, L8688 when associated diagnosis codes are included:
    - G60.9
    - G89.28-G89.29
    - M47.20-M47.28
    - M47.811-M47.819
    - M48.062
    - M50.10-M50.13
    - M50.121-M50.123
    - M54.10-M54.13

    - M51.14-M51.17
    - M54.16-M54.17
    - M54.30-M54.32
    - M54.40-M54.42
    - M54.5
    - M79.2
    - G89.4
    - M96.1
- If treatment is for other than this indication, Regence medical policy applies.

Spinal Injections

- Spinal Injections for UMP members are subject to HTCC Decision (PDF)
- Notes:
    - CPT 62292 for Therapeutic Medial Branch Nerve Block, Intradiscal and Facet Spinal Injections are not a covered benefit, reference the HTCC Decision (PDF):
    - CPT 27096, 62320, 62321, 62322, 62323, 64451, 64479, 64480, 64483, 64484, 64490, 64491, 64492, 64493, 64494, 64495 and G0260 may be subject to HTCC Decision. Pre-authorization is not required but may be subject to HTCC Decision (PDF) and require a provider attestation.
    - Attestation is needed for timely and accurate processing of claims
        - Use the electronic authorization tool on the Availity Portal and select the attestation criteria during the clinical documentation process on MCG Health
        - If an attestation is not completed pre-service using the Availity tool, fax the completed attestation form (PDF) to 1 (877) 357-3418
    - This coverage policy does not apply to those with systemic inflammatory disease such as ankylosing spondylitis, psoriatic arthritis or enteropathic arthritis

Spinal Surgery - Artificial Disc Replacement

- UMP is subject to HTCC Decision (PDF): 22856, 22858, 22861, 0095T, 0098T
- Lumbar artificial disc is not a covered benefit: 22857, 22860, 22862, 22865, 0163T, 0164T, 0165T

Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy

- UMP is subject to HTCC Decision (PDF): 32701, 61796, 61797, 61798, 61799, 61800, 63620, 63621, 77301, 77338, 77371, 77372, 77373, 77432, 77435, C9794, C9795, G0339, G0340
- This determination is specific to the treatment of localized prostate cancer, non-small cell and small cell lung cancer, pancreatic adenocarcinoma, oligometastatic disease, hepatocellular carcinoma, cholangiocarcinoma, Central Nervous System (CNS) primary and metastatic tumors, cancers of spine/paraspinal structures, as well as primary bone, head and neck, adrenal, melanoma, Merkel cell, breast, ovarian, and cervical cancers.
- Regence medical policies:

    - Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites (PDF)
    - Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites (PDF)

Surgery for Lumbar Radiculopathy

- UMP is subject to HTCC Decision (PDF): CPT 62380, 63030, 63035, 63042, 63044, 63047, 63048, 63056, 63057, 63090, 63091
- NOTES:
    - Pre-authorization is required only with diagnosis codes M47.20, M47.25, M47.26, M47.27, M47.28, M51.15, M51.16, M51.17, M51.26, M51.27, M54.10, M54.15, M54.16, M54.17, M54.18, M54.30, M54.31, M54.32, M54.40, M54.41, M54.42
    - CPT 62380 when billed without one of the listed diagnosis will be denied as an investigational denial based on Regence Medical Policy Automated Percutaneous and Percutaneous Endoscopic Discectomy

Surgical Treatments for Hyperhidrosis (PDF)

- 32664, 64818, 69676
- Code 32664 only requires pre-authorization for hyperhidrosis diagnoses L74.510 L74.511, L74.512, L74.513, L74.519, L74.52, R61

Surgical Treatments for Lymphedema and Lipedema (PDF)

- Code 15832, 15833, 15834, 15835, 15836, 15837, 15838, 15839, 15876, 15877, 15878, 15879 requires pre-authorization for Lipedema only with diagnosis codes Q82.0, R60.0, R60.9

Sleep Apnea Diagnosis and Treatment

- UMP is subject to HTCC Decision (PDF): 21121, 21122, 21141, 21145, 21196, 21198, 21199, 21685, 41120, 42140, 42145, 42160
- Codes 21145, 21196, 21198, 41120, 42160 do not require pre-authorization when the procedure is performed for oral cancer diagnosis codes: C01, C02-C02.9, C03-C03.9, C04-C04.9, C05-C05.9, C06, C06.2-C06.9, C09-C09.9, C10-C10.0, C41-C41.1, C46.2, D00-D00.00, D10, D10.1-D10.9, D16.4-D16.5, D37-D37.0, D49-D49.0
- HTCC does not apply to those under age 18. See Regence medical policy Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome (PDF)

Temporomandibular Joint (TMJ) Surgical Interventions

- Visit MCG's website for information on purchasing their criteria, or contact us for a copy of the specific guideline.
- 21010 - MCG A-0522
- 21050 - MCG A-0523
- 29800, 29804 - MCG A-0492
- 21240, 21242, 21243 - MCG A-0523

Transcatheter Aortic-Valve Implantation for Aortic Stenosis (PDF)

- 33361, 33362, 33363, 33364, 33365, 33366

Transcutaneous Bone Conduction and Bone-Anchored Hearing Aids (PDF)

- 69714, 69710, 69716, 69717, 69719, 69726, 69729, 69730, L8690, L8691, L8692, L8694

Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD) (PDF)

- 43192, 43201, 43236
- Note: Codes 43201 and 43236 may also be used for the administration of Botox for indications unrelated to GERD. Botox requires pre-authorization by Regence. Learn more about submitting a pre-authorization request for Boxtox.

Transurethral Water Vapor Thermal Therapy and Transurethral Water Jet Ablation (Aquablation) of the Prostate (PDF)

- 0421T, 53854, C2596

Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) and Gastrointestinal (GI) Symptoms

- Upper Endoscopy for GERD and GI Symptoms for UMP members are subject to HTCC Decision (PDF)
- CPT 43200, 43202, 43235, 43237, 43238, 43239, 43242 and 43259 do not require pre-authorization, but may be subject to HTCC Decision and require a provider attestation
- Attestation is needed for timely and accurate processing of claims for adults (members 18 years and older):
    - Use the electronic authorization tool on the Availity Portal and select the attestation criteria during the clinical documentation process on MCG Health
    - If an attestation is not completed pre-service using the Availity tool, fax the completed attestation form (PDF) to 1 (877) 357-3418.

Vagus Nerve Stimulation (PDF)

- 0720T, 61885, 61886, 64553, 64568, 64569, C1822, E0735, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688, C1827
- UMP is subject to HTCC Decision (PDF): for treatment of epilepsy and depression: 0720T, 61885, 61886, 64553, 64568, C1822, E0735, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688, C1827
- If treatment is for other than these indications, Regence medical policy applies.
- The HTCC does not apply to members under age 4. Please use Regence Medical Policy for requests for members under age 4.

Varicose Vein Treatment (PDF)

- UMP is subject to HTCC Decision (PDF): 0524T, 36465, 36466, 36470, 36471, 36475, 36476, 36478, 36479, 36482, 36483, 37700, 37718, 37722, 37735, 37760, 37761, 37765, 37766, 37780, 37785, S2202
- Notes:

    - Requests for multiple treatment sessions should refer to Regence medical policy
    - Code 37241 is not appropriate to use in the coding of varicose vein treatment

Ventral (Including Incisional) Hernia Repair (PDF)

- 15734, 49591, 49593, 49595, 49613, 49615, 49617, 49621
- Pre-authorization for 15734 required only with diagnosis code K42.0, K42.1, K42.9 K43.0, K43.1, K43.2 K43.6, K43.7, K43.9, K45.0, K45.1, K45.8, K46.0, K46.1, K46.9 or M62.0 for component separation technique (CST)
- Pre-authorization for codes 49591, 49593, 49595, 49613, 49615, 49617, 49621 only required with diagnoses codes K43.2 and K43.9 for ventral hernia repair

Transplants and ventricular assist devices

Transplants - Cell

- 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
- Stem Cell Therapy for Musculoskeletal Condition is subject to HTCC Decision (PDF) criteria: 38205, 38206, 38212, 38215, 38230, 38232, 38240, 38241
- Regence medical policy criteria will be used for codes and conditions not reviewed by the HTCC criteria

Transplants - Islet Transplantation (PDF)

- 48160, 0584T, 0585T, 0586T, G0341, G0342, G0343

Transplants - Heart (PDF)

- 33945

Transplants - Heart-Lung (PDF)

- 33935

Transplants - Lung and Lobar Lung (PDF)

- 32851, 32852, 32853, 32854, S2060

Transplants - Small Bowel, Small Bowel/Liver, and Multivisceral Transplant (PDF)

- 44135, 44136, 47135, 48554, S2053, S2054, S2152

Transplants - Liver Transplant (PDF)

- 47135

Transplants - Pancreas Transplant (PDF)

- 48554, S2065, S2152

Ventricular Assist Devices and Total Artificial Hearts (PDF)

- 33927, 33928, 33929, 33975, 33976, 33977, 33978, 33979, L8698

Utilization management

Air Ambulance Transport (PDF)

- A0435, A0430, S9960
- Pre-authorization is required prior to elective fixed wing air ambulance transport.
- Emergency air ambulance transports may be reviewed retrospectively for medical necessity.

Uniform Medical Plan

ABA Assessment and Treatment Plan

This report is confidential and for professional use only. The content may not be divulged to any person or agency without consent of the parent, legal guardian, or patient, as appropriate. Fax to Regence BlueShield **1-888-496-1540** *or by mail to: Regence BlueShield PO Box 1271 MS E9H, Portland, OR 97207-1271*

Patient Name:	**Treatment Agency Name:**
Patient Birth Date:	**Lead Behavior Therapist Name:**
UMP ID Number (Include Alpha Characters):	**Therapist Assistant Name(s):**

RECOMMENDED TREATMENT HOURS/SESSIONS

	Direct Patient Support - hours (weekly)	**Caregiver/Parent Training - 1 session per day (monthly)**
Recommended Hours and Setting (indicate # of Sessions for Caregiver/Parent Training)	*e.g., 10 hours in home* *2 hours in community*	

	Program Supervision - **includes observation of the treatment being delivered, observation of the child in his/her natural setting, and communication with BCBAs/Techs delivering ABA services.** **(weekly)**	**ABA treatment day program in a clinic or outpatient hospital setting (weekly)**
Recommended Hours and Setting	*e.g., 10 hours in home* *2 hours in community*	

Rationale for this treatment plan should be reflected in the body of the report below, as well as the severity ratings on the Applied Behavior Analysis Authorization Request Form submitted with this treatment plan.

BACKGROUND AND HISTORY *Indicate at least the following or indicate NA.*

Past psychiatric history:

For diagnosis of autism spectrum disorder, include date of diagnosis and diagnosing provider name. Also include initial diagnosis documentation and comorbid diagnoses if this is an initial preauthorization request.

Chief Complaint and History of Present Illness (HPI): *Include all core deficit areas of autism, challenging behaviors, adaptive, motor, vocational, and cognitive skills, and any other related relevant areas. In addition to addressing the chief complaint, one should be able to understand the patient's level of functioning by reading this section. Please provide a detailed summary of information below for both Preauthorization and Concurrent review requests.*

Social Communication: *includes persistent deficits in social communication and social interaction, as outlined in DSM-5*

Behavior: *includes restricted interests and repetitive behaviors, as well as related challenging behaviors (e.g., tantrums, aggression, etc.)*

Adaptive skills:

Motor:

Vocational:

Cognitive:

Family history: *Focus on relevant family psychiatric history and related family training in support of performing ABA therapy*

Social history: *Information about where the patient lives, with whom, as well as any other relevant information about social context or stressors.*

Medical history:

Active medical problems:

Current medical providers:

Current medications, dose, purpose, and potential major side effects:

Allergies, special diets, etc.:

Past medical problems:

Educational History: *Summarize past and current educational plan, including what services are being provided in the educational setting. Discuss whether functional behavior assessments, behavior plans, and/or aversive plans have been used in the school setting. State where the information was obtained (e.g., review of records, interview, etc.).*

History:

Current:

Past and Current Services: *Outline all additional services being provided outside school through any other agency or funding source. Include frequency, provider, and funding source.*

Ensure there is not redundancy with recommended ABA treatment plan.

Outline previous courses of ABA therapy; including dates, setting, and the outcome.

ASSESSMENTS COMPLETED FOR EVALUATION

Measures used: *Discuss all sources of information used in evaluating the patient, including standardized (norm-referenced) and curriculum-based measures, interviews (e.g., parent, caregivers, teacher), direct observation at home/school/community, etc. Please complete the Applied Behavior Analysis Authorization Form and attach to this treatment plan.*

Evaluation Findings: *Briefly summarize findings, including test scores if available. Summary can be brief; a couple sentences per measure. E.g., Vineland-II results demonstrated delays in communication and socialization are present. Tables and score reports can be used if easier to present information. Present in appendices if desired. Briefly summarize findings derived from observations in natural settings (e.g., home, school).*

Functional behavior assessment/analysis findings: *Functional assessment or analysis results should be included here. The following components should be included:*

1) *Operational definition of behavior*

2) *Hypotheses or analysis about functions supported by indirect and direct assessment results*

3) *Functional assessment or analysis data to support function hypotheses or analyses*

4) *Baseline data, including frequency, duration, and intensity data, as appropriate to behavior.*

Include assessment of risk (e.g., due to elopement or other unsafe behavior) as appropriate.

Goal domains derived from assessment: *Include statement about how the information obtained supports goals in specific areas. E.g., Assessment information suggests CHILD needs treatment goals in the areas of Social Communication, Behavior, Adaptive skills, Motor skills, Vocational skills, and Cognitive skills.*

TREATMENT PLAN IMPLEMENTATION

Treatment Plan: *This section should include a brief overview of the treatment plan, including:*

1) *How ABA will be applied to the patient (e.g., ABA as applied to CHILD will include home and community based 1-1 intervention for (x) hours per week to target social, communication, and adaptive goals)*

2) *Whether a positive behavior support plan is required to address challenging behaviors*

3) *The parent/caregiver training plan*

4) *How the treatment plan will be coordinated with other providers, including school (e.g., speech pathologist, medical providers, outpatient psychologist, teachers, etc.).*

Goals and objectives can be found in Appendices A, B and C of this report.

Maintenance/Generalization/Discharge Plan: *This section should include a statement about how maintenance and generalization will be addressed, how services will be reduced or transitioned to the parents and/or how the patient will be transitioned into other less intensive services (e.g., school, outpatient, etc.). This should be more specific as the patient progresses in therapy. The transition or discharge plan should be specific, data driven, and include criterion for discharge.*

Goals and objectives can be found in Appendix D of this report.

ABA Agency or ABA Service Coordinator: _____

_____	_____
Print Name of Lead Behavior Therapist	Signature of Lead Behavior Therapist
_____	_____
Print Name of Therapist Assistant	Signature of Therapist Assistant
_____	_____
Print Name of Therapist Assistant	Signature of Therapist Assistant
_____	_____
Print Name of parent/caregiver	Signature of parent/caregiver

Appendix A: Goals and Objectives for Skill Acquisition

Include goals and objectives in all relevant areas. Goals should be worded in such a way that they can be measured to track progress. Objectives should be clear steps toward a goal. Goals and objectives should be worded in such a way that they are easily interpretable to readers who are not familiar with behavioral terminology (i.e., parents, case managers, etc). The specified domains were decided upon by the HCA and include social communication, behavior (restricted interests, repetitive behaviors, other challenging behaviors), adaptive, motor, vocational, and cognitive. Broadly defined, all relevant goals (e.g., play skills, self-help, etc.) should fit into one of these categories. Goals for reduction of problem behavior should be outlined in Appendix B: Positive Behavior Support Plan.

Skill Acquisition Goals: *All skill acquisition goals and their corresponding objectives should be outlined here. Goals should be organized by skill area (e.g., social communication), should be titled with a short 2-3 word title, should include a broad goal that demonstrates the expected outcome, and then be broken down into specific objectives(also titled) that clearly outline target skills to be taught (e.g., within communication, expressive labels and requesting might be two specific objectives). Objectives should be measurable and measurement strategies, including mastery criteria, should be clearly stated (e.g., mastery criteria are met when a correct response occurs on 9 out of 10 opportunities across three sessions). Goals should be written in a manner that is consistent with how the therapists are taking data so data can easily be reported back for utilization review of progress. If progress will be documented by using a formal assessment tool (e.g., a measure associated with a curriculum), this should be stated in how the goal is written (e.g., patient will show improvement according to the ____ assessment).*

If the patient is receiving ABA therapy services primarily to address reduction of challenging behaviors, this section may be marked NA and the Positive Behavior Support Plan should be outlined in Appendix B.

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:

Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:
Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:
Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:

Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:
Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Appendix B: Positive Behavior Support Plan

Positive Behavior Support (PBS) Plan for Reducing Challenging Behaviors: *Should follow from functional assessment/analysis results discussed above and include, 1)operational definitions of behaviors, 2) a brief statement of identified functions of behavior, 3) suggested parent/caregiver/staff response to behaviors when they occur, 4) recommended antecedent interventions to prevent behaviors, 5) plan for teaching replacement behaviors with clear goals, 6) statement about how the proposed interventions were derived from the functional assessment/analysis, 7) plan for coordinating PBS Plan across settings.*

If the patient has minimal challenging behaviors and the primary focus of their ABA treatment plan is on skill acquisition, this section may be marked NA and the skill acquisition goals should be outlined in Appendix A.

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:
Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Appendix C: Parent/Caregiver Training Goals

This section should address caregiver goals for skill acquisition (e.g., parents will learn to implement the PBS Plan). It should include clear goals and objectives, written in the same format as the patient's skill acquisition goals.

All children should have parent/caregiver training goals in their treatment plan, regardless of the nature of the child's goals/objectives. If the treatment plan is for an adult or an individual living in a group setting, this portion of the plan should focus on training caregivers. This section may not be marked NA.

Goal 1:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 1A	
	Baseline:
	Progress:
Goal 2:	
	Baseline:
	Treatment Approaches to be Used:
	Progress:
Objective 2A	
	Baseline:
	Progress:

Appendix D: Maintenance/Generalization/Discharge Plan

This section should include a statement about how maintenance and generalization will be addressed, how services will be faded and/or how the patient will be transitioned into other less intensive services (e.g., school, outpatient, etc.). This should be more specific as the patient progresses in therapy. The fading plan should be specific, data driven, and include criterion for discharge.

Statement about how maintenance and generalization will be addressed, etc.

Goal 1:	
	Criterion for Discharge:
	Referral Program:
Objective 1A	
	Criterion for Discharge:
	Referral Program:
Goal 2:	
	Criterion for Discharge:
	Referral Program:
Objective 2A	
	Criterion for Discharge:
	Referral Program:

Goal 1:	
	Criterion for Discharge:
	Referral Program:
Objective 1A	
	Criterion for Discharge:
	Referral Program:
Goal 2:	
	Criterion for Discharge:
	Referral Program:
Objective 2A	
	Criterion for Discharge:
	Referral Program:

Goal 1:	
	Criterion for Discharge:
	Referral Program:
Objective 1A	
	Criterion for Discharge:
	Referral Program:

Goal 2:	
	Criterion for Discharge:
	Referral Program:
Objective 2A	
	Criterion for Discharge:
	Referral Program:

Goal 1:	
	Criterion for Discharge:
	Referral Program:
Objective 1A	
	Criterion for Discharge:
	Referral Program:
Goal 2:	
	Criterion for Discharge:
	Referral Program:
Objective 2A	
	Criterion for Discharge:
	Referral Program:

Goal 1:	
	Criterion for Discharge:
	Referral Program:
Objective 1A	
	Criterion for Discharge:
	Referral Program:
Goal 2:	
	Criterion for Discharge:
	Referral Program:
Objective 2A	
	Criterion for Discharge:
	Referral Program:

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Allied Health, Policy No. 32

Biofeedback

Effective: April 1, 2023

Next Review: August 2023
Last Review: December 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Biofeedback is intended to increase awareness and control of certain body functions normally considered to be outside conscious control.

MEDICAL POLICY CRITERIA

Note: Services described in this medical policy are not routinely reviewed; however, claims may be subject to audit including but not limited to review of member benefit application, medical appropriateness, frequency utilization, documentation requirements, accurate code selection, and reimbursement. Some devices or services may be subject to the health plan's reimbursement policy manual or may not be covered based on benefit contracts. Claim adjudication is also subject to claim processing guidelines and provider contracts.

I. Biofeedback as part of the overall treatment plan may be **medically necessary** for one or more of the following indications:

   A. Migraine or tension headaches

B. Stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT)

C. Dyssynergia-type constipation in adults when all of the following criteria (1.-3.) are met:

1. Symptoms of functional constipation that meet all of the following ROME IV criteria (see Policy Guidelines)
2. Objective physiologic evidence of pelvic floor dyssynergia when one or both of the following criteria are met:
   a. Inappropriate contraction of the pelvic floor muscles
   b. Less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
3. Failed 3-month trial of standard treatments for constipation including laxatives, dietary changes, and pelvic floor exercises

II. Unsupervised biofeedback in the home setting is considered **investigational** for all indications.

III. Biofeedback is considered **investigational** for all other indications, including but not limited to the following: chronic pain, fecal incontinence, encopresis, and constipation other than dyssynergia type in adults, fibromyalgia, headaches other than migraine and tension (e.g., cluster headaches), myalgia or muscle pain, neck pain, orofacial pain, shoulder pain, temporomandibular joint disorders, and urinary disorders not meeting criteria, including but not limited to: post- prostatectomy urinary dysfunction, urinary incontinence not administered in conjunction with pelvic floor muscle training (PFMT), urinary retention, vesicoureteral reflux and voiding dysfunction.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Rome IV diagnostic criteria for functional constipation are as follows:[1]

1. Must include 2 or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (Bristol Stool Form Scale1-2) for more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation for more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage for more than one-fourth (25%) of defecations
   e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than 3 spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical documenting symptoms and treatment specific to policy criteria
- If for constipation, three months of chart note documentation. Indicate if symptom onset is at least six months prior to diagnosis (please include dates).
- Clinical documentation with physiologic evidence of pelvic floor dyssynergia

CROSS REFERENCES

1. Neurofeedback, Medicine, Policy No. 65
2. Sphenopalatine Ganglion Block for Headache and Pain, Medicine, Policy No. 160
3. Percutaneous Neuromodulation Therapy (PNT), Surgery, Policy No. 44

BACKGROUND

Biofeedback is a technique intended to teach patients self-regulation of certain physiologic processes not normally considered to be under voluntary control. The technique involves the feedback of a variety of types of information not normally available to the patient, followed by a concerted effort on the part of the patient to use this feedback to help alter the physiological process in some specific way. Biofeedback training is done either in individual or group sessions, alone, or in combination with other behavioral therapies designed to teach relaxation. A typical program consists of 10 to 20 training sessions of 30 minutes each. Training sessions are performed in a quiet, non-arousing environment. Subjects are instructed to use mental techniques to affect the physiologic variable monitored, and feedback is provided for successful alteration of that physiologic parameter. The feedback may be in the form of lights or tone, verbal praise, or other auditory or visual stimuli.

REGULATORY STATUS

A variety of biofeedback devices are cleared for marketing though the Food and Drug Administration's (FDA) 510(k) process. The FDA defines a biofeedback device as "an instrument that provides a visual or auditory signal corresponding to the status of one or more of a patient's physiological parameters (e.g., brain alpha wave activity, muscle activity, skin temperature, etc.) so that the patient can control voluntarily these physiological parameters." Freespira from Palo Alto Health Sciences, Inc. is an example of a biofeedback device that has received FDA approval (K180173).

EVIDENCE SUMMARY

There are several methodologic challenges that arise in assessing biofeedback for any indication. For example, most interventions that include biofeedback are multimodal and include relaxation and behavioral instruction which may have effects separate from those that may occur due to biofeedback. While studies may report a beneficial effect of multimodality treatment, without appropriate control conditions, it is difficult to isolate the specific contribution of biofeedback to the overall treatment effect. In addition, behavioral therapies (non-drug treatments including biofeedback) result in both nonspecific and specific therapeutic effects. Nonspecific effects, sometimes called the placebo effect, occur as a result of therapist contact,

positive expectancies on the part of the patient and therapist, and other beneficial effects that occur as a result of being a patient in a therapeutic environment. Specific effects are those that occur only because of the active treatment, above any nonspecific effects that may be present.

In order to isolate the independent contribution of biofeedback on health outcomes (specific effects) and properly control for nonspecific treatment effects, well-designed randomized controlled trials (RCT) with the following attributes are necessary:

- Randomization helps to achieve equal distribution of individual differences by randomly assigning patients to either biofeedback or sham-biofeedback treatment groups. This promotes the equal distribution of patient characteristics across the two study groups. Consequently, any observed differences in the outcome may, with reasonable assuredness, be attributed to the treatment under investigation.
- A comparable sham control group helps control for expected high placebo effects as well as for the variable natural history of the condition being treated.
- Blinding of study participants, caregivers, and investigators to active or sham assignments helps control for bias for or against the treatment. Blinding assures that placebo effects do not get interpreted as true treatment effects.
- Small studies limit the ability to rule out chance as an explanation of study findings.
- Follow-up periods must be long enough to determine the durability of any treatment effects.

Therefore, the focus of the evidence review for biofeedback for all indications is on RCTs with the attributes noted above.

ASTHMA

SYSTEMATIC REVIEWS

Yorke (2015) published a SR of studies evaluating nonpharmacologic interventions for the treatment of adults with asthma.[2] The literature search, conducted through May 2014, identified 23 studies for inclusion. The nonpharmacologic interventions were organized into groups: relaxation-based therapies (n=9 studies); cognitive behavioral therapies (n=5 studies); biofeedback techniques (n=3 studies); and mindfulness (n=1 study). Five studies incorporated multicomponent interventions. The three biofeedback RCTs used different techniques: exhaled carbon dioxide capnography (pooled n=12)[3]; HRV using a physiograph (pooled n=94 patients)[4]; and respiratory sinus arrhythmia by electrocardiographic feedback and muscle tension by electromyography (EMG; pooled n=17 patients).[5] Common outcomes in the 3 studies included peak expiratory flow and respiratory impedance. Two of the trials reported on medication use. While differences were detected in exhaled carbon dioxide, HRV, and muscle tension, no changes in forced expiratory volume in one second (FEV_1) were found and medication use decreased in only one trial. Reviewers concluded that larger sample sizes were needed to demonstrate effects and that, while certain parameters that patients received biofeedback on may have differed between treatment groups, those differences did not translate into meaningful clinical benefits.

RANDOMIZED CONTROLLED TRIALS

Lehrer and colleagues[4] reported the results of 94 asthma patients randomized to one of the following four groups:

1. "Full protocol" including heart rate variability (HRV) biofeedback and training in pursed-lips abdominal breathing with prolonged exhalation;
2. HRV biofeedback alone;
3. Placebo biofeedback involving bogus "subliminal suggestions designed to help asthma", with no other details provided and no actual suggestions given plus biofeedback training to alternately increase and decrease frontal EEG alpha rhythms; and
4. A waiting list control group.

Although reported improvement was greater in the two treatment groups, scientific conclusions cannot be drawn from this data due to several limitations, as discussed in the Background section above, including possible selection bias due to lack of randomization, short study duration, lack of follow-up to assess long-term effects, and differences between groups in task involvement and assessment frequency. The authors concluded that further research is needed. They advise caution in the use biofeedback for the treatment of asthma until the mechanisms of action are better understood and the long-term effects have been documented.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with asthma. Additional evidence is needed from well-designed comparative studies.

AUTISM SPECTRUM DISORDER

Autism Spectrum Disorders (ASD) can vary in severity of disease and therefore treatments utilized to treat the disease, making it difficult to isolate outcomes associated with biofeedback. The following literature review for biofeedback as a treatment of ASD focuses on SRs and RCTs.

SYSTEMATIC REVIEW

Coben and Myers (2010) reviewed the literature on EEG biofeedback for ASDs.[6] The authors identified two published small, non-RCTs evaluating EEG biofeedback in the treatment of ASDs. As described in the review, a study published by Jarusiewicz and colleagues in 2002 compared treatment with 20 to 69 sessions of biofeedback in 12 autistic children to a matched control group that did not receive biofeedback. Mean reduction in autistic symptoms, as measured by the Autism Treatment Evaluation Checklist (ATEC), was 26% in the biofeedback group and 3% in the comparison group; this difference was statistically significant. The other study was published by Coben and Padolsky in 2007. It compared 20 sessions of EEG biofeedback in 37 patients to a waiting-list control group. After treatment, parents reported reduction in symptoms in 89% of the treatment group compared to 17% of the control group (p-value not reported). Studies differed in their biofeedback protocols and number of sessions. The review article concluded that RCTs are needed to determine the effectiveness of biofeedback to treat ASDs.

RANDOMIZED CONTROLLED TRIALS

Yang (2015) conducted a RCT to explore the effects of visual condition and target size during four reach-to-grasp tasks between 20 autistic and 20 matched control children subjects.[7] The autistic children showed longer movement time, larger normalized jerk score, more movement when compared to controls, especially in non-visual feedback and small target blocks. This study is limited by the small sample size and other methodological considerations making it hard to determine the efficacy of visual effects for autism.

Kouijzer (2013) published a RCT evaluating electroencephalography (EEG) biofeedback as a treatment for ASD.[8] The trial included 35 teenagers between 12 and 18 years-old with confirmed diagnoses of ASD. Participants were randomly assigned to receive EEG biofeedback (n=13), skin conductance biofeedback (n=12), or a waiting-list control group (n=13). The biofeedback interventions included 40 sessions provided twice a week. Patients and parents in the biofeedback groups but not on the waiting-list were blinded to treatment allocation. The primary outcome measure was change in symptoms at three months as measured by the total score on the Social Communication Questionnaire (SCQ) which has a potential range of 0 to 36. In the primary analysis, the investigators only included participants who successfully influenced their EEG activity (called “EEG-regulators”) in the primary analysis. The justification for this was to be able to identify the specific effects of biofeedback on symptoms. Among the 19 of 35 (54%) regulators, there was no statistically significant difference in the SCQ scores between participants treated with EEG- or skin-conductance biofeedback. The investigators evaluated non-specific effects of EEG biofeedback by examining the SCQ scores among EEG-non-regulators as rated by the parents. There was no statistically significant difference in scores among participants in the EEG biofeedback group, the skin conductance biofeedback group and the control group.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with ASDs. The scientific evidence on the effectiveness of biofeedback for treatment of autism consists of one small RCT and a limited number of small, non-randomized studies. The RCT did not report a significant benefit of biofeedback on autism-related symptoms.

BELL’S PALSY (IDIOPATHIC FACIAL PARALYSIS)

SYSTEMATIC REVIEWS

A 2011 Cochrane SR of physical therapy modalities for the treatment of Bell’s palsy.[9] The authors identified two case series and one small RCT. However, no analysis of these studies was performed because they did not meet the minimum methodological quality to be included in the review.

Cardoso (2008) examined the effects of facial exercises associated either with mirror or EMG biofeedback with respect to complications of delayed recovery in Bell's palsy.[10] Patients with unilateral idiopathic facial palsy treated with facial exercises associated with mirror and/or EMG biofeedback were included in this review. Four studies (n=132) met the eligibility criteria. The studies described mime therapy versus control (n=50), mirror biofeedback exercise versus control (n=27), "small" mirror movements versus conventional neuromuscular retraining (n=10), and EMG biofeedback plus mirror training versus mirror training alone. The treatment length varied from one to twelve months. The authors concluded that “…because of the small number of RCTs, it was not possible to analyze if the exercises, associated either with mirror

or EMG biofeedback, were effective. In summary, the available evidence from ran RCTs is not yet strong enough to become integrated into clinical practice."

RANDOMIZED CONTROLLED TRIALS

No RCTs identified after the above SRs.

SECTION SUMMARY

Current evidence from small RCTs with variable biofeedback protocols and type of comparison interventions is insufficient to permit conclusions on the impact of biofeedback on Bell's palsy.

BRUXISM AND SLEEP BRUXISM

SYSTEMATIC REVIEWS

Manfredini (2015) published a SR which included 14 studies, 12 of the studies were RCTs.[11] Two of the studies evaluated bruxism. The authors concluded that the potential benefit of biofeedback (BF) and cognitive-behavioral (CB) approaches to sleep bruxism management is not fully supported.

Wang (2013) published a SR of RCT and non-RCTs on biofeedback treatment for sleep bruxism.[12] The full text of 17 articles was reviewed and seven studies with a total of 240 participants met the inclusion criteria. Studies were generally small; onlytwo included more than 50 participants. Four studies used audio biofeedback, two used contingent electrical stimulation and 1 used visual biofeedback. Treatment duration ranged from one night to six weeks. In four of the studies, the duration of treatment was two weeks. Three of the studies were considered to be at moderate risk of bias and the other four were considered to be at high-risk of bias. The primary outcome of the analysis was the number of sleep bruxism episodes per hour detected by EMG recording. Only two studies (total n=27) reported this outcome and had data suitable for meta-analysis. A pooled analysis did not find a statistically significant difference between the biofeedback and control groups; mean difference: -4.47 (95% CI: -12.33 to 3.38). Findings were not pooled for any other outcomes.

RANDOMIZED CONTROLLED TRIALS

Sato (2015) published a RCT limited in size on the use of EMG biofeedback training for daytime clenching and its effect on sleep bruxism.[13] Patients were monitored for five hours of daytime and night time and were randomized to EMG biofeedback (n=7) or to a control group (n=5). Patients in the biofeedback group received a small auditory signal in the daytime when clenching activity was detected. There were significant decreases in EMG events during weeks two and three in the biofeedback group during the daytime, and the decreases in events carried over into the night time. There were no decreases in EMG events in the control group.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with bruxism. Additional evidence is needed from well-designed comparative studies.

CHRONIC PAIN (NON-HEADACHE)

As discussed in the Background section above, the focus of the evidence review was on RCTs. This study design is particularly important when studying treatments for pain. The most clinically relevant outcomes of therapy for pain are improvement in symptoms, function, and quality of life. These outcomes are subjective and can be influenced by nonspecific effects such as placebo response and the natural history of the disease. Randomized treatment allocation and the inclusion of a control group are needed to isolate the effect of biofeedback therapy.

GENERAL NON-HEADACHE PAIN

Systematic Reviews

A Cochrane SR by Williams on psychological therapies (cognitive-behavioral therapy [CBT] and behavioral therapy, including biofeedback) for chronic non-headache pain in adults was updated in 2012.[14] Forty-two trials provided analyzable data, thirteen of which had not been included in previous updates of this review. The SR found that although the quality of trial design had improved over time, the quality of treatments, reporting, or both had not improved. CBT (not behavioral therapy) had weak effects in improving pain, but only immediately following treatment. CBT also had small effects on pain-related disability, altering mood, and catastrophizing outcomes compared with usual treatment or waiting list patients, with some maintenance at six months follow-up. However, it was not possible to isolate the results for the individual components of CBT, including biofeedback. Behavioral therapy had no effect on mood but showed an effect on catastrophizing immediately post-treatment. The authors recommended against future general RCTs, recommending instead, studies to identify which components of CBT work for which type of patient.

Another Cochrane SR review by Eccleston and colleagues evaluated psychological therapies for the management of chronic and recurrent pain in children and adolescents. Included studies were RCTs with at least 10 participants in each arm. Although psychological therapies were found to improve pain, only one of the five studies on non-headache pain evaluated biofeedback.

Polermo conducted an SR of RCTs to update previously published SRs on psychological therapies for management of chronic non-headache pain in children and adolescents was published by Palermo and colleagues in 2010.[15] RCTs included in previous SRs were automatically eligible for inclusion in this SR. The review did not identify any new RCTs that had not been included in previous SRs. It was not possible to isolate the results of the individual components of the psychological therapies, including biofeedback.

Randomized Controlled Trials

No RCTs were identified that were published after the above SRs.

ARTHRITIS

Systematic Reviews

Richards (2017) published a SR evaluating the application of real-time biofeedback to reduce knee adduction movement (KAM) during gait training, for patients with knee osteoarthritis (KOA).[16] Twelve studies met the inclusion criteria. The authors concluded there are limited controlled studies, but found value for further research in the outcomes of biofeedback to reduce KAM.

In a SR with meta-analysis of psychological interventions for rheumatoid arthritis including relaxation, biofeedback, and cognitive-behavioral therapy, Astin and colleagues concluded that psychological interventions may be important adjunctive therapies in rheumatoid arthritis treatment.[17] In the 25 studies analyzed, significant pooled effect sizes were found for pain after an intervention. However, the same effect was not seen long term, and the meta-analysis did not isolate biofeedback from other psychological interventions. Therefore, the specific effects of biofeedback, as discussed in the Background section above, could not be isolated.

Randomized Controlled Trials

Eid (2016) published a RCT that evaluated the outcomes of electromyographic (EMG) biofeedback training on pain, quadriceps strength and functional ability for 11 boys and 25 girls with polyarticular juvenile rheumatoid arthritis (JRA).[18] Children were assigned to the EMG biofeedback group (n=18) or the control group (n=18). Treatments occurred over 12 weeks, with evaluation at six and 12 weeks. Both groups showed significant improvement at 12 weeks.

FIBROMYALGIA

Systematic Reviews

In 2015 a Cochrane SR was published by Theodom examining mind and body therapy for fibromyalgia. Sixty-one trails were included in the review.[19] The study participants were predominately women and their nature of fibromyalgia varied from mild to severe across the study population. No adverse events were reported. The authors found there was very low quality evidence that biofeedback in comparison to usual care controls had an effect on physical functioning, (SMD -0.1,95% CI-0.4 to 0.3, - 1.2% absolute change, 1 oint shift on a 0-100 scale) pain(SMD -2.6, 95% CI -91.3 to 86.1, -2.6% absolute change, and mood ((SMD 0.1, 95% CI -0.3 to 0.5, 1.9% absolute change, less than 1 point shift on a 0 to 90 scale) post-intervention. Due to the very low quality evidence, it is unclear what role biofeedback has fibromyalgia.

In 2013 Glombiewski published the results of a meta-analysis that included three studies on EEG-biofeedback (neurofeedback) and four studies on EMG-biofeedback for fibromyalgia (N=321).[20] Studies in which biofeedback was evaluated only as part of multicomponent interventions were excluded from the review. A sham intervention was used as a control condition in four studies, two using EEG biofeedback and two using EMG- biofeedback. A pooled analysis was conducted for each therapy. EMG-biofeedback was reported to have significantly reduced pain intensity compared to control groups (effect size, Hedges *g*: 0.86, 95% CI, 0.11 to 0.62). Pooled analyses of studies of EMG and EEG biofeedback did not find a significant benefit of the intervention on other outcomes including sleep problems, depression and health-related quality of life. None of the studies included in this review were high quality, with risk of bias assigned by the authors as either unclear or high for all included studies. In addition, all of the studies reported on short-term outcomes, resulting in a lack of evidence on whether longer-term outcomes are improved. The authors recommended further research focused on long-term effects and predictors of treatment response.

Randomized Controlled Trials

No RCTs identified after the SR above.

KNEE PAIN

Systematic Reviews

A number of SRs have been published that included trials of biofeedback in the treatment of anterior knee pain[21], patellofemoral pain syndrome,[22] and in post-meniscal repair rehabilitation.[22] Mixed results have been reported by the SRs, but no standardized treatment protocols or patient selection criteria have been established for biofeedback for knee pain of any etiology.

Randomized Controlled Trials

No RCTs were published after the above SR.

LOW BACK PAIN

Systematic Review

Sielski (2017) published a SR evaluating the impact of biofeedback for chronic back pain.[23] Twenty-one studies met all inclusion criteria, one of which had to be biofeedback at least 25% of the time. Outcomes were determined for pain, disability, depression, reduced muscle tension, and coping skills. The authors concluded that although the outcomes of biofeedback are promising, the SR had limitations including heterogeneity of how biofeedback and back pain were defined and the positive results should be interpreted with caution.

Qaseem (2017) published a guideline from the American College of Physicians (ACP) that by using the ACP was based on a SR of RCTs and SRs published through April 2015.[24] For patients with acute or sub-acute low back pain, biofeedback was not mentioned. For patients with chronic low back pain the recommendation was to initially try nonpharmacological treatments including biofeedback based on “low quality evidence”. For patients with chronic low back pain who have not responded to nonpharmacological treatments, pharmacological treatment may be considered.

Haines (2017) published an economic evaluation that was done alongside a pilot randomized trial that evaluated motion-sensor biofeedback for sub-acute and chronic low back pain over 12 months.[25] Patients received motion-sensor biofeedback with guideline based care (n=38) or guideline based care alone (n=45) over ten weeks and completed a three, six, and 12 month assessment. The authors concluded that motion-sensor biofeedback is both clinically and economically effective, but more studies are needed.

Daffada (2015) conducted a SR to identify and assess the current evidence regarding the effectiveness of interventions (i.e. graded motor imagery and mirror visual feedback) which target cortical remapping in the management of chronic low back pain (CLBP).[26] Five articles were included in the review, which were comprised of three RCTs, one randomized cross-over study, and one multiple case study design. Although the authors report these interventions, including visual feedback, could be effective, the paucity of literature, small sample sizes, and methodological constraints of the studies included in the review make it difficult to determine the effectiveness of the interventions in the management of CLBP.

A 2010 Cochrane review[27] on behavioral treatments for chronic low-back pain included a meta-analysis of three small RCTs[28-31] comparing electromyography (EMG) biofeedback to a waiting-list control group. These studies were graded as low to very low quality due to methodological limitations and imprecision. In the pooled analysis there were a total of 34 patients in the intervention group and 30 patients in the control group. The standard mean

difference in short-term pain was -0.80 (95% confidence interval [CI]:-1.32 to -0.28); this difference was statistically significant favoring the biofeedback group. One additional RCT was not included in the pooled analysis due to differences in reporting.[28] This small RCT (n=44) was determined to have a low risk of bias and reported no significant differences in outcomes between groups. The Cochrane review did not conduct meta-analyses of trials comparing biofeedback to sham biofeedback.

Randomized Controlled Trials

Tan (2015) conducted a four arm RCT of hypnosis compared with biofeedback for 100 veterans adults with chronic low back pain (CLBP).[32] Group one included an eight-session self-hypnosis training intervention without audio recordings for home practice; group two consisted of an eight-session self-hypnosis training intervention with recordings; group three had a two-session self-hypnosis training intervention with recordings and brief weekly reminder telephone calls; and group four had an eight-session active biofeedback control intervention. All four groups reported significant pre-to post-treatment improvements in pain intensity, pain interference, and sleep quality. This study was limited by the small sample size and other methodological constraints making it hard to determine the efficacy of biofeedback for adults with CLBP.

In a 2010 study published after the above Cochrane SR, Kapitza compared the efficacy of respiratory biofeedback to sham biofeedback in 42 patients with lower back pain.[33] All participants were instructed to perform daily breathing exercises with a portable respiratory feedback machine; exercises were performed for 30 minutes on 15 consecutive days. Patients were randomized to an intervention group that received visual and auditory feedback of their breathing exercises or a control group that received a proxy signal imitating breathing biofeedback. Patients recorded pain levels in a diary three times a day, measuring pain on a visual analogue scale (VAS). Both groups showed reduction in pain levels at the end of the intervention period and at the three month follow-up, but there were no significant differences in pain between groups. For example, the mean change in pain with activity three months after the intervention was a reduction in 1.12 points on a 10-point VAS scale in the intervention group and 0.96 points in the sham control group; $p>0.05$. The mean change in pain at rest after three months was a reduction of 0.79 points in the intervention group and 0.49 points in the control group; $p>0.05$.

Another 2010 RCT, by Glombiewski, assessed whether the addition of EMG biofeedback to CBT improved outcomes in 128 patients with lower back pain.[34] Patients with musculoskeletal pain of the low, mid, or upper back, with pain duration of at least six months on most days of the week, were randomized to CBT, CBT plus biofeedback, or a waiting-list control; 116 patients began the 1-hour weekly sessions (17-25 treatments) and were included in the final analysis. CBT alone included breathing exercises and progressive muscle relaxation; biofeedback was used for 40% of the CBT treatment time in the combined treatment condition. Both treatments were found to improve outcomes including pain intensity compared to a waiting-list control (moderate effect size of 0.66 for pain intensity in the CBT plus biofeedback group). However, the addition of biofeedback did not improve outcomes over CBT alone.

NECK AND SHOULDER PAIN

Systematic Reviews

Campo (2021) published a systematic review and meta-analysis that evaluated the effectiveness of biofeedback for improving pain, disability, and work ability in adults with neck pain.[35] The review included 15 RCTs with eight studies utilizing EMG biofeedback and seven studies pressure biofeedback. There was no restriction on the control intervention (eg, no treatment, placebo, active treatment) or co-intervention, provided the independent effects of biofeedback could be elucidated. Results suggest that biofeedback has a moderate effect on reducing short-term disability and a small effect on reducing intermediate-term disability with no effect on pain or work ability in the short- and intermediate-term. Of note, there were a variety of control interventions across included studies (eg, exercise, electroacupuncture, electrotherapy, education) with few studies directly comparing biofeedback to no treatment or placebo.

Kamonseki (2021) completed a systematic review and meta-analysis of 5 RCTs (N=272) that examined the effects of EMG biofeedback for shoulder pain and function.[36] Very-low quality of evidence found that electromyographic biofeedback was not superior to control for reducing shoulder pain (standardized mean differences = -0.21, 95% confidence interval: -0.67 to 0.24, p=0.36) or shoulder function (standardized mean differences = -0.11, 95% confidence interval: -0.41 to 0.19, p=0.48). The authors state the very low quality of evidence does not permit a definitive recommendation regarding EMG biofeedback in the treatment of shoulder pain.

Shearer (2016) published a SR evaluating the impact of psychological interventions, one of which was biofeedback for neck pain and associated disorders (NAD) and whiplash disorders.[37] The SR included RCTs, cohort and case control studies. No clear positive effects were seen for biofeedback and the authors noted more sound methodological research is needed.

Hesselstrand (2015) published a SR of 19 studies called Occupational Therapy Interventions in Chronic Pain-A SR.[38] One RCT addressed surface EMG biofeedback training for persons with neck and shoulder complaints after whiplash-associated disorders, concerning activities of daily living and pain. The SR concluded that no support exists for the effectiveness of electromyographic biofeedback training as a supplement and that more studies are needed to confirm this result.

Randomized Controlled Trial

Ma (2011) published an RCT that included 72 patients with chronic (at least three months) computer work-related neck and shoulder pain.[39] Patients were randomized to one of four six-week interventions: Biofeedback, exercise, passive treatment (e.g., hot packs), or a control group receiving only an educational pamphlet. Members of the biofeedback group were given a portable EMG biofeedback machine and were instructed to use it for two hours daily while performing computer work. The active exercise group was given an exercise routine to perform on their own for no longer than 20 minutes, four times a day. Sixty of 72 (83%) participants were available for the post-intervention follow-up assessment (n=15 per group). At the end of the intervention, the average VAS score and neck disability index (NDI) scores were significantly lower in the biofeedback group than in the other three groups. For example, the mean VAS post-intervention was 1.87 (standard deviation [SD]: 0.74) in the biofeedback group and 2.10 (SD: 1.34) in the active exercise group ($p< 0.05$).

This study found a short-term benefit of a biofeedback intervention, but the magnitude of difference in the VAS scores and the NDI index was small and of uncertain clinical significance. In addition, there were several methodologic limitations. The study was of small

size and had a substantial number of dropouts; data were available on only 39 of 72 (54%) participants at six months. The interventions were not balanced in intensity, as the biofeedback intervention was more intensive (two hours per day) than the other interventions, such as the passive treatment arm, which received two 15-minute sessions per week. Long-term data were not available due to the low follow-up rate, which at six months was too small for meaningful analysis.

OROFACIAL PAIN (INCLUDING TEMPOROMANDIBULAR JOINT DISORDER)

Systematic Reviews

A 2011 Cochrane SR identified 17 trials evaluating non-pharmacological psychological interventions for adults with chronic orofacial pain (e.g., temporomandibular joint (TMJ) disorder).[40] For the outcome short-term pain relief (three months or less), there was a significantly greater reduction in pain with interventions that combined CBT and biofeedback compared to usual care (two studies). However, there was not a significant benefit of a combined CBT/biofeedback on longer-term i.e., six-month pain relief, and there were no studies that compared CBT alone to CBT combined with biofeedback. For biofeedback-only interventions, a pooled analysis of two studies on short-term pain relief did not find a significant benefit compared to usual care. There was only one study reporting long-term pain relief after a biofeedback-only intervention, so a pooled analysis could not be conducted. The authors concluded that there is weak evidence to support psychosocial interventions for managing chronic orofacial pain and the most promising evidence is for CBT, with or without biofeedback. They noted that the trials in the review were few in number and had a high risk of bias, and they recommended additional high-quality trials.

The conclusions of the Cochrane review are similar to previous SRs on treatment of TMJ disorder. The reviews also concluded that there is weak evidence that psychosocial/physical therapy interventions, including biofeedback among others, are beneficial for treating TMJ but that there were few studies and they tended to be of poor methodologic quality. For example, Medlicott and colleagues recommended caution in interpreting results due to heterogeneity in study design and interventions used.[41] Since biofeedback was not isolated from other therapies, no conclusions could be reached for biofeedback alone. Based on two poor-qualityRCTs, McNeely and colleagues concluded that biofeedback did not reduce pain more than relaxation or occlusal splint therapy for TMJ, but did improve oral opening when compared with occlusal splints.[42]

Randomized Controlled Trials

No RCTs identified after the above SR.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systematic Reviews

No SRs were identified for biofeedback for the treatment of SLE.

Randomized Controlled Trial

In an RCT of 92 patients with Systemic Lupus Erythematosus (SLE), Greco and colleagues reported that patients treated with six sessions of biofeedback-assisted cognitive-behavioral treatment for stress reduction had a statistically significant greater improvement in pain post

treatment than a symptom-monitoring support group (p=0.044) and a usual care group (p=0.028).[43] However, these improvements in pain were not sustained at a nine-month follow-up and further studies are needed to determine the incremental benefits of biofeedback-assisted cognitive-behavioral treatment over other interventions in SLE patients.

RECURRENT ABDOMINAL PAIN

Systematic Reviews

No SRs were identified using biofeedback for the treatment of recurrent abdominal pain.

Randomized Controlled Trial

Humphrey's and Everts randomly assigned 64 patients with recurrent abdominal pain to groups treated with: 1) increased dietary fiber; 2) fiber and biofeedback; 3) fiber, biofeedback, and cognitive-behavioral therapy; and 4) fiber, biofeedback, cognitive-behavioral therapy, and parental support.[44] The three multi-component treatment groups were similar and had better pain reduction than the fiber-only group. This study does not address placebo effects. In a SR of recurrent abdominal pain therapies in children, Weider and colleagues concluded that behavioral interventions (cognitive-behavioral therapy and biofeedback) had a general positive effect on nonspecific recurrent abdominal pain and were safe.[45] However, the specific effects of biofeedback were not isolated in this SR.

VESTIBULODYNIA/VULVODYNIA/VULVAR VESTIBULITIS

Systematic Reviews

Morin published a SR to evaluate the outcomes of different physical therapies, one of which was biofeedback for women with provoked vestibulodynia.[46] The SR included RCTs, prospective and retrospective studies, case reports and study protocols, most of which had methodological limitations. The authors concluded more well designed RCTs are needed.

Randomized Controlled Trial

An RCT by Bergeron of 78 patients with vulvar vestibulitis compared biofeedback, surgery and cognitive-behavioral therapy.[47] Surgery patients had significantly better pain scores than patients who received biofeedback or cognitive-behavioral therapy. No placebo treatment was used.

OTHER CHRONIC PAIN

Other pain for which there are no publications sufficient to demonstrate the effectiveness of biofeedback include muscle pain or myalgia.

SECTION SUMMARY

The current evidence base is insufficient to allow scientific conclusions concerning the contribution of biofeedback to improvements in health outcomes for the treatment of chronic non-headache pain. [Headache is discussed separately below]

DEPRESSION, ANXIETY, AND POST-TRAUMATIC STRESS DISORDERS

Systematic Reviews and Technology Assessments

In 2018, the Canadian Agency for Drugs and Technology in Health (CADTH) published an updated “Post-Traumatic Stress Disorder: Summary of Evidence of the Clinical Effectiveness of Treatments”.[48] They reviewed 26 treatments, one of which was biofeedback. They continued their stance that there is no evidence-based guidelines for the treatment of any mood or anxiety disorders. Additional well-designed, controlled clinical studies are needed to determine the clinical effectiveness of biofeedback on PTSD.

A 2017 CADTH evidence report on biofeedback for mood and anxiety disorders states the following:[49]

> Evidence from single randomized controlled trials suggests that compared with no treatment there is a statistically significant improvement in symptoms with neurofeedback treatment in patients with post-traumatic stress disorder (PTSD) or generalized anxiety disorder (GAD).
>
> A single randomized controlled trial (RCT) showed that for patients with PTSD there was improvement in symptoms with biofeedback (BF) plus treatment as usual (TAU) and also with TAU alone but the improvement occurred faster in the BF plus TAU group.
>
> A single RCT showed that for patients with PTSD there were no between group differences for BF and various mindfulness related treatment modalities. A single RCT showed that for patients with major depressive disorder, there was a statistically significant improvement in depression with BF plus TAU.
>
> Results need to be interpreted in the light of limitations (such as small sample size, lack of randomization details, lack of reporting of adverse events, lack of long-term data).
>
> No relevant studies on the clinical effectiveness of biofeedback using home equipment for treatment of PTSD, GAD, or depression without continued support from health professionals were identified.
>
> No relevant evidence based guidelines regarding the use of neurofeedback or biofeedback for the treatment of PTSD, GAD, or depression were identified.

Goessl (2017) published a SR on the effect of heart rate variability (HRV) biofeedback training in patients with stress and anxiety.[50] HRV is a measure of cardiac vagal tone. Low HRV is associated with certain psychological states such as anxiety. The literature search identified 24 studies (total N=484 patients), published between 1976 and 2015, for inclusion. Sample sizes ranged from five to 106 patients (median, 14 patients). The Cochrane risk of bias tool was used to assess study quality. Many studies had high or unclear risk of bias due to the following factors: inadequate randomization descriptions, improper randomization, undescribed allocation concealment, and missing data that was either not described or mishandled; 13 studies included a comparison group (six waitlist, three standard of care, two sham, one daily thought record, one progressive muscle relaxation). The average within-group effect size among the 24 studies, measured by Hedges’ *g*, was 0.81, indicating a large effect on anxiety. The average between-group effect size among the 13 studies with comparators, also measured by Hedges’ *g*, was 0.83, indicating HRV had a larger effect on anxiety than the comparators.

Schoenberg and David (2014) published a systematic review (SR) on biofeedback for psychiatric disorders, one of which was anxiety.[51] They identified 227 articles and 63 met the criteria for review. The authors concluded that development of standardized controlled

methodology protocols tailored for specific disorders and guidelines are needed to determine the benefit of biofeedback on health outcomes for those with anxiety.

Randomized Controlled Trials

In addition to those included in the systematic reviews, the following RCTs have been published. Maynart (2021) compared respiratory and heart rate biofeedback plus usual care to usual care alone in 36 patients with moderate to severe depression or dysthymia.[52] After six weeks (six sessions of biofeedback training), the biofeedback plus usual care group had less severe depression as measured by the Beck Depression Inventory (BDI) than the usual care alone group.

A preliminary open-label RCT by Park and Jung (2020) compared respiratory sinus arrhythmia biofeedback plus usual care to usual care alone in 30 patients with major depressive disorder.[53] After four weeks (six sessions of biofeedback), the biofeedback plus usual care group had greater improvements in Hamilton Depression Rating Scale (HAM-D) scores compared to the group receiving usual care alone. Improvements in other clinical measures, including the BDI, were not significantly different between groups.

Chen (2016) published an RCT comparing diaphragmatic breathing relaxation (DBR) with routine respiration activities in the treatment of 46 patients with anxiety.[54] DBR is a technique that uses diaphragm muscle contractions to force air downward into the body, increasing diaphragm length and breathing efficiency. Outcomes were anxiety level, measured by Beck Anxiety Inventory, and four physiological measures (skin conductivity, peripheral blood flow, heart rate, breathing rate). All patients participated in an individualized eight-week course in breathing relaxation, but only 30 completed it. Fifteen were randomized to DBR training and 15 to routine breathing relaxation training. Researchers and patients were blinded to randomization, with only the trainer being aware of group allocation. After eight weeks, the DBR group experienced statistically significant decreases in Beck Anxiety Inventory scores compared with baseline, while the control group did not experience significant decreases from baseline. The DBR group also experienced significant improvements in all four physiological measurements, while the control group did not. The authors noted this therapy is promising, but more well-controlled studies are needed.

A RCT by Meuret (2010) included 41patients with panic disorder and agoraphobia who were randomized to receive four weeks of capnometry-assisted respiratory training (Freespira) or cognitive training.[55] Although capnometry-assisted respiratory training, but not cognitive training, was associated with a shift from hypocapnic to normocapnic levels, reductions in panic symptom severity and panic-related cognitions was well as improvements in perceived control were significant and comparable in both treatment groups.

FECAL INCONTINENCE AND CONSTIPATION

The relevant clinical outcome in studies of biofeedback as a treatment of fecal incontinence, encopresis, and constipation should be the overall change in the bowel symptoms. Reduction in episodes of fecal incontinence, encopresis, and constipation, and an increase in voluntary bowel movements as a result of biofeedback are the primary clinical outcomes of interest. Patient symptoms are usually assessed through diary, questionnaire, or interview. However, changes in anorectal physiological assessment (e.g., anal pressure, sensory threshold) often do not correlate with symptom relief (i.e., clinical outcomes).

FECAL INCONTINENCE IN ADULTS

Systematic Reviews

A 2014 Cochrane SR of RCTs compared one method of biofeedback to sham-biofeedback, no treatment, or another method of biofeedback in adults (> 18 years of age) with chronic idiopathic (functional) constipation.[56] Seventeen RCTs (25 individual reports) were included (N=931); biofeedback was compared to conventional nonsurgical treatment in 7 studies[57-63], to different methods of biofeedback in six studies[64-69], to surgical intervention in two studies[70, 71], to sham treatment in one study[72] and to electrical stimulation in one crossover study[73, 74]. No studies compared biofeedback to no treatment. Meta-analysis was not possible due to between-study heterogeneity and evidence was rated as low or very low quality due poor methodological quality with high risk of bias. The length of follow-up was determined to be inadequate in many RCTs. There was significant heterogeneity between groups and between studies that precluded meta-analysis. These included between-group differences at baseline, between-study differences in symptoms measured, symptom measurement tools used, and difference in protocols for biofeedback including the type of biofeedback, the number, frequency, and duration of sessions, and patient education (e.g., diet, normal bowel function, lifestyle advice). In addition, the review noted that many of the included RCTs were likely to be underpowered to detect between-group differences. The authors concluded that there is insufficient evidence to allow conclusions on the efficacy and safety of biofeedback for chronic constipation.

This Cochrane SR also reviewed four prior SRs[75-78] of RCTs that included systematic literature searches. The review reported methodological limitations in all four of these SRs including incomplete reporting of review methods, limited or non-comprehensive literature search strategies, failure to exclude non-SRs, and meta-analyses of heterogeneous studies. These reviews all reported generally poor quality evidence and the need for further research.

A 2013 SR by Vonthein et al. identified 13 RCTS on biofeedback, electrical stimulation, or the combination for treatment of fecal incontinence.[79] Ten RCTs included comparisons of biofeedback and an alternative treatment; some of the biofeedback interventions also involved other components such as sensory training and pelvic floor exercises. A meta-analysis of studies comparing biofeedback to a control intervention significantly favored biofeedback (relative risk, 2.12; 95% CI, 1.42 to 3.16). This study did not attempt to isolate the effect of biofeedback in multicomponent interventions that included pelvic floor exercise or other treatments.

In 2012, an updated Cochrane SR of randomized and quasi-randomized trials for biofeedback and/or sphincter exercises for the treatment of fecal incontinence in adults was published.[80] Almost half of the 21 trials were considered low risk for bias. Due to the variety of different treatment combinations, treatment delivery techniques, and outcome measures, comparison between studies was difficult. In addition, most studies reported immediate post-treatment outcomes with follow-up of only a few weeks. The authors reached the following conclusions:

- Biofeedback or electrical stimulation “may offer an advantage over exercises alone” in patients who have failed conservative management (e.g., diet changes, medications).
- Biofeedback following surgical sphincter repair does not improve health outcomes.
- The evidence does not permit conclusions about best practices in the clinical setting, including but not limited to the technique for biofeedback delivery and which patients are suitable for and most likely to benefit from biofeedback.

- Biofeedback is unlikely to cause harm as no study has reported any adverse events or worsening of symptoms.
- There is a need for large, long-term, well-designed RCTs that use validated outcome measures to compare outcomes of biofeedback with other treatments.

Randomized Controlled Trials

One new RCT was published after the above SRs. Damon randomized 157 patients with fecal incontinence to either a treatment group (n=77) receiving perineal retraining including biofeedback and standard conservative treatment, or a control group (n=80) receiving standard conservative treatment.[81] This RCT reported only short-term outcomes, with a follow-up of four months. The perineal retraining group had a significantly higher success rate than the control group for daily stool frequency, leakage, and urgency (57% versus 37%, respectively; $p<0.021$). However, there was no significant difference in quality of life scores between the two groups.

FECAL INCONTINENCE IN CHILDREN

Systematic Reviews

A 2011 updated Cochrane SR[82] combined the results of nine trials that compared conventional treatment (i.e., laxatives, toilet training, and dietary advice) with versus without biofeedback in children with fecal incontinence.[83-91] The majority of the trials included fewer than 50 participants. Pooling of data was difficult due to the variety of outcome measures; the only outcome reported by all nine trials was the number of children not cured or improved. Combined results of nine trials showed higher rather than lower rates of persisting symptoms of fecal incontinence up to 12 months when biofeedback was added to conventional treatment. In addition, any short-term benefit from biofeedback training did not correspond with later treatment success. The authors concluded that there is no evidence that biofeedback training added any benefit to conventional treatment in the management of functional fecal incontinence in children.

These results confirm the conclusions of prior versions of this Cochrane SR and other SRs.[92-94]

Randomized Controlled Trials

Since the above SRs, one additional randomized trial was published in which the authors reported that the results at six-months follow-up did not differ between biofeedback and customary care.[83]

CONSTIPATION IN ADULTS

Systematic Review

For the treatment of constipation, a SR of 11 RCTs found a benefit of biofeedback as a treatment of constipation in adults.[75] Conclusions of the SR were limited by variability in patient populations, comparison treatments, and outcomes measures. However, detailed examination of several well-conducted RCTs focusing on patients with dyssynergia-type constipation suggested benefits in a sub-group of patients who met criteria similar to trial participants.[58, 59, 72] Studies for other types of constipation were limited to poorly-designed

RCTs and case series. These unreliable studies do not permit conclusions on the effect of biofeedback on other types of constipation in adults.

Randomized Controlled Trials

Hart (2012) published an RCT that studied anorectal biofeedback (AB) for constipation. Twenty-one patients with pelvic floor dyssynergia were randomized into two groups.[59] One group learned to isolate the anal sphincter using an electromyography probe and the other learned to relax trapezius or temporalis muscles with EMG feedback. The authors concluded that although the sample size was statistically underpowered, AB produced clinical improvements in the severity of constipation. The authors also noted there were several study limitations, including patient selection and long-term follow-up; thus, the evaluation of long-term effects on health outcomes needs to be determined in future studies.

CONSTIPATION IN CHILDREN

Systematic Reviews

A systematic review conducted by Wegh (2021) assessed the effectiveness of nonpharmacological interventions for functional constipation in children.[95] Studies included in the review were RCTs that enrolled children aged 0 to 18 years with functional constipation as defined by Rome III or IV criteria and reported defecation outcomes and/or QOL outcomes. The review included three RCTs comparing biofeedback alone with biofeedback in conjunction with laxative use. The trials were all assessed as having a high risk of bias. Meta-analysis found no difference between groups in study-defined treatment success (risk difference, 0.23; 95% CI, -0.08 to 0.54) and heterogeneity was high (I^2=86%). Other clinical outcomes and harms of treatment were not reported.

Randomized Controlled Trials

A RCT conducted by Van Ginkel (2001) evaluated biofeedback in the treatment of constipation in children.[96] Groups included standard treatment i.e., education, laxatives (n=111) or standard treatment plus two sessions of anorectal manometry (n=91). Manometry measurements were viewed by the child and parent during measurement sessions and the data discussed after each session with instructions in home exercises. At six weeks follow-up, there was no significant different in success between the standard treatment group (4%) and the biofeedback group (7%). At the final 104 week follow-up, 43%of the standard treatment group and 35% of the biofeedback group were considered treatment successes. This difference was not significant. The authors noted that 30% of the randomized patients were missing at the final follow-up.

Section Summary

The current evidence from several well-designed, well-conducted RCTs is sufficient to determine that biofeedback as a treatment of dyssynergia-type constipation may be beneficial in adult patients who meet the policy criteria.

The evidence base is insufficient to draw conclusions or demonstrate a significant health benefit as a result of biofeedback treatments for the treatment of incontinence or constipation other than dyssynergia-type constipation in adults. The evidence is limited to data from studies with significant methodological limitations including inadequate randomization, lack of a

placebo control group, heterogeneity between patient groups and between study protocols, and short-term follow-up periods.

HEADACHE

TENSION AND MIGRAINE HEADACHE

Systematic Reviews

Sullivan (2016) published a SR to evaluate the outcomes of psychological interventions, one of which was biofeedback for migraines.[97] Twenty-four studies were reviewed. The authors noted there were methodological limitations from the study review and that biofeedback was not superior to relaxation training or cognitive behavioral therapy.

A number of other SRs, including two Cochrane SRs, have reported small beneficial effects in children and medium to large beneficial effects in adults when biofeedback is used in conjunction with other prevention measures such as relaxation techniques.[15, 98-104]

Randomized Controlled Trials

Despite the poor quality of case series and RCTs, biofeedback has evolved into a standard of care as part of comprehensive regimens, including medication and relaxation techniques, for treatment and prevention of tension-type headaches, and the prevention of migraine headaches.

Data from case series and RCTs is difficult to interpret due to poor study design, high drop-out rates, and inconsistent outcomes.[105-110]

OTHER HEADACHE

The evidence is insufficient to determine the effect of biofeedback for the prevention or treatment of headaches other than migraine and tension headaches, including but not limited to cluster headaches.

SECTION SUMMARY

Despite the poor quality of studies, biofeedback has evolved into a standard of care as part of comprehensive regimens, including medication and relaxation techniques, for treatment and prevention of tension-type headaches and the prevention of migraine headaches.

There is not enough research to show that biofeedback improves outcomes in patients with headaches other than migraine and tension headaches.

HYPERTENSION

SYSTEMATIC REVIEWS

Nagele (2014) published a SR with meta-analysis on stress-reduction techniques in adults with essential hypertension.[111] The review included SRs and RCTs with a no-treatment control group and at least 24 weeks follow-up that were published through September 2012. Outcomes of interest were mortality, cardiovascular morbidity/mortality, end-stage renal disease, health related quality of life, adverse events, change in blood pressure, and changes in antihypertensive medication. Biofeedback was one of a number of the stress-reduction

techniques included in the review. The review found that data were not reported for most of the patient-relevant outcomes. No benefit was found for use of antihypertensives. Some beneficial effect was found for lowering blood pressure; however, studies were limited by methodological limitations such as heterogeneity between studies, short-term follow-up. The authors concluded that a beneficial effect of stress-reduction techniques on hypertension remains unproven.

In a 2010 SR, Greenhalgh concluded, "…we found no convincing evidence that consistently demonstrates the effectiveness of the use of any particular biofeedback treatment in the control of essential hypertension when compared with pharmacotherapy, placebo, no intervention or other behavioral therapies."[112] Trials generally had small sample sizes; only four included more than 100 patients. Trials included a variety of biofeedback techniques, and some included more than one modality. Results were not pooled due to differences in interventions and outcomes and the generally poor quality of the studies. Only one trial was identified that compared a biofeedback combination intervention to sham biofeedback, and this study did not find a significant difference in the efficacy of the two interventions. Only four studies on biofeedback alone and four on a combined biofeedback intervention reported data beyond six months; most of these found no significant differences in efficacy between the biofeedback and control groups.

Rainforth reviewed RCTs and all previous meta-analyses related to stress reduction programs including biofeedback.[113] Each type of therapy was analyzed separately. No significant reduction in blood pressure was achieved using biofeedback alone or biofeedback combined with relaxation training.

RANDOMIZED CONTROLLED TRIALS

Wang (2016) published an RCT evaluating the effect of direct blood pressure biofeedback on patients with prehypertension or stage I hypertension.[114] A trained nurse instructed patients in blood pressure self-regulation by using slow diaphragmatic breathing and passive attitude. During the eight-week training (one session per week), patients in the treatment group received real-time blood pressure feedback signals (n=29) and controls received pseudo-feedback signals (n=28). Outcomes were systolic and diastolic blood pressure, measured at baseline and one and eight weeks after training. Both groups significantly decreased blood pressure following training. The decreases were equal in magnitude, suggesting that blood pressure self-regulation training can effectively lower blood pressure, regardless of the type of feedback signal.

Landman (2013) conducted a randomized, double-blind, sham-controlled trial comparing the effects on blood pressure of lowering breathing frequency in patients with type two diabetes and hypertension using active (n=21) and sham (n=24) biofeedback.[115] The changes in systolic blood pressure from baseline favored the control group while differences in diastolic blood pressure favored the intervention group. However, these differences from baseline, and the differences between the two groups were not statistically significant.

SECTION SUMMARY

Although there are RCTs evaluating biofeedback for treating hypertension, evidence is insufficient due to the shortage of studies isolating the effect of biofeedback, the generally poor quality of the trials, and the variability among interventions.

INSOMNIA

SYSTEMATIC REVIEWS

No SRs were identified using biofeedback for the treatment of insomnia.

RANDOMIZED CONTROLLED TRIALS

No RCTs were identified using biofeedback for the treatment of insomnia.

MOTOR FUNCTION AFTER STROKE, INJURY, OR LOWER LIMB SURGERY

SYSTEMATIC REVIEWS

Several SRs have been published; none of these conducted quantitative pooling of results due to heterogeneity among study populations, interventions, and outcome measures.

Knee Injury

A 2010 SR by Silkman evaluated the effectiveness of electromyography (EMG) biofeedback for improving muscle function during knee rehabilitation after injury.[116] Four RCTs that compared knee rehabilitation exercise programs with and without biofeedback were identified. Sample sizes in individual studies ranged from 26 to 60 patients. Two of the four studies found a statistically significantly greater benefit in the programs that included biofeedback, and the other two did not find a significant difference between groups. The positive studies assessed intermediate outcomes e.g., contraction values of the quadriceps muscles. None of the studies were designed to assess functional outcomes.

Post-Stroke Motor Function

Stanton (2017) updated a SR published in 2011 which evaluated the effect of biofeedback on lower-limb activities in patients who have had a stroke.[117] Only high-quality RCTs or quasi-RCTs with Physiotherapy Evidence Database (PEDro) scores greater than four were included. The literature search, conducted through September 2015, identified 18 trials (total N=429 patients) for inclusion. Training activities were walking (nine trials), standing (eight trials), and standing up (one trial). Trials were small, with study populations ranging from 12 to 50 patients. Biofeedback techniques included weight distribution from a force platform or sensor (11 trials), muscle activity from EMG (three trials), linear gait parameters (three trials), and joint angle from a goniometer (one trial). Visual feedback was used in seven trials, auditory in seven trials, and a combination of visual/auditory in four trials. Pooled standardized mean difference of the short-term effect of biofeedback from 17 trials (n=417) was significant (0.50; 95% confidence interval [CI], 0.3 to 0.7). Long-term effects could not be calculated because only four trials provided that information.

Stanton (2011) conducted a SR with meta-analysis of RCTs evaluating biofeedback to improve activities involving lower limb function after stroke.[118] A total of 22 trials with 591 participants met inclusion criteria. All of the trials had relatively small sample sizes; the largest trial had 54 participants and 15 trials had 30 or fewer participants. The majority of trials (n=17) compared biofeedback plus usual therapy to usual therapy alone. The specific interventions varied; the types of biofeedback included biofeedback of ground reaction force from a force platform with visual and/or auditory feedback (13 trials), muscle activity via visual and/or auditory feedback (five trials), joint position from an electrogoniometer via visual and/or auditory feedback (three

trials), and limb position via auditory feedback one trial). The duration of interventions ranged from two to eight weeks, and intensity ranged between one to five days per week.

A pooled analysis of data from 17 trials on short-term effect (i.e. one month or less) found that biofeedback significantly improved lower limb activities compared to usual care or placebo (standardized mean difference [SMD]: 0.41; 95% CI: 0.21 to 0.62). Outcomes included activities such as directional control during standing, weight distribution between the lower limbs, and gait parameters such as stride length. There was heterogeneity among studies. Trials did not report functional outcomes such as ability to perform activities of daily living (ADL). A sensitivity analysis determined that the heterogeneity was best explained by study quality. When lower quality trials were excluded, biofeedback was still found to improve lower limb activity compared to control conditions (SMD: 0.49, 95% CI: 0.22 to 0.75). A sub-group analysis was also done by type of activity. There was only one high-quality trial on standing up (n=40). A pooled analysis of five high-quality trials on short-term effect found that biofeedback significantly improved standing outcomes compared to control (SMD: 0.42, 95% CI: 0.05 to 0.78). A pooled analysis of four short-term trials on walking also found better outcomes with biofeedback compared to control (SMD: 0.57, 95% CI: 0.10 to 1.03). Five high-quality trials with a total sample size of 136 contributed data to an analysis of long-term term efficacy i.e., one-five months after cessation of the intervention. In this pooled analysis, biofeedback was found to improve outcomes compared to control (SMD: 0.41, 95% CI: 0.06 to 0.75).

A Cochrane SR that assessed EMG biofeedback for the recovery of motor function after stroke was published in 2007.[119] It included 13 randomized or quasi-randomized studies with a total of 269 patients. All of the trials compared EMG biofeedback plus standard physiotherapy to standard physiotherapy; in addition to standard physiotherapy, several studies also included a sham biofeedback group. The studies tended to be small and poorly designed. The authors did not find support for EMG biofeedback to improve motor power, functional recovery, or gait quality when compared to physiotherapy alone.

A 2010 SR by Zijlstra searched for studies evaluating biofeedback-based training to improve mobility and balance in adults older than 60 years of age.[120] Although the review was not limited to studies on motor function after stroke, more than half of the studies included older adults post-stroke. For inclusion in this review, studies needed to include a control group of patients who did not receive biofeedback and to assess at least one objective outcome measure. A total of 97 potentially relevant articles were identified, and 21 (22%) studies, including 17 RCTs, met the selection criteria. Twelve of the 21 (57%) studies included individuals post-stroke; three included older adults who had lower-limb surgery and six included frail older adults without a specific medical condition. Individual studies were small with sample sizes that ranged from five to thirty patients. The added benefit of using biofeedback could be evaluated in 13 of 21 (62%) studies. Nine of the 13 studies found a significantly greater benefit with interventions that used biofeedback compared to control interventions. However, the outcomes assessed were generally not clinical outcomes but were laboratory-based measures related to executing a task, e.g., moving from sitting to standing in a laboratory setting and platform-based measures of postural sway. The applicability of improvements in these types of measures to clinical outcomes such as the ability to perform activities of daily living or the rate of falls is unknown. Only one study cited in this review reported an improvement in fall rates, and this trial could not isolate the effect of biofeedback from other components of treatment. In addition, only three studies reported long-term outcomes, and none of these reported a significant effect of biofeedback. Conclusions about the efficacy of biofeedback for improving mobility and balance in older adults cannot be drawn

from these data due to the lack of evidence on clinical outcomes. Other methodologic limitations included limited data on the durability of effects and the inability to isolate the effect of biofeedback in many studies.

RANDOMIZED CONTROLLED TRIALS

Kim (2017) published a RCT on the effect of EMG on upper-extremity functions in patients who have had a stroke.[121] Patients were randomized to traditional rehabilitation therapy (n=15) or traditional rehabilitation therapy plus EMG biofeedback training (n=15). Upper-limb function was measured by Fugl-Meyer Assessment (FMA) and Manual Function Test (MFT), and activities of daily living were measured using the FIM instrument. Both FMA and MFT scores improved significantly more in the patients receiving EMG biofeedback. However, there was not a significant difference in functional independence measurement (FIM) score improvement between groups.

Yang (2016) published a limited in size RCT on the effect of biofeedback weight-bearing training on the ability to sit/stand/sit and on stability among patients who have had a stroke.[122] Patients were randomized to biofeedback weight-bearing training (n=15) or functional weight-bearing training (n=15). Outcomes were time to sit/stand/sit and stability (measured by BioRescue, which detects an area of center of pressure). Comparison statistics were calculated for pre- and post training results, and between treatment groups. Both outcomes significantly improved in the biofeedback group but not in the control group.

Ghomashchi (2016) published a RCT evaluating the effect of visual biofeedback on postural balance disorders in patients who have had a stroke.[123] Patients received conventional physical therapy and balance training exercises. During balance training, 16 patients were randomized to visual biofeedback and 15 patients to no visual information. Outcomes were the center of pressure and approximate entropy. Both groups experienced improvements in postural control, with no significant differences between rehabilitation methods.

In a small RCT published after the above SR, Barcala randomized 20 adults with hemiplegia following stroke to balance training with visual biofeedback or to conventional physical therapy alone.[124] Patients received interventions twice a week for five weeks. Both groups demonstrated significant improvement, but no statistically significant differences were found between the two groups.

SECTION SUMMARY

The evidence on biofeedback for improving motor function after stroke is limited by small studies, most of which are methodologically limited. There is variability in the type, duration, and intensity of interventions. Conclusions about the efficacy of biofeedback for improving mobility and balance in older adults cannot be drawn from the current evidence base.

MOVEMENT DISORDERS

SYSTEMATIC REVIEWS

A Cochrane SR assessing EMG biofeedback for the recovery of motor function after stroke included thirteen randomized or quasi-randomized studies.[119] The authors reported that EMG biofeedback did not improve motor power, functional recovery, or gait quality when compared to physiotherapy alone, although the results were limited due to small, poorly designed trials. Use of different assessment scales made pooling data for meta-analysis impossible.

RANDOMIZED CONTROLLED TRIALS

No RCTs identified after the above SR.

SECTION SUMMARY

The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of movement disorders.

MULTIPLE SCLEROSIS

SYSTEMIC REVIEWS

No SRs were identified for biofeedback for the treatment of multiple sclerosis.

RANDOMIZED CONTROLLED TRIAL

van der Logt (2016) published a crossover study that evaluated the effect of vibrotactile biofeedback for trunk sway on balance control in patients with multiple sclerosis.[125] Ten patients performed a series of stance and gait tasks while trunk sway was measured using a SwayStar device attached to the waist. Patients underwent the series of tasks with and without an add-on to the SwayStar device, which provided patients with direction-specific vibrotactile feedback during the tasks. When patients performed the tasks with vibrotactile biofeedback, there was a general reduction in trunk sway, though not all the reductions differed significantly with trunk sway when performing the tasks without vibrotactile biofeedback. Studies with larger sample sizes are needed.

A 2015, MacKay published results from an (RCT) that evaluated the addition of biofeedback to standard care in 40 patients with relapsing-remitting multiple sclerosis patients to help improve emotional symptoms, coping, and fatigue in patients with multiple sclerosis.[126] The standard care psychosocial intervention consisted of relaxation, mindfulness, social support, and education. All patients attended a one-hour training and assessment sessions at weekly intervals. During the first session, all patients had training in mindfulness breathing exercises and progressive muscle relaxation techniques. Patients randomized to the biofeedback arm received additional instruction on use of biofeedback equipment for self-regulation. Following the 3 weekly sessions, patients were instructed to practice the exercises at home, with or without use of biofeedback equipment. Outcomes included breathing rate and anxiety, depression, fatigue, and muscle tension measures. At the end of treatment, there were not statistically significant differences between groups in any outcomes. However, some variables were marginally significant. The difference between the intervention and control group in breathing rate was 3.06 (95% CI, -0.17 to 6.280; p=0.06) and the difference in muscle tension was -13.91 (95% CI, -30.06 to 2.25; p=0.09). This study is limited by the small sample size, and other methodological constraints that make it hard to determine the efficacy of biofeedback for anxiety, fatigue, and stress in patients with multiple sclerosis.

SECTION SUMMARY

There is not enough research to show that biofeedback improves health outcomes for the treatment of multiple sclerosis. Additional well-designed, comparative studies are needed.

ORTHOSTATIC HYPOTENSION IN PATIENTS WITH A SPINAL CORD INJURY

SYSTEMATIC REVIEW

Gillis conducted a SR to identify and describe the body of literature pertaining to nonpharmacologic management of orthostatic hypotension during the early rehabilitation of persons with a spinal cord injury.[127] Participants with any level or degree of completeness of spinal cord injury and any time elapsed since their injuries were included. Interventions must have measured at least systolic blood pressure and have induced orthostatic stress in a controlled manner and have attempted to control orthostatic hypotension during an orthostatic challenge. Four distinct nonpharmacologic interventions for orthostatic hypotension were identified: application of compression and pressure to the abdominal region and/or legs, upper body exercise, functional electrical stimulation applied to the legs, and biofeedback. Methodologic quality varied dramatically between studies. The authors concluded that "…The clinical usefulness of compression/pressure, upper body exercise and biofeedback for treating OH [orthostatic hypotension] has not been proven."

RANDOMIZED CONTROLLED TRIALS

No RCTs identified after the above SR.

SECTION SUMMARY

There is insufficient evidence from high-quality comparative studies to permit conclusions about the impact of biofeedback on orthostatic hypotension in patients with a spinal cord injury.

PRETERM BIRTH PREVENTION

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback used to prevent preterm birth.

RANDOMIZED CONTROLLED TRIALS

In 2014, Siepmann published data on 48 women who had experienced threatened preterm labor between the 24th and 32nd gestational week.[128] Twenty-four patients received six biofeedback sessions over two weeks, and the other 24 patients were in a usual care group. Preterm delivery occurred in three patients (13%) in the biofeedback group and eight patients (33%) in the control group; the difference between groups was not statistically significant ($p>0.05$). Other gestational outcome data, such as the gestational duration and birthweight, also did not differ significantly between groups.

SECTION SUMMARY

There is insufficient evidence that biofeedback is effective in preventing preterm birth in pregnant women with a history of threatened preterm labor.

RAYNAUD'S PHENOMENON

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback for Raynaud's phenomenon.

RANDOMIZED CONTROLLED TRIALS

The Raynaud's Treatment Study Investigators conducted a randomized comparison of sustained-release nifedipine and thermal biofeedback in 313 patients with primary Raynaud's phenomenon.[129] In addition to these two treatment groups, there were two control treatments: pill placebo and EMG biofeedback. EMG biofeedback was chosen as a control because it did not address the physiological mechanism of Raynaud's phenomenon. Nifedipine significantly reduced Raynaud's attacks compared with placebo pill ($p<0.001$), but thermal biofeedback did not differ from EMG biofeedback ($p=0.37$). Better outcome for nifedipine relative to thermal biofeedback was nearly significant ($p=0.08$). With a larger sample size, the rate of 56% fewer attacks with nifedipine relative to thermal biofeedback would likely have been statistically significant. Thus, it cannot be concluded that thermal biofeedback is as effective as this form of medical therapy.

A 2009 SR identified five RCTs that reported a variety of outcomes. A pooled analysis from four RCTs (total n=110) on the change in frequency of attacks favored the sham control group over the biofeedback group.[130]

SECTION SUMMARY

There is insufficient evidence from a small number of RCTs that biofeedback is effective as a treatment of Raynaud's disease. A meta-analysis of the available RCTs did not find that biofeedback was more effective than the control intervention.

STRESS REDUCTION

SYSTEMIC REVIEWS

No SRs were identified for biofeedback for stress reduction.

RANDOMIZED CONTROLLED TRIALS

A 2015 Van der Zwan published an RCT comparing the efficacy of self-help physical activity (PA), mindfulness meditation (MM), and heart rate variability biofeedback (HRV-BF) in reducing stress and its related symptoms.[131] This study, which was limited in size and objective outcomes indicated that all interventions were equally effective in reducing stress and its related symptoms. The current evidence base is insufficient to permit conclusions on the impact of biofeedback on stress reduction.

SECTION SUMMARY

There is not enough research to show that biofeedback improves health outcomes for stress reduction. Additional well-designed, comparative studies are needed.

TINNITUS

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback for tinnitus.

RANDOMIZED CONTROLLED TRIALS

Weise investigated the efficacy of a biofeedback-based cognitive-behavioral treatment for tinnitus in Germany. Tinnitus patients (n=130) were randomly assigned to an intervention or a wait-list control group.[132] Treatment consisted of 12 sessions of a biofeedback-based

behavioral intervention over a three-month period. The primary outcome measures were global tinnitus annoyance and a daily rating of tinnitus disturbance measured by a Tinnitus Questionnaire (TQ) and a daily diary using visual analog scale (VAS) scores. Patients in the wait-list group participated in the treatment after the intervention group had completed the treatment. Results showed improvements regarding the following: tinnitus annoyance; diary ratings of loudness; feelings of controllability; changes in coping cognitions; changes in depressive symptoms; TQ: total score (range 0–84) pre-assessment mean 54.7, post-assessment mean 32.52; TQ: emotional distress (range 0–24) pre-assessment mean 16.00, post-assessment mean 8.15; and diary: loudness VAS (range 0–10) pre-assessment mean 5.68, post-assessment mean 4.38. Improvements were maintained over a six-month follow-up period in which variable effect sizes were observed. The study did not investigate the possible additive effect of biofeedback with cognitive-behavioral therapy and did not include an active treatment control group.

SECTION SUMMARY

The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of tinnitus.

URINARY DISORDERS

POST-PROSTATECTOMY URINARY INCONTINENCE

Systematic Reviews

Hsu (2016) published a SR evaluating pelvic floor muscle training (PFMT) with biofeedback in men who had radical prostatectomy.[133] Thirteen trials met reviewers' inclusion criteria. However, on closer inspection, not all trials included a biofeedback intervention, and other trials did not compare PFMT alone to PFMT plus biofeedback. Thus, conclusions about the added efficacy of biofeedback cannot be determined from the results of this SR.

In 2015 a Cochrane SR was conducted by Anderson to determine the effectiveness of conservative management interventions for urinary incontinence in men after a prostatectomy, which updated the 2012 review by Campbell et all.[134, 135] Conservative therapies include pelvic floor muscle training with or without feedback, electrical stimulation, extra-corporeal magnetic innervation, compression devices, lifestyle changes, or a combination of methods. Fifty randomized and quasi-Rs were included in the review; however, just eight of these trials examined biofeedback compared to pelvic floor muscle training. Per the rating of moderate quality studies, the authors found no evidence that pelvic floor muscle training with or without biofeedback was better than control for men who had urinary incontinence up to 12 months after radical prostatectomy.

A SR of PMFT to improve post-prostatectomy urinary incontinence identified three studies (281 men) that focused on the incremental value of biofeedback over written/verbal PME.[136] Although PPMFT appeared to reduce the time to recover continence compared to no training, there was no evidence for an advantage of training with biofeedback over written/verbal instructions. None of the individual trials found a statistically significant difference in outcomes between groups.

A 2003 randomized trial by Wille randomized 139 men prior to radical prostatectomy to one of three groups.[137] Group one received verbal and written instructions about PFMT from a

physical therapist. Group two received PFMT instruction and instruction on using an electrical stimulation device. Group three received the previous two intervention components and training on using biofeedback with the electrical stimulation device. Patients had regular contact with a health care provider for the first five weeks after surgery. In the immediate postsurgical period, 20.5% in group one, 22.9% in group two, and 20.7% in group three were continent (p=0.815). After six and 12 months, continence rates remained similar among the groups. Twelve-month continence rates were 88% in group one, 81% in group two, and 88.6% in group three (p=0.524).

Bales (2000) randomized 100 men scheduled to undergo radical prostatectomy to PFMT plus biofeedback intervention (n=50) or to a control group (n=50) that received written and brief verbal instructions performing PFMT [138] The intervention consisted of a single session with a trained nurse two to four weeks before surgery. Three men dropped out of the PFMT plus intervention group. At six months after surgery, the incidence of urinary incontinence was 94% (44/47) in the PFMT plus biofeedback group and 96% (948/40) in the control group. The difference between groups was not statistically significant.

Randomized Controlled Trials

Oh (2020) randomized 84 patients undergoing robot-assisted laparoscopic radical prostatectomy to receive biofeedback with an extracorporeal perineometer plus PFMT or PFMT alone.[139] Although the average urine loss volume was lower in the biofeedback plus PFMT group compared to PFMT alone at month 1 after catheter removal (p=0.028), there was no difference between groups at months 2 or 3 after catheter removal. At study end (month 3), the percentage of continent patients was not significantly different between the biofeedback plus PFMT group (67.5%) and PFMT alone (61.9%).

A 2013 trial by Dijkstra-Eshuis compared the impact of preoperative pelvic floor muscle training (PFMT) with biofeedback (n=65) to standard care (n=56) on postoperative SUI in men undergoing laparoscopic radical prostatectomy.[140] Patients in the intervention group received four weekly sessions of biofeedback-assisted muscle training before surgery. Patients assigned to the control group did not have a presurgical intervention. The primary outcome was the rate of continence one year after surgery. Among the 74 patients available for follow-up analysis, 66% in the intervention group and 80% in the control group were continent at one year. The investigators originally planned to enroll 248 patients. However, an interim analysis after 122 patients were enrolled showed no significant benefit for the intervention group, even if the trial was completed as planned and therefore the trial was halted prematurely.

In 2012, Tienforti compared biofeedback (a session before and after surgery) in combination with written/verbal instructions on performing pelvic floor muscle exercises to a control intervention of written/verbal instructions alone.[141] The study included 34 patients, 32 of whom (16 in each group) were available for the final 6-month analysis. By six months, 10 of 16 patients (62.5%) in the treatment group and one of sixteen patients (6.3%) in the control group had achieved continence; this difference was statistically significant (p value not reported). The mean number of incontinence episodes per week was also significantly lower in the intervention group (2.7) than the control group (13.1) at six months.

STRESS, URGE OR MIXED URINARY INCONTINENCE

Systematic Reviews

Zhu (2022) performed a meta-analysis of 17 RCTs in postpartum women with lower urinary tract symptoms.[142] Fifteen studies (n=1965) compared PMFT plus biofeedback and electrical stimulation with PMFT alone. The analysis reported a significantly greater likelihood of achieving a therapeutic effect with combined PFMT plus biofeedback and electrical stimulation versus PMFT alone (risk ratio, 1.20; 95% confidence interval [CI], 1.15 to 1.24; I^2=0%). Pelvic floor muscle strength was also significantly higher with combination therapy (p<0.0001), but there was high heterogeneity among studies for this outcome (I^2=66%). Limitations of this analysis include risk of bias, lack of blinding, and heterogeneity in the definition of therapeutic effect.

Wu (2021) conducted a meta-analysis (N=21 studies; 13 RCTs, 8 nonrandomized) of PMFT with biofeedback versus PMFT alone in women with stress incontinence or pelvic floor dysfunction.[143] Most studies were conducted in China and none were from the U.S. There was a significant benefit of PMFT with biofeedback compared to PMFT alone in patients with both urinary incontinence (odds ratio, 4.82; 95% CI, 2.21 to 10.51; I^2=85.3%; n=11 studies) and pelvic floor dysfunction (odds ratio, 2.81; 95% CI, 2.04 to 3.86; I^2=13.1%; n=6 studies). Analyses of quality of life and quality of sexual life results were limited by substantial heterogeneity (>80%). Limitations of this analysis include an unclear, moderate, or high risk of bias in all studies and use of Kegel exercises only in some studies rather than a complete PMFT program.

An updated Agency for Healthcare Research and Quality (AHRQ) SR and comparative effectiveness report of nonsurgical treatments for urinary incontinence in women was published by Blak (2018).[144] Biofeedback was considered among nonpharmacological behavioral therapy approaches. The report evaluated 42 studies that compared 19 active nonpharmacological interventions (including combinations of nonpharmacological interventions) with each other. One study reported statistically significant improvements in the daily activities domain with PFMT and biofeedback compared with PFMT alone, and one study reported significant improvements in distress for bladder training combined with PFMT and biofeedback when compared to bladder training, however, nine studies either reported discordant or nonsignificant differences across all other domains for this comparison. No adverse events were reported for any of the studies evaluating biofeedback. The report concludes that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- and second-line interventions alone for both stress and urgency UI.

A SR by Mateus-Vasconcelos (2018) assessed various physiotherapy methods to strengthen the pelvic floor muscles for women with stress urinary incontinence.[145] Their review included six studies which were RCTs, quasi-experimental trials, and systematic reviews. One study (an uncontrolled RCT) included biofeedback as a comparator; the effectiveness of pelvic floor muscle training (PFMT) with biofeedback (group n=6) to PFMT with palpation (group n=5) was evaluated. The exercises for the biofeedback group consisted of achieving the same number of rapid and slow contractions of the same duration as that achieved during the PERFECT scheme (8 series). The palpation group strengthened the pelvic floor muscles while a physiotherapist performed palpations on the central perineal tendon and vagina (4 sessions). At the end of treatment, there was no statistical difference in improvement between the biofeedback group and the palpation group in power, endurance, or rapidity of contractions. This RCT was limited in its small sample size and lack of control group and masking of assessors.

Oliveira (2017) published a SR that evaluated the protocols and/or PFMT parameters for women with stress urinary incontinence.[146] Seven studies were included, two of which involved biofeedback. The authors concluded that strengthening exercises for pelvic floor training combined with biofeedback was the most effective training protocol, but because of the limited studies and heterogeneity of the intervention protocols they could not identify what the most effective training protocol would be.

Moroni (2016) published a SR of 37 RCTs on conservative treatment of stress urinary incontinence in women.[147] Five trials (N=250) were identified that compared PFMT plus biofeedback with biofeedback alone. A pooled analysis of four studies found significantly more urine loss as measured by a posttreatment pad test with PFMT alone than with PFMT plus biofeedback (mean difference [MD], 0.90; 95% confidence interval [CI], 0.71 to 1.10). Reviewers noted that the difference between groups was likely not clinically significant because there was only about a one-gram difference. Moreover, the finding was largely due to the effect of one study. Results on other outcomes (eg, quality of life, number of incontinence episodes) could not be pooled due to imprecision of the estimates.

A 2011 Cochrane SR evaluated feedback or biofeedback in conjunction with pelvic floor muscle training (PFMT) for treating urinary incontinence (UI) in women.[148] The review included RCTs in women with stress, urge or mixed UI in which at least two arms of the study included exercise training and at least one arm included feedback and/or biofeedback. Feedback was defined as verbal feedback by a clinician, whereas biofeedback involved use of an instrument or device. After examining 36 full-text articles, 24 trials were found to meet the review's inclusion criteria and 17 contributed data to the analysis of at least one primary outcome measure. Sixteen of the 24 trials included a comparison of PFMT plus biofeedback to PFMT alone; nine of these included the same PFMT programs in both groups. The primary outcomes of the review were quality of life and improvement or cure. Nine trials used one of several validated quality-of-life instruments; however, only four of these reported data in a form that could be used for meta-analysis. Thus, quality-of-life results were not pooled. Data were pooled for the other primary outcome, improvement or cure, but there were a sufficient number of studies only for the comparison between PFMT with and without biofeedback. In a pooled analysis of seven studies, there was a significant reduction in the proportion of women reporting 'no improvement or cure' when biofeedback was added to muscle exercise (risk ratio [RR]: 0.75, confidence interval [CI]: 0.66 to 0.86). The authors noted that there may have been other differences between groups, such as more frequent contact with a healthcare professional or a greater number of treatment sessions, which might partially explain the difference in the improvement or cure rate in women who did or did not receive biofeedback. Moreover, when only the outcome 'no cure' was examined, there was not a significant difference between groups that did and did not receive biofeedback (5 studies: RR: 0.92, 95% CI: 0.81-1.05). Among secondary outcomes, a pooled analysis of seven trials did not find a significant difference in leakage episodes in a 24-hour period after treatment (mean difference: -0.01, 95% CI: -0.21 to 0.01). For the outcomes frequency and nocturia, data could not be combined but the review authors reported that the pattern was one of no difference between groups.

A number of significant design flaws in the 24 trials that met inclusion criteria (N=1583 women) limit the reliability of the reported outcomes. These flaws included:

- It was common for the women in the biofeedback arm to have more contact with healthcare professionals than those who did not receive biofeedback;

- Many of the trials were at moderate to high risk of bias; and
- There was significant variation in the regimens proposed for feedback and biofeedback, and the intervention's purpose and composition were often unclear.

The authors concluded that feedback or biofeedback may provide additional benefit to pelvic floor muscle exercises (PME) alone; however, further research is needed to differentiate whether the beneficial effect was due to feedback, biofeedback, or some other difference between the trial arms.

Randomized Controlled Trials

Hagen (2020) conducted a multicenter RCT in 600 women with stress or mixed urinary incontinence. Participants were randomized to 16 weeks of PMFT with electromyographic biofeedback or PMFT alone. Both groups received supervised PMFT during clinic appointments and a home PMFT regimen. The mean number of appointments attended was about four in both groups. Urinary incontinence symptoms (self-reported at month 24 via the International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form [ICIQ-UI-SF]) were similar in both groups (mean difference, -0.09; 95% CI, -0.92 to 0.75; p=.84). ICIQ-UI-SF scores were also similar between groups at earlier times (6 and 12 months). At 24 months, the proportion of patients who achieved the study's definition of cure, improvement, and symptoms that were very much better or much better was similar between groups. Pelvic floor muscle strength and endurance was assessed at 6 months, with similar findings in both groups. A limitation of this study is the short duration of the intervention compared to the length of follow-up.

A double-blind, sham-controlled RCT by Terlikowski (2013) compared transvaginal electrical stimulation (TVES) with active (n=68) or sham (n=34) EMG-biofeedback in premenopausal women with stress urinary incontinence (SUI).[149] The group receiving active biofeedback had significantly better results than the sham group for reduction in urinary leakage, pelvic floor muscle strength, and incontinence-related quality of life. No significant between group difference was found in urodynamic data. The authors concluded that TVES with active EMG biofeedback "is a trustworthy method for treating premenopausal women with stress urinary incontinence; however reliability needs to be established."

Other RCTs comparing the efficacy of PFMT alone with PFMT with biofeedback have been published. Statistically significant differences in outcomes between interventions were not consistently found, however, sample sizes were small (<25 per group) and thus the studies may have been underpowered.

VOIDING DYSFUNCTION

Systematic Reviews

Fazeli published a SR with meta-analysis to better understand how biofeedback has been used to treat children, up to age 18, with symptoms of bladder dysfunction not responding to standard therapy alone.[150] Five eligible studies were included in the SR. Four of the studies were pooled in the meta-analysis for a total of 382 participants. The overall proportion of cases with resolved incontinence at six months was similar in biofeedback and control groups (OR1.37 [95% CI 0.64 to 2.93], RD 0.0.7 [-0.9, 0.23]). There was no significant different in mean maximum urinary flow rate mean difference 0.50 ml, range -0.56 to 1.55) or likelihood of

urinary tract infection (OR 1.30 [95% CI 0.65 to 2.58]). This SR was limited by the paucity of research, high quality studies, and small sample sizes.

Randomized Controlled Trials

In 2015, Sener published results from a retrospective RCT that compared the outcomes of four biofeedback sessions (group one; n=20) with six to ten biofeedback sessions (group two; n=20) on treating children with dysfunctional voiding. [151] Normalized voiding after the treatment was determined in 18 subjects from group one, and 19 subjects in group two. Fifteen out of the 40 total study sample were determined to have reflux. At the six month evaluation of group one, voiding dysfunction had resolved in seven, had improved in three, and persisted in one. In group two, voiding dysfunction had resolved in ten, improved in three. This study is limited by a small sample size and other methodological constraints that make it difficult to determine the efficacy of biofeedback for children with dysfunctional voiding.

In 2015, Minardi published results from a four arm RCT to evaluate the therapeutic effects of tamsulosin and biofeedback on recurrent urinary tract infections in 155 women with dysfunctional voiding.[152] The study consisted of four groups: group one received uroflowmetry biofeedback, group two received α1-adrenoceptor antagonists, group three received uroflowmetry biofeedback combined with α1-adrenoceptor antagonists, and group four received no treatment. Patients were evaluated by the American Urological Association Symptom Index. Urodynamics was carried out in patients of groups one, two and three at three, six and 12 months, whereas urodynamics was only carried out at 12 months in group four. The incidence of storage and emptying symptoms, mean post-void residual, mean flow rate, flow time, voiding volume, and urinary tract infections decreased at three, six, and twelve month for all four groups. This study was limited by the small sample size, attrition, and other methodological constraints making it hard to determine the efficacy of biofeedback for women with recurrent urinary tract infections and dysfunctional voiding.

OTHER URINARY INCONTINENCE

Systemic Reviews

No SRs were identified for biofeedback for the treatment of other urinary incontinence.

Randomized Control Trials

An RCT of 74 patients with multiple sclerosis reported that the addition of neuromuscular electrical stimulation with biofeedback training resulted in 85% incontinence reduction, compared to a 47% incontinence reduction in the control group trained only with biofeedback.[153]

Section Summary

The available evidence for the use of biofeedback in the treatment of stress and/or or urge urinary incontinence in female patients includes several RCTs and SRs. Although there is some heterogeneity across these studies, there is enough research to show that biofeedback improves outcomes in women with urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT). The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of urinary incontinence other than in this setting.

OTHER INDICATIONS

Other indications for which there are no clinical trial publications sufficient to demonstrate the effectiveness of biofeedback include, but are not limited to the following:

- Cardiovascular disorders
- Chronic fatigue syndrome
- Chronic obstructive pulmonary disease (COPD)
- Epilepsy[154]
- Facial palsy
- Hand hemiplegia
- Low vision
- Side-effects of cancer chemotherapy

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF SLEEP MEDICINE (AASM)

In 2008, an AASM special committee released a guideline on evaluation and management of chronic insomnia in adults.[155] The AASM considers biofeedback as one of a number of common therapies that are "effective and recommended in the treatment of chronic primary and comorbid (secondary) insomnia (Guideline)" The AASM definition for guideline is "a patient-care strategy, which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level two Evidence (RCTs with high alpha and beta error) or a consensus of Level three Evidence (non-randomized concurrently controlled studies)."

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2014, the American College of Gastroenterology (ACG) published guidelines on the management of fecal incontinence.[156] The guideline indicated that pelvic floor rehabilitation techniques (eg, biofeedback, therapeutic exercises) are effective in patients with fecal incontinence who do not respond to conservative measures (strong recommendation, moderate quality of evidence).

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)[157]

In 2015 ACOG reaffirmed their 2009 clinical practice guidelines on urinary incontinence in women. Biofeedback was not included in these recommendations.

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians published a guideline titled "Noninvasive Treatments for Acute, Subacute, and Chronic Back Pain: a Clinical Practice Guideline From the American College of Physicians". The guideline stated low quality evidence supports biofeedback for chronic low back pain.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE (ACOEM)

In 2020, the ACOEM updated their guideline on noninvasive and minimally invasive management of low back disorders.[158] The role of biofeedback is not addressed in this updated guideline.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

The updated AGA position statement (2013) on constipation considers biofeedback a possible treatment for patients with dyssynergia-type constipation with severe symptoms and proven pelvic floor dysfunction "to train patients to relax their pelvic floor muscles during straining and to correlate relaxation and pushing to achieve defecation (Strong Recommendation, High-Quality Evidence)."[159, 160]

The following statement on biofeedback was included: "Pelvic floor retraining by biofeedback therapy rather than laxatives is recommended for defecatory disorders (Strong Recommendation, High-Quality Evidence)."

AMERICAN HEART ASSOCIATION

A 2013 the American Heart Association published a statement based on a systematic literature review on alternatives to diet and medication for lowering blood pressure (BP) in patients with hypertension.[161] The report found meta-analyses to have had mixed results, though some recent trials showed reduction in BP with certain biofeedback techniques. However, recommendations for any specific techniques could not be made due to the paucity of data. The statement recommended that biofeedback could be considered for treatment of hypertension. This recommendation was rated as Class IIB, Level of Evidence B recommendation, defined as usefulness/efficacy less well-defined based on conflicting evidence from a single RCT or nonrandomized studies; additional studies with broad objectives needed.

AMERICAN NEUROGASTROENTEROLOGY AND MOTILITY SOCIETY

In 2015, the American Neurogastroenterology and Motility Society and the European Society of Neurogastroenterology and Mobility jointly published consensus-based guidelines on biofeedback therapy for anorectal disorders.[162] The guidelines included the following recommendations:

- "Biofeedback is recommended for the short-term and long-term treatment of constipation with dyssynergic defecation."
- "Biofeedback therapy is recommended for the short-term and long-term treatment of fecal incontinence"
- "Biofeedback therapy is not recommended for the routine treatment of children with functional constipation, with or without overflow fecal incontinence."

AMERICAN SOCIETY OF COLON AND RECTAL SURGEONS (ASCRS)

In 2016, ASCRS published guidelines on the evaluation and management of constipation.[163] The guideline states that biofeedback therapy is a first-line treatment for symptomatic pelvic floor dyssynergia (strong recommendation, moderate quality of evidence).

An American Society of Colon and Rectal Surgeons practice parameter recommended biofeedback "as an initial treatment for motivated patients with incontinence with some voluntary sphincter contraction. Biofeedback may be considered a first-line option for many patients with fecal incontinence who have not responded to simple dietary modification or medication. Supportive counseling and practical advice regarding diet and skin care can improve the success of biofeedback. Biofeedback may be considered before attempting sphincter repair or for those who have persistent or recurrent symptoms after sphincter repair. It may have a role in the early postpartum period in females with symptomatic sphincter weakness. Biofeedback and a pelvic floor exercise program can produce improvement that lasts more than two years. Biofeedback home training is an alternative to ambulatory training programs, especially in the elderly." The authors assigned a level of evidence of III and grade of recommendation B, defined as well-designed, quasi-experimental nonrandomized studies with generally consistent findings.

AMERICAN UROLOGICAL ASSOCIATION AND THE SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE & UROGENITAL RECONSTRUCTION (AUA/SUFU)[164]

The 2014 AUA/SUFU evidence-based practice guidelines recommended offering behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training) as first line therapy to all patients with overactive bladder. This recommendation was rated as a Standard, defined as a directive statement that an action should or should not be taken. The strength of evidence was rated as Grade B (moderate quality; moderate certainty). Biofeedback was included among a number of other modalities as a component of behavioral therapies. The guideline reported that the limited literature did not show any single component of behavioral therapy to be essential to efficacy or to be superior in efficacy.

TENSION AND MIGRAINE HEADACHES

Clinical practice guidelines from professional associations include biofeedback in their recommendations for prevention of tension and migraine headaches.[165-168] The associations included the American Academy of Neurology, the National Institute of Neurologic Disorders and Stroke, the U.S. Headache Consortium, and the European Federation of Neurological Societies.

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

In 2017, the National Institute for Clinical Excellence (NICE) issued evidence-based guidance on constipation in children and young people, which was reaffirmed in 2014.[169] The guidance indicated that biofeedback should not be used for ongoing treatment.

SUMMARY

It appears that biofeedback may improve health outcomes for some people for prevention of tension-type and migraine headaches. Clinical guidelines based on research recommend biofeedback for people with tension and migraine headaches. Therefore, biofeedback may be considered medically necessary when policy criteria are met.

There is enough research to show that biofeedback improves health outcomes for people with dyssynergia-type constipation. Clinical guidelines based on research recommend biofeedback for pelvic floor training for dyssynergia constipation in adults. Therefore,

biofeedback may be considered medically necessary when policy criteria are met.

There is enough research to show that biofeedback improves outcomes in individuals with stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT). Clinical practice guidelines recommended behavioral therapies including biofeedback as to patients with overactive bladder. Therefore, biofeedback may be considered medically necessary in individuals with stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT).

There is not enough research to show that biofeedback improves health outcomes for people with the variety of investigational indications listed in the criteria. In addition, no clinical guidelines based on research recommend biofeedback for these indications. Therefore, biofeedback is considered investigational for all other indications.

REFERENCES

1. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. *Gastroenterology.* 2016. PMID: 27144627
2. Yorke J, Fleming S, Shuldham C, et al. Nonpharmacological interventions aimed at modifying health and behavioural outcomes for adults with asthma: a critical review. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology.* 2015;45(12):1750-64. PMID: 25675860
3. Meuret AE, Ritz T, Wilhelm FH, et al. Targeting pCO(2) in asthma: pilot evaluation of a capnometry-assisted breathing training. *Appl Psychophysiol Biofeedback.* 2007;32(2):99-109. PMID: 17564826
4. Lehrer PM, Vaschillo E, Vaschillo B, et al. Biofeedback treatment for asthma. *Chest.* 2004;126(2):352-61. PMID: 15302717
5. Lehrer P, Carr RE, Smetankine A, et al. Respiratory sinus arrhythmia versus neck/trapezius EMG and incentive inspirometry biofeedback for asthma: a pilot study. *Appl Psychophysiol Biofeedback.* 1997;22(2):95-109. PMID: 9341966
6. Coben R, Myers TE. The relative efficacy of connectivity guided and symptom based EEG biofeedback for autistic disorders. *Appl Psychophysiol Biofeedback.* 2010;35(1):13-23. PMID: 19649702
7. Yang HC, Lee IC. Visual feedback and target size effects on reach-to-grasp tasks in children with autism. *Journal of autism and developmental disorders.* 2014;44(12):3129-39. PMID: 24974254
8. Kouijzer ME, van Schie HT, Gerrits BJ, et al. Is EEG-biofeedback an effective treatment in autism spectrum disorders? A randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2013;38(1):17-28. PMID: 22903518
9. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev.* 2011(12):CD006283. PMID: 22161401
10. Cardoso JR, Teixeira EC, Moreira MD, et al. Effects of exercises on Bell's palsy: systematic review of randomized controlled trials. *Otol Neurotol.* 2008;29(4):557-60. PMID: 18520590
11. Manfredini D, Ahlberg J, Winocur E, et al. Management of sleep bruxism in adults: a qualitative systematic literature review. *Journal of oral rehabilitation.* 2015;42(11):862-74. PMID: 26095208
12. Wang LF, Long H, Deng M, et al. Biofeedback treatment for sleep bruxism: a systematic review. *Sleep & breathing = Schlaf & Atmung.* 2013. PMID: 23756884

13. Sato M, Iizuka T, Watanabe A, et al. Electromyogram biofeedback training for daytime clenching and its effect on sleep bruxism. *Journal of oral rehabilitation.* 2015;42(2):83-9. PMID: 25256380
14. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev.* 2012;11:CD007407. PMID: 23152245
15. Palermo TM, Eccleston C, Lewandowski AS, et al. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *Pain.* 2010;148(3):387-97. PMID: 19910118
16. Richards R, van den Noort JC, Dekker J, et al. Gait Retraining With Real-Time Biofeedback to Reduce Knee Adduction Moment: Systematic Review of Effects and Methods Used. *Arch Phys Med Rehabil.* 2017;98(1):137-50. PMID: 27485366
17. Astin JA, Beckner W, Soeken K, et al. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum.* 2002;47(3):291-302. PMID: 12115160
18. Eid MA, Aly SM, El-Shamy SM. Effect of Electromyographic Biofeedback Training on Pain, Quadriceps Muscle Strength, and Functional Ability in Juvenile Rheumatoid Arthritis. *American journal of physical medicine & rehabilitation.* 2016;95(12):921-30. PMID: 27149595
19. Theadom A, Cropley M, Smith HE, et al. Mind and body therapy for fibromyalgia. *Cochrane Database Syst Rev.* 2015;4:CD001980. PMID: 25856658
20. Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-Biofeedback in Fibromyalgia Syndrome: A Meta-Analysis and a Systematic Review of Randomized Controlled Trials. *Evidence-based complementary and alternative medicine : eCAM.* 2013;2013:962741. PMID: 24082911
21. Collins NJ, Bisset LM, Crossley KM, et al. Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials. *Sports Med.* 2012;42(1):31-49. PMID: 22149696
22. Rixe JA, Glick JE, Brady J, et al. A review of the management of patellofemoral pain syndrome. *The Physician and sportsmedicine.* 2013;41(3):19-28. PMID: 24113699
23. Sielski R, Rief W, Glombiewski JA. Efficacy of Biofeedback in Chronic back Pain: a Meta-Analysis. *Int J Behav Med.* 2017;24(1):25-41. PMID: 27307013
24. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-30. PMID: 28192789
25. Haines T, Bowles KA. Cost-effectiveness of using a motion-sensor biofeedback treatment approach for the management of sub-acute or chronic low back pain: economic evaluation alongside a randomised trial. *BMC musculoskeletal disorders.* 2017;18(1):18. PMID: 28095832
26. Daffada PJ, Walsh N, McCabe CS, et al. The impact of cortical remapping interventions on pain and disability in chronic low back pain: a systematic review. *Physiotherapy.* 2015;101(1):25-33. PMID: 25442672
27. Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev.* 2010(7):CD002014. PMID: 20614428
28. Bush C, Ditto B, Feuerstein M. A controlled evaluation of paraspinal EMG biofeedback in the treatment of chronic low back pain. *Health Psychol.* 1985;4(4):307-21. PMID: 2932330
29. Nouwen A. EMG biofeedback used to reduce standing levels of paraspinal muscle tension in chronic low back pain. *Pain.* 1983;17(4):353-60. PMID: 6229707

30. Newton-John TR, Spence SH, Schotte D. Cognitive-behavioural therapy versus EMG biofeedback in the treatment of chronic low back pain. *Behaviour research and therapy.* 1995;33:691-7. PMID: 7654161
31. Stuckey SJ, Jacobs A, Goldfarb J. EMG biofeedback training, relaxation training, and placebo for the relief of chronic back pain. *Perceptual and motor skills.* 1986;63(3):1023-36. PMID: 2949196
32. Tan G, Rintala DH, Jensen MP, et al. A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain. *Eur J Pain.* 2015;19(2):271-80. PMID: 24934738
33. Kapitza KP, Passie T, Bernateck M, et al. First non-contingent respiratory biofeedback placebo versus contingent biofeedback in patients with chronic low back pain: a randomized, controlled, double-blind trial. *Appl Psychophysiol Biofeedback.* 2010;35(3):207-17. PMID: 20237953
34. Glombiewski JA, Hartwich-Tersek J, Rief W. Two psychological interventions are effective in severely disabled, chronic back pain patients: a randomised controlled trial. *Int J Behav Med.* 2010;17(2):97-107. PMID: 19967572
35. Campo M, Zadro JR, Pappas E, et al. The effectiveness of biofeedback for improving pain, disability and work ability in adults with neck pain: A systematic review and meta-analysis. *Musculoskelet Sci Pract.* 2021;52:102317. PMID: 33461043
36. Kamonseki DH, Calixtre LB, Barreto RPG, et al. Effects of electromyographic biofeedback interventions for shoulder pain and function: Systematic review and meta-analysis. *Clin Rehabil.* 2021;35(7):952-63. PMID: 33517777
37. Shearer HM, Carroll LJ, Wong JJ, et al. Are psychological interventions effective for the management of neck pain and whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *The spine journal : official journal of the North American Spine Society.* 2016;16(12):1566-81. PMID: 26279388
38. Hesselstrand M, Samuelsson K, Liedberg G. Occupational Therapy Interventions in Chronic Pain--A Systematic Review. *Occupational therapy international.* 2015;22(4):183-94. PMID: 26076994
39. Ma C, Szeto GP, Yan T, et al. Comparing biofeedback with active exercise and passive treatment for the management of work-related neck and shoulder pain: a randomized controlled trial. *Arch Phys Med Rehabil.* 2011;92(6):849-58. PMID: 21621660
40. Aggarwal VR, Lovell K, Peters S, et al. Psychosocial interventions for the management of chronic orofacial pain. *Cochrane Database Syst Rev.* 2011(11):CD008456. PMID: 22071849
41. Medlicott MS, Harris SR. A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. *Phys Ther.* 2006;86(7):955-73. PMID: 16813476
42. McNeely ML, Armijo Olivo S, Magee DJ. A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders. *Phys Ther.* 2006;86(5):710-25. PMID: 16649894
43. Greco CM, Rudy TE, Manzi S. Effects of a stress-reduction program on psychological function, pain, and physical function of systemic lupus erythematosus patients: a randomized controlled trial. *Arthritis Rheum.* 2004;51(4):625-34. PMID: 15334437
44. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. *J Pediatr Gastroenterol Nutr.* 2000;31(1):47-51. PMID: 10896070

45. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. *Pediatrics.* 2003;111(1):e1-11. PMID: 12509588
46. Morin M, Carroll MS, Bergeron S. Systematic Review of the Effectiveness of Physical Therapy Modalities in Women With Provoked Vestibulodynia. *Sexual medicine reviews.* 2017;5(3):295-322. PMID: 28363763
47. Bergeron S, Binik YM, Khalife S, et al. A randomized comparison of group cognitive--behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain.* 2001;91(3):297-306. PMID: 11275387
48. CADTH. Post-Traumatic Stress Disorder: Summary of Evidence of the Clinical Effectiveness of Treatments. [cited 8/18/2022]. 'Available from:' https://www.cadth.ca/post-traumatic-stress-disorder-summary-evidence-clinical-effectiveness-treatments.
49. Neurofeedback and Biofeedback for Mood and Anxiety Disorders: A Review of the Clinical Evidence and Guidelines. [cited 8/18/2022]. 'Available from:' https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0939%20Neurofeedback%20Biofeedback%20Final.pdf.
50. Goessl VC, Curtiss JE, Hofmann SG. The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychological medicine.* 2017:1-9. PMID: 28478782
51. Schoenberg PL, David AS. Biofeedback for psychiatric disorders: a systematic review. *Appl Psychophysiol Biofeedback.* 2014;39(2):109-35. PMID: 24806535
52. Maynart W, Albuquerque M, Santos RCS, et al. The use of biofeedback intervention in the improvement of depression levels: a randomised trial. *Acta Neuropsychiatr.* 2021;33(3):126-33. PMID: 33427129
53. Park SM, Jung HY. Respiratory sinus arrhythmia biofeedback alters heart rate variability and default mode network connectivity in major depressive disorder: A preliminary study. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology.* 2020;158:225-37. PMID: 33148502
54. Chen YF, Huang XY, Chien CH, et al. The Effectiveness of Diaphragmatic Breathing Relaxation Training for Reducing Anxiety. *Perspectives in psychiatric care.* 2016. PMID: 27553981
55. Meuret AE, Rosenfield D, Seidel A, et al. Respiratory and cognitive mediators of treatment change in panic disorder: evidence for intervention specificity. *J Consult Clin Psychol.* 2010;78(5):691-704. PMID: 20873904
56. Woodward S, Norton C, Chiarelli P. Biofeedback for treatment of chronic idiopathic constipation in adults. *Cochrane Database Syst Rev.* 2014;3:CD008486. PMID: 24668156
57. Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. *Gastroenterology.* 2006;130:657-64. PMID: 16530506
58. Heymen S, Scarlett Y, Jones K, et al. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. *Dis Colon Rectum.* 2007;50(4):428-41. PMID: 17294322
59. Hart SL, Lee JW, Berian J, et al. A randomized controlled trial of anorectal biofeedback for constipation. *International journal of colorectal disease.* 2012;27(4):459-66. PMID: 22159695

60. Farid M, El Monem HA, Omar W, et al. Comparative study between biofeedback retraining and botulinum neurotoxin in the treatment of anismus patients. *International journal of colorectal disease.* 2009;24(1):115-20. PMID: 18719924
61. Simon MA, Bueno AM. Behavioural treatment of the dyssynergic defecation in chronically constipated elderly patients: a randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2009;34(4):273-7. PMID: 19618262
62. You YT WJ, ChangChien CR, et al. The treatment of outlet obstruction constipation. . *Formosan Journal of Surgery.* 2001;34:3-10. PMID: No PMID Entry
63. Hu WH LJ, Chan AO, et al Biofeedback is an effective treatment for functional constipation: a randomized controlled study. *Gastroenterology.* 2001;130(4Suppl 2):A287. PMID: No PMID Entry
64. Koutsomanis D, Lennard-Jones JE, Roy AJ, et al. Controlled randomised trial of visual biofeedback versus muscle training without a visual display for intractable constipation. *Gut.* 1995;37(1):95-9. PMID: 7672690
65. Heymen S, Wexner SD, Vickers D, et al. Prospective, randomized trial comparing four biofeedback techniques for patients with constipation. *Dis Colon Rectum.* 1999;42(11):1388-93. PMID: 10566525
66. Pourmomeny AA, Emami MH, Amooshahi M, et al. Comparing the efficacy of biofeedback and balloon-assisted training in the treatment of dyssynergic defecation. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie.* 2011;25(2):89-92. PMID: 21321680
67. Bleijenberg G, Kuijpers HC. Biofeedback treatment of constipation: a comparison of two methods. *The American journal of gastroenterology.* 1994;89(7):1021-6. PMID: 8017359
68. Glia A, Gylin M, Gullberg K, et al. Biofeedback retraining in patients with functional constipation and paradoxical puborectalis contraction: comparison of anal manometry and sphincter electromyography for feedback. *Dis Colon Rectum.* 1997;40(8):889-95. PMID: 9269803
69. Chang HS, Myung SJ, Yang SK, et al. Effect of electrical stimulation in constipated patients with impaired rectal sensation. *International journal of colorectal disease.* 2003;18(5):433-8. PMID: 12677456
70. Faried M, El Nakeeb A, Youssef M, et al. Comparative study between surgical and non-surgical treatment of anismus in patients with symptoms of obstructed defecation: a prospective randomized study. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2010;14(8):1235-43. PMID: 20499203
71. Lehur PA, Stuto A, Fantoli M, et al. Outcomes of stapled transanal rectal resection vs. biofeedback for the treatment of outlet obstruction associated with rectal intussusception and rectocele: a multicenter, randomized, controlled trial. *Dis Colon Rectum.* 2008;51(11):1611-8. PMID: 18642046
72. Rao SS, Seaton K, Miller M, et al. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. *Clin Gastroenterol Hepatol.* 2007;5(3):331-8. PMID: 17368232
73. Jung KW MS, Byeon JS, et al. Combined therapy with electrical stimulation and biofeeback in pelvic floor dyssynergia. *Neurogastroenterology and Motility* 2007;19(Suppl S3):74. PMID: No PMID Entry
74. Jung KW MS, Byeon JS, et al. Electrical stimulation therapy in pelvic floor dyssynergia: prospective, randomized study combined with biofeedback. *Journal of Gastroenterology and Hepatology* 2007;22(Suppl 2):A209. PMID: No PMID Entry

75. Enck P, Van der Voort IR, Klosterhalfen S. Biofeedback therapy in fecal incontinence and constipation. *Neurogastroenterol Motil.* 2009;21(11):1133-41. PMID: 19566591
76. Koh CE, Young CJ, Young JM, et al. Systematic review of randomized controlled trials of the effectiveness of biofeedback for pelvic floor dysfunction. *The British journal of surgery.* 2008;95(9):1079-87. PMID: 18655219
77. Chiarelli P. Systematic review: the management of constipation using physical therapies including biofeedback. Australian and New Zealand Continence Journal. *Australian and New Zealand Continence Journal.* 2008;14(1):6-13. PMID: No PMID Entry
78. Zhou LK CM, Ke MY. Systematic review of biofeedback for adult chronic constipation. *Journal of Gastroenterology and Hepatology* 2008;23(Suppl 5):A115. PMID: No PMID Entry
79. Vonthein R, Heimerl T, Schwandner T, et al. Electrical stimulation and biofeedback for the treatment of fecal incontinence: a systematic review. *International journal of colorectal disease.* 2013;28(11):1567-77. PMID: 23900652
80. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. *Cochrane Database Syst Rev.* 2012;7:CD002111. PMID: 22786479
81. Damon H, Siproudhis L, Faucheron JL, et al. Perineal retraining improves conservative treatment for faecal incontinence: a multicentre randomized study. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver.* 2014;46(3):237-42. PMID: 24444704
82. Brazzelli M, Griffiths PV, Cody JD, et al. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev.* 2011(12):CD002240. PMID: 22161370
83. Borowitz SM, Cox DJ, Sutphen JL, et al. Treatment of childhood encopresis: a randomized trial comparing three treatment protocols. *J Pediatr Gastroenterol Nutr.* 2002;34(4):378-84. PMID: 11930093
84. Davila E, de Rodriguez GG, Adrianza A, et al. [The usefulness of biofeedback in children with encopresis. A preliminary report]. *G E N.* 1992;46(4):297-301. PMID: 1340834
85. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. *J Pediatr.* 1990;116(2):214-22. PMID: 2299491
86. Loening-Baucke V, Desch L, Wolraich M. Biofeedback training for patients with myelomeningocele and fecal incontinence. *Dev Med Child Neurol.* 1988;30(6):781-90. PMID: 3234607
87. Nolan T, Catto-Smith T, Coffey C, et al. Randomised controlled trial of biofeedback training in persistent encopresis with anismus. *Arch Dis Child.* 1998;79(2):131-5. PMID: 9797593
88. van der Plas RN, Benninga MA, Buller HA, et al. Biofeedback training in treatment of childhood constipation: a randomised controlled study. *Lancet.* 1996;348(9030):776-80. PMID: 8813983
89. van der Plas RN, Benninga MA, Redekop WK, et al. Randomised trial of biofeedback training for encopresis. *Arch Dis Child.* 1996;75(5):367-74. PMID: 8957948
90. Wald A, Chandra R, Gabel S, et al. Evaluation of biofeedback in childhood encopresis. *J Pediatr Gastroenterol Nutr.* 1987;6(4):554-8. PMID: 3430263
91. Sunic-Omejc M, Mihanovic M, Bilic A, et al. Efficiency of biofeedback therapy for chronic constipation in children. *Collegium antropologicum.* 2002;26 Suppl:93-101. PMID: 12674840

92. Brazzelli M, Griffiths P. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev.* 2006(2):CD002240. PMID: 16625557
93. Brazzelli M, Griffiths P. Behavioral and cognitive interventions with or without other treatments for defaecation disorders in children. *Cochrane Database of Systematic Reviews.* 2003(2). PMID: No PMID Entry
94. Coulter ID, Favreau JT, Hardy ML, et al. Biofeedback interventions for gastrointestinal conditions: a systematic review. *Altern Ther Health Med.* 2002;8(3):76-83. PMID: 12017503
95. Wegh CAM, Baaleman DF, Tabbers MM, et al. Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis. *J Pediatr.* 2022;240:136-49 e5. PMID: 34536492
96. van Ginkel R, Buller HA, Boeckxstaens GE, et al. The effect of anorectal manometry on the outcome of treatment in severe childhood constipation: a randomized, controlled trial. *Pediatrics.* 2001;108(1):E9. PMID: 11433088
97. Sullivan A, Cousins S, Ridsdale L. Psychological interventions for migraine: a systematic review. *Journal of neurology.* 2016;263(12):2369-77. PMID: 27159991
98. Nestoriuc Y, Martin A. Efficacy of biofeedback for migraine: a meta-analysis. *Pain.* 2007;128(1-2):111-27. PMID: 17084028
99. Nestoriuc Y, Rief W, Martin A. Meta-analysis of biofeedback for tension-type headache: efficacy, specificity, and treatment moderators. *J Consult Clin Psychol.* 2008;76(3):379-96. PMID: 18540732
100. Trautmann E, Lackschewitz H, Kroner-Herwig B. Psychological treatment of recurrent headache in children and adolescents--a meta-analysis. *Cephalalgia.* 2006;26(12):1411-26. PMID: 17116091
101. Damen L, Bruijn J, Koes BW, et al. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. *Cephalalgia.* 2006;26(4):373-83. PMID: 16556238
102. Verhagen AP, Damen L, Berger MY, et al. Behavioral treatments of chronic tension-type headache in adults: are they beneficial? *CNS Neurosci Ther.* 2009;15(2):183-205. PMID: 19499626
103. Verhagen AP, Damen L, Berger MY, et al. Lack of benefit for prophylactic drugs of tension-type headache in adults: a systematic review. *Fam Pract.* 2010;27(2):151-65. PMID: 20028727
104. Eccleston C, Palermo TM, Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev.* 2009(2):CD003968. PMID: 19370592
105. Martin PR, Forsyth MR, Reece J. Cognitive-behavioral therapy versus temporal pulse amplitude biofeedback training for recurrent headache. *Behav Ther.* 2007;38(4):350-63. PMID: 18021950
106. Mullally WJ, Hall K, Goldstein R. Efficacy of biofeedback in the treatment of migraine and tension type headaches. *Pain Physician.* 2009;12(6):1005-11. PMID: 19935987
107. Bussone G, Grazzi L, D'Amico D, et al. Biofeedback-assisted relaxation training for young adolescents with tension-type headache: a controlled study. *Cephalalgia.* 1998;18(7):463-7. PMID: 9793698
108. Scharff L, Marcus DA, Masek BJ. A controlled study of minimal-contact thermal biofeedback treatment in children with migraine. *Journal of pediatric psychology.* 2002;27(2):109-19. PMID: 11821495

109. Sartory G, Muller B, Metsch J, et al. A comparison of psychological and pharmacological treatment of pediatric migraine. *Behaviour research and therapy.* 1998;36(12):1155-70. PMID: 9745800
110. Gerber WD, Petermann F, Gerber-von Muller G, et al. MIPAS-Family-evaluation of a new multi-modal behavioral training program for pediatric headaches: clinical effects and the impact on quality of life. *J Headache Pain.* 2010;11(3):215-25. PMID: 20376520
111. Nagele E, Jeitler K, Horvath K, et al. Clinical effectiveness of stress-reduction techniques in patients with hypertension: systematic review and meta-analysis. *J Hypertens.* 2014;32(10):1936-44; discussion 44. PMID: 25084308
112. Greenhalgh J, Dickson R, Dundar Y. Biofeedback for hypertension: a systematic review. *J Hypertens.* 2010;28(4):644-52. PMID: 20090553
113. Rainforth MV, Schneider RH, Nidich SI, et al. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr Hypertens Rep.* 2007;9(6):520-8. PMID: 18350109
114. Wang MY, Chang NC, Hsieh MH, et al. Effect of feedback signal on blood pressure self-regulation capability in individuals with prehypertension or stage I hypertension: a randomized controlled study. *The Journal of cardiovascular nursing.* 2016;31(2):166-72. PMID: 25774838
115. Landman GW, Drion I, van Hateren KJ, et al. Device-guided breathing as treatment for hypertension in type 2 diabetes mellitus: a randomized, double-blind, sham-controlled trial. *JAMA Intern Med.* 2013;173:1346-50. PMID: 23752780
116. Silkman C, McKeon J. The effectiveness of electromyographic biofeedback supplementation during knee rehabilitation after injury. *J Sport Rehabil.* 2010;19(3):343-51. PMID: 20811082
117. Stanton R, Ada L, Dean CM, et al. Biofeedback improves performance in lower limb activities more than usual therapy in people following stroke: a systematic review. *Journal of physiotherapy.* 2017;63(1):11-16. PMID: 27989731
118. Stanton R, Ada L, Dean CM, et al. Biofeedback improves activities of the lower limb after stroke: a systematic review. *Journal of physiotherapy.* 2011;57(3):145-55. PMID: 21843829
119. Woodford H, Price C. EMG biofeedback for the recovery of motor function after stroke. *Cochrane Database Syst Rev.* 2007(2):CD004585. PMID: 17443550
120. Zijlstra A, Mancini M, Chiari L, et al. Biofeedback for training balance and mobility tasks in older populations: a systematic review. *J Neuroeng Rehabil.* 2010;7:58. PMID: 21143921
121. Kim JH. The effects of training using EMG biofeedback on stroke patients upper extremity functions. *J Phys Ther Sci.* 2017;29(6):1085-88. PMID: 28626331
122. Yang DJ. Influence of biofeedback weight bearing training in sit to stand to sit and the limits of stability on stroke patients. *J Phys Ther Sci.* 2016;28(11):3011-14. PMID: 27942111
123. Ghomashchi H. Investigating the effects of visual biofeedback therapy on recovery of postural balance in stroke patients using a complexity measure. *Topics in stroke rehabilitation.* 2016;23(3):178-83. PMID: 27077976
124. Barcala L, Grecco LA, Colella F, et al. Visual Biofeedback Balance Training Using Wii Fit after Stroke: A Randomized Controlled Trial. *J Phys Ther Sci.* 2013;25:1027-32. PMID: 24259909
125. van der Logt RP, Findling O, Rust H, et al. The effect of vibrotactile biofeedback of trunk sway on balance control in multiple sclerosis. *Mult Scler Relat Disord.* 2016;8:58-63. PMID: 27456875

126. Mackay AM, Buckingham R, Schwartz RS, et al. The Effect of Biofeedback as a Psychological Intervention in Multiple Sclerosis: A Randomized Controlled Study. *International journal of MS care.* 2015;17(3):101-8. PMID: 26052255
127. Gillis DJ, Wouda M, Hjeltnes N. Non-pharmacological management of orthostatic hypotension after spinal cord injury: a critical review of the literature. *Spinal Cord.* 2008;46(10):652-9. PMID: 18542098
128. Siepmann M, Hennig UD, Siepmann T, et al. The effects of heart rate variability biofeedback in patients with preterm labour. *Appl Psychophysiol Biofeedback.* 2014;39(1):27-35. PMID: 24271650
129. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med.* 2000;160(8):1101-8. PMID: 10789602
130. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology (Oxford).* 2009;48(7):791-5. PMID: 19433434
131. van der Zwan JE, de Vente W, Huizink AC, et al. Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2015;40:257-68. PMID: 26111942
132. Weise C, Heinecke K, Rief W. Biofeedback-based behavioral treatment for chronic tinnitus: results of a randomized controlled trial. *J Consult Clin Psychol.* 2008;76(6):1046-57. PMID: 19045972
133. Hsu LF, Liao YM, Lai FC, et al. Beneficial effects of biofeedback-assisted pelvic floor muscle training in patients with urinary incontinence after radical prostatectomy: A systematic review and metaanalysis. *International journal of nursing studies.* 2016;60:99-111. PMID: 27297372
134. Anderson CA, Omar MI, Campbell SE, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev.* 2015;1:CD001843. PMID: 25602133
135. Campbell SE, Glazener CM, Hunter KF, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev.* 2012;1:CD001843. PMID: 22258946
136. MacDonald R, Fink HA, Huckabay C, et al. Pelvic floor muscle training to improve urinary incontinence after radical prostatectomy: a systematic review of effectiveness. *BJU Int.* 2007;100(1):76-81. PMID: 17433028
137. Wille S, Sobottka A, Heidenreich A, et al. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomized trial. *J Urol.* 2003;170(2 Pt 1):490-3. PMID: 12853806
138. Bales GT, Gerber GS, Minor TX, et al. Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy. *Urology.* 2000;56(4):627-30. PMID: 11018619
139. Oh JJ, Kim JK, Lee H, et al. Effect of personalized extracorporeal biofeedback device for pelvic floor muscle training on urinary incontinence after robot-assisted radical prostatectomy: A randomized controlled trial. *Neurourol Urodyn.* 2020;39(2):674-81. PMID: 31793032
140. Dijkstra-Eshuis J, Van den Bos TW, Splinter R, et al. Effect of preoperative pelvic floor muscle therapy with biofeedback versus standard care on stress urinary incontinence and quality of life in men undergoing laparoscopic radical prostatectomy: A randomised control trial. *Neurourol Urodyn.* 2013. PMID: 24249542

141. Tienforti D, Sacco E, Marangi F, et al. Efficacy of an assisted low-intensity programme of perioperative pelvic floor muscle training in improving the recovery of continence after radical prostatectomy: a randomized controlled trial. *BJU Int.* 2012;110(7):1004-10. PMID: 22332815
142. Zhu D, Xia Z, Yang Z. Effectiveness of physiotherapy for lower urinary tract symptoms in postpartum women: systematic review and meta-analysis. *International urogynecology journal.* 2022;33(3):507-21. PMID: 34302516
143. Wu X, Zheng X, Yi X, et al. Electromyographic Biofeedback for Stress Urinary Incontinence or Pelvic Floor Dysfunction in Women: A Systematic Review and Meta-Analysis. *Adv Ther.* 2021;38(8):4163-77. PMID: 34176082
144. Balk E, Adam GP, Kimmel H, et al. Nonsurgical Treatments for Urinary Incontinence in Women: A Systematic Review Update. Rockville (MD), 2018.
145. Mateus-Vasconcelos ECL, Ribeiro AM, Antonio FI, et al. Physiotherapy methods to facilitate pelvic floor muscle contraction: A systematic review. *Physiother Theory Pract.* 2018;34(6):420-32. PMID: 29278967
146. Oliveira M, Ferreira M, Azevedo MJ, et al. Pelvic floor muscle training protocol for stress urinary incontinence in women: A systematic review. *Rev Assoc Med Bras (1992).* 2017;63(7):642-50. PMID: 28977091
147. Moroni RM, Magnani PS, Haddad JM, et al. Conservative treatment of stress urinary incontinence: a systematic review with meta-analysis of randomized controlled trials. *Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia.* 2016;38(2):97-111. PMID: 26883864
148. Herderschee R, Hay-Smith EJ, Herbison GP, et al. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev.* 2011(7):CD009252. PMID: 21735442
149. Terlikowski R, Dobrzycka B, Kinalski M, et al. Transvaginal electrical stimulation with surface-EMG biofeedback in managing stress urinary incontinence in women of premenopausal age: a double-blind, placebo-controlled, randomized clinical trial. *International urogynecology journal.* 2013;24(10):1631-8. PMID: 23443345
150. Fazeli MS, Lin Y, Nikoo N, et al. Biofeedback for nonneuropathic daytime voiding disorders in children: a systematic review and meta-analysis of randomized controlled trials. *J Urol.* 2015;193(1):274-9. PMID: 25072179
151. Sener NC, Altunkol A, Unal U, et al. Can a four-session biofeedback regimen be used effectively for treating children with dysfunctional voiding? *International urology and nephrology.* 2015;47(1):5-9. PMID: 25218618
152. Minardi D, Pellegrinelli F, Conti A, et al. alpha1-Blockers for the treatment of recurrent urinary tract infections in women with dysfunctional voiding: a prospective randomized study. *International journal of urology : official journal of the Japanese Urological Association.* 2015;22(1):115-21. PMID: 25141907
153. McClurg D, Ashe RG, Lowe-Strong AS. Neuromuscular electrical stimulation and the treatment of lower urinary tract dysfunction in multiple sclerosis--a double blind, placebo controlled, randomised clinical trial. *Neurourol Urodyn.* 2008;27(3):231-7. PMID: 17705160
154. Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. *Cochrane Database Syst Rev.* 2008(3):CD002029. PMID: 18646083
155. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2008;4(5):487-504. PMID: 18853708

156. Wald A, Bharucha AE, Cosman BC, et al. ACG clinical guideline: management of benign anorectal disorders. *The American journal of gastroenterology.* 2014;109:1141-57; (Quiz) 058. PMID: 25022811
157. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 155: Urinary Incontinence in Women. *Obstet Gynecol.* 2015;126:e66-81. PMID: 26488524
158. Hegmann KT, Travis R, Andersson GBJ, et al. Non-Invasive and Minimally Invasive Management of Low Back Disorders. *J Occup Environ Med.* 2020;62(3):e111-e38. PMID: 31977923
159. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. *Gastroenterology.* 2013;144(1):211-7. PMID: 23261064
160. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical review on constipation. *Gastroenterology.* 2013;144(1):218-38. PMID: 23261065
161. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the american heart association. *Hypertension.* 2013;61:1360-83. PMID: 23608661
162. Rao SS, Benninga MA, Bharucha AE, et al. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. *Neurogastroenterol Motil.* 2015;27(5):594-609. PMID: 25828100
163. Paquette IM, Varma M, Ternent C, et al. The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Evaluation and Management of Constipation. *Dis Colon Rectum.* 2016;59:479-92. PMID: 27145304
164. American College of Occupational and Environmental Medicine (ACOEM). Low back disorders. 2011. [cited 1/4/2019]. 'Available from:' http://www.guideline.gov/content.aspx?id=38438&search=acoem+low+back+disorders.
165. National Institute of Neurological Disorders and Stroke. Headache information page. [cited 8/17/2022]. 'Available from:' http://www.ninds.nih.gov/disorders/headache/headache.htm.
166. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. *Am Fam Physician.* 2000;62(10):2359-60, 63. PMID: 11126860
167. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55(6):754-62. PMID: 10993991
168. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *Eur J Neurol.* 2010;17(11):1318-25. PMID: 20482606
169. National Institue of Health and Care Excellence (NICE): Constipation in children and young people: diagnosis and management. [cited 8/17/2022]. 'Available from:' https://www.nice.org.uk/guidance/cg99/chapter/1-Guidance#psychological-interventions.

CODES

Codes	Number	Description
CPT	90875-90876	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (e.g.,

Codes	Number	Description
		insight oriented, behavior modifying, or supportive psychotherapy); code range
	90901	Biofeedback training by any modality
	90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient
	90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health care professional contact with the patient (List separately in addition to code for primary procedure)
HCPCS	E0746	Electromyography (EMG), biofeedback device
ICD-10-PCS	GZC9ZZZ	Mental health, biofeedback, other biofeedback

Date of Origin: *March 2009*

Regence

Medical Policy Manual Allied Health, Policy No. 35

Administrative Guidelines to Determine Dental vs Medical Services

Effective: March 1, 2024

Next Review: November 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Coverage under medical or dental benefits is determined by the condition that is being diagnosed and treated, regardless of whether the service is provided by a dentist or a medical doctor.

MEDICAL POLICY CRITERIA

Notes: Member contracts for covered services vary. Member contract language takes precedence over medical policy. Medical necessity criteria must also be met when applicable.

I. Services are considered under medical benefits if the condition being diagnosed and treated is one which is non-contiguous to the teeth and/or gums or is systemic. (See Policy Guidelines for examples of medical services)

II. Services are considered under dental benefits when the condition being diagnosed and treated is contiguous or localized to the teeth and/or gums or when services are intended to restore lost function of the teeth. (See Policy Guidelines for examples of dental services)

III. General anesthesia services and related facility charges provided in conjunction with **any** (i.e., covered or excluded) dental procedure that is *performed in a hospital or in an ambulatory surgery* center are eligible for coverage under the medical benefit when one or more criteria below (A - C) are met:

A. The patient is under the age of seven, with a dental condition that cannot be safely and effectively treated in a dental office; or

B. The patient is physically or developmentally disabled, with a dental condition that cannot be safely and effectively treated in a dental office; or

C. The patient has a medical condition that the physician determines would place him/her at undue risk if the dental procedure is performed in a dental office. The procedure must be approved by the patient's physician.

Reimbursement Note:

If anesthesia is processed under the medical benefit, it is subject to anesthesia guidelines and must be performed by an independent anesthetist/anesthesiologist. Anesthesia will not be reimbursed to the physician or dentist performing the procedure. The dental procedure may be performed by a dentist or other appropriate provider.

IV. General anesthesia services by a medical provider *provided in a dental office* in conjunction with any covered dental procedure are eligible for coverage under the medical benefit when either criteria 1 or 2 below is met:

A. The patient is under the age of seven; or

B. The patient is physically or developmentally disabled.

Reimbursement Note:

When anesthesia services are provided by a dentist or under the direct supervision of a dentist, the anesthesia services as well as the dental procedure are eligible for dental coverage if applicable. The dentist must have appropriate state certification to perform general anesthesia. When anesthesia services are provided by an anesthesia provider (such as an anesthesiologist or CRNA), the anesthesia services are eligible for medical coverage if applicable.

V. Hospitalization with or without general anesthesia for non-preventive necessary dental treatment is eligible for coverage under the medical benefit when a patient has an existing medical condition for which dental treatment in an office setting is contraindicated and medical necessity exists for hospitalization and/or general anesthesia. Examples of such medical conditions include but are not limited to hemophilia or malignant hyperthermia.

VI. Non-dental services provided in conjunction with any dental procedure are considered **not medically necessary** when Criterion III. IV .or V. is not met.

POLICY GUIDELINES

Examples of **medical services** include but are not limited to:

- Treatment of a blocked salivary gland billed by a dentist

- Cleft palate obturator devices made by a dentist to allow for proper swallowing
- Closure of a cleft palate defect and, for defects extending into the maxilla, associated dental work and orthodontia
- Construction and management of a Tongue Retaining Device (TRD)/sleep apnea appliance, when provided by a dentist as a treatment of documented obstructive sleep apnea
- Soft tissue biopsies (tongue, cheeks, lips and floor of the mouth) except for gum tissues
- Hospital emergency room treatment for a serious condition that is related to the teeth, gums or contiguous structures, such as an acute abscess that results in an extraction

  Note: Facility and professional physician ER charges are covered by medical benefits; however, follow-up services related to dental treatment are covered under dental benefits, if available.
- Conditions where there is documentation of a direct link between destroyed bone or gums and chemotherapy or radiation and when there is documentation that the teeth were in reasonable condition prior to the initiation of the treatment(s)
- Treatment of leukoplakia or pigmented tissue, when confirmed on pathology as malignant

Examples of **dental services** include but are not limited to:

- Initial dental implants and implant removal due to infection caused by the implant
- Initial and replacement crowns
- Pathology studies for tooth-related conditions, such as apical cysts and odontogenic cysts
- Biopsies with extractions for cellulitis localized to the gums
- Dental evaluation and treatment related to other conditions, such as prior to transplantation or chemotherapy, including:
- Prophylactic work-up (i.e., exam, x-rays)
- Dentition history
- Prophylactic extractions of teeth which are necessary due to dental caries or periodontal infection

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical indicating if the condition is localized to the teeth and/or gums or contiguous structures. Or, indicate if non-contiguous to the teeth/gums or is systematic. Specify in detail. Indicate place of service (e.g., office, ER) and contributing factors such as cancer treatment or radiation etc.
- If general anesthesia is being used, indicate in the chart notes if the member is physically or developmentally disabled and has a documented dental condition that is

not safe to treat in the dental office or the member has a documented condition that will place him/her at undue risk if in the dental office.

CROSS REFERENCES

1. Dental and Orthodontic Treatment for Craniofacial Anomalies, Allied Health, Policy No. 33
2. Prefabricated Oral Appliances for Obstructive Sleep Apnea, Allied Health, Policy No. 36
3. Orthognathic Surgery, Surgery, Policy No. 137

CODES

NOTE: This code list is not intended to be an all-inclusive list, and the absence of a code from this medical policy does not imply coverage.

Codes	Number	Description
CPT	21245	Reconstruction of mandible or maxilla, subperiosteal implant; partial
	21246	Reconstruction of mandible or maxilla, subperiosteal implant; complete
	21248	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); partial
	21249	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); complete
	40899	Unlisted procedure, vestibule of mouth
	41800	Drainage of abscess, cyst, hematoma from dentoalveolar structures
	41805	Removal of embedded foreign body from dentoalveolar structures; soft tissues
	41806	Removal of embedded foreign body from dentoalveolar structures; bone
	41820	Gingivectomy, excision gingiva, each quadrant
	41821	Operculectomy, excision pericoronal tissues
	41822	Excision of fibrous tuberosities, dentoalveolar structures
	41823	Excision of osseous tuberosities, dentoalveolar structures
	41825	Excision of lesion or tumor (except listed above), dentoalveolar structures; without repair
	41826	Excision of lesion or tumor (except listed above), dentoalveolar structures; with simple repair
	41827	Excision of lesion or tumor (except listed above), dentoalveolar structures; with complex repair
	41828	Excision of hyperplastic alveolar mucosa, each quadrant (specify)
	41830	Alveolectomy, including curettage of osteitis or sequestrectomy
	41850	Destruction of lesion (except excision), dentoalveolar structures
	41870	Periodontal mucosal grafting
	41872	Gingivoplasty, each quadrant (specify)
	41874	Alveoloplasty, each quadrant (specify)
	41899	Unlisted procedure, dentoalveolar structures
HCPCS	None	

Date of Origin: *April 2013*

Uniform Medical Plan

ASD DOCUMENTATION REQUIREMENTS

Documentation of the diagnosis of an Autism Spectrum Disorder will be based on criteria defined by the most current DSM version (such as DSM-5 299.00). The diagnosis must be made by a neurologist, pediatric neurologist, developmental pediatrician, psychiatrist, or doctorate level psychologist for an Autism Spectrum Disorder (ASD).

For a diagnosis to be accepted there must be:

- Documentation of the confirmed presence of the core symptoms of autism: communication, behavioral, and social impairments; AND
- Documentation of the tool **and/or** observations used to make/confirm the diagnosis.

To determine eligibility for services, there must be a report documenting a diagnostic assessment, comprehensive evaluation, and treatment plan with recommendations. The report must include these elements:

Specific to Diagnostic Assessment & Comprehensive Evaluation Report (cannot be more than a year old)

For children who are current patients, it is acceptable to send the initial evaluation, most current notes or recent evaluation, as well as a letter certifying the diagnosis and providing any other required elements below that are not in other documentation being submitted. The letter should serve as an addendum and refer to the documentation being submitted, rather than reiterate this content. The following documentation is required:

a. Documentation of routine developmental surveillance performed by providers at well child visits; Examples of source documentation are: IEP, primary care practitioner or health care provider who referred the child, e.g. Occupational therapist, etc. if available;

b. Audiology and vision assessment results if available; or that vision and hearing were determined to be within normal limits during assessment and not a barrier to completing a valid evaluation;

c. If applicable, name of screening questionnaire, date completed, and significant results;

d. If applicable, documentation of formal diagnostic procedures performed by an experienced clinician, including name of measure, date and results, including scores. Examples of diagnostic measures are:
    - Autism Diagnostic Observation Schedule (ADOS);
    - Autism Diagnostic Interview (ADI);

e. Documentation of formal cognitive and/or developmental assessment performed by a qualified clinician, including name of measure, dates, results, and standardized scores providing verbal, nonverbal, and full scale scores, as available. Examples are:
    - Mullen;
    - Weschler; or
    - Bayley;

01/22/2014

f. Documentation of formal adaptive behavior assessment performed by a qualified clinician, including name of measure, dates, results, and standardized scores providing scores for each domain as available. Examples are:

- Vineland Adaptive Behavior Scales; or
- Adaptive Behavior Assessment System (ABAS);

e. Documentation of the observed or family reported behaviors having an adverse impact on development, communication and of the injurious behavior, as applicable;

f. Expanded laboratory evaluation, if clinically indicated;

g. Documentation of less intrusive or less intensive behavioral interventions have been tried and not been successful; **OR** that there is no equally effective and substantially less costly alternative available for reducing interfering behaviors, increasing pro-social behaviors, or maintaining desired behaviors, if ABA is included on the treatment plan;

Specific to Treatment Plan with Recommendations:
(If child not a new patient, can be in prescription.)

A multi-disciplinary Individualized Treatment Plan (ITP) with recommendations that consider the full range of autism treatments with ABA as one treatment component, if clinically indicated;

The Prescription must include these elements:

a. The order or prescription for ABA for the child, without specifying hours or how services are to be provided;

b. Documentation that the child's behaviors are having an adverse impact on development and/or communication, and/or demonstrating injurious behavior, such that

- The child cannot adequately participate in home, school, or community activities because behavior interferes; OR
- The child presents a safety risk to self or others;

c. A statement that the requested ABA services will result in measurable improvement in the child's behavior and/or skills.

Aversion Therapy for Chemical Dependency

Effective: February 1, 2021

Next Review: October 2021
Last Review: December 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Aversion therapy is an in-patient substance abuse treatment strategy that has been used for alcohol and cocaine dependence at the Schick Shadel Hospitals (Universal Health Inc.). The treatment generally includes aversion counter conditioning designed to make the sight, smell, taste and thought of the alcohol and/or cocaine unpalatable.

MEDICAL POLICY CRITERIA

Aversion therapy and pentothal interviews are considered **investigational** for all indications including but not limited to the treatment of chemical dependency.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Aversion therapy is an in-patient substance abuse treatment strategy that has been used for many years for alcohol and cocaine dependence at the Schick Shadel Hospitals (Universal

Health Services, Inc.). The treatment generally includes a 10-day in-patient stay during which the patient receives aversion counter conditioning designed to make the sight, smell, taste and thought of the alcohol and/or cocaine unpalatable. Narcotherapy (pentothal interview) is a component of the aversion therapy program designed to gather initial psychological diagnostic information and to monitor the development of aversion to the addictive substances. Under light anesthesia, patients are queried about the level of desire for each type of substance. Aversion therapy with pentothal interview is provided within a comprehensive treatment program that includes detoxification, counseling, addiction education, and introduction to a 12-step program for follow-up care.

EVIDENCE SUMMARY

Currently, the components of standard outpatient substance abuse therapy consist of individual, group and family psychotherapy, relapse prevention therapy, and introduction to a 12-step program for follow up. Agonist substitution therapy (methadone or levo-alpha-acetyl-methadol [LAAM]) and medications to decrease the reinforcing effects of abused substances, also known as withdrawal drugs (e.g., naltrexone, clonidine/naltrexone, buprenorphine), may also be included as a component of standard therapy.

Long-term outcomes from prospective, randomized controlled trials comparing aversion therapy to standard substance abuse therapy are needed to demonstrate the independent contribution of aversion therapy in the overall treatment program.

RANDOMIZED CONTROLLED TRIALS

There are no randomized controlled trials comparing aversion therapy or pentothal interviews to other treatments for chemical dependency.

NONRANDOMIZED STUDIES

The available published evidence consists of outcomes from patients treated at Schick Shadel Hospitals which are summarized below.

In a pilot study, by Frawley and Smith, 20 patients (9 treated for cocaine only and 11 treated for cocaine/alcohol) completed a program which included chemical aversion therapy to develop a conditioned aversion to the sight, smell, and taste of a cocaine substitute (tetracaine, mannitol, and quinine with Psychem).[1] Ninety-five percent of patients were followed up in six months with a total abstinence rate from cocaine of 56% in the cocaine only group and total abstinence from cocaine of 70% for the cocaine/alcohol group. After 18 months out of the ninety percent of patients that were followed up, 38% of the cocaine only group had been totally abstinent (75% were currently abstinent) and 50% of the cocaine/alcohol group had been totally abstinent (80% were currently abstinent).

Smith and Frawley reported outcomes for 200 patients randomly selected from a group of patients that completed an initial 10 days of treatment at a Schick Shadel Hospital in 1983.[2] During the initial 10-day hospitalization, patients received 5 days of aversion therapy and 5 days of narcotherapy, given on alternating days. This was followed at 30-day and 90-day intervals with 2-day inpatient admissions for reinforcement treatment consisting of 1 day each of aversion therapy and narcotherapy. Follow up was by telephone interview at 12-months. Of the 200 patients, 20% were lost to follow up. In addition, 22 patients were known to have relapsed prior to the 12-month telephone interview.

The same authors followed several other groups of patients for up to 20 months post-aversion therapy, reported in 1990 and 1993.[3 4] Patients in these cohorts were addicted to alcohol alone, cocaine alone, cocaine and alcohol, or cocaine and marijuana. As with the first study, there was either significant loss to follow-up (29%-36%) or small initial sample size (n=20) and therefore conclusions about the study effects could not be determined.

In a 1991 retrospective matched case-control study, 249 patients in the Schick Shadel System were matched to an equal number of patients in the alcohol treatment database and were followed for up to 12 months.[5] As with previous studies there was significant patient attrition: only 33% (248/754) of patients who were contacted for participation remained in the study at 6 months and at 12 months another 17% (41/248) were lost to follow-up.

Based on the same study described above, the same 249 patients were compared for faradic aversion and chemical aversion.[6] The two groups were separately analyzed and authors concluded that no significant differences in outcomes were found.

SECTION SUMMARY

Conclusions concerning the impact of aversion therapy and narcotherapy on health outcomes cannot be reached from the current evidence base. The evidence is limited due to methodological limitations including but not limited to lack of randomization, selection bias (individuals may not be representative of all those with chemical dependency issues), high loss to follow-up, and the inability to isolate the independent contribution of aversion therapy and pentothal interview from the overall substance abuse treatment program.

PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines that recommend the use of aversion therapy for the treatment of chemical dependency.

SUMMARY

The use of aversion therapy has been proposed as an alternative treatment for chemical dependency. There is not enough research to show that aversion therapy improves health outcomes. More research is needed with longer term follow-up. In addition, no evidence-based clinical practice guidelines recommend aversion therapy. Therefore, aversion therapy is considered investigational for all indications.

REFERENCES

1. Frawley PJ,Smith JW. Chemical aversion therapy in the treatment of cocaine dependence as part of a multimodal treatment program: treatment outcome. *J Subst Abuse Treat.* 1990;7(1):21-9. PMID: 2313768
2. Frawley PJ,Smith JW. One-year follow-up after multimodal inpatient treatment for cocaine and methamphetamine dependencies. *J Subst Abuse Treat.* 1992;9(4):271-86. PMID: 1336066
3. Smith JW,Frawley PJ. Long-term abstinence from alcohol in patients receiving aversion therapy as part of a multimodal inpatient program. *J Subst Abuse Treat.* 1990;7(2):77-82. PMID: 2167389

4. Smith JW,Frawley PJ. Treatment outcome of 600 chemically dependent patients treated in a multimodal inpatient program including aversion therapy and pentothal interviews. *J Subst Abuse Treat.* 1993;10(4):359-69. PMID: 8105103
5. Smith JW, Frawley PJ,Polissar L. Six- and twelve-month abstinence rates in inpatient alcoholics treated with aversion therapy compared with matched inpatients from a treatment registry. *Alcohol Clin Exp Res.* 1991;15(5):862-70. PMID: 1755521
6. Smith JW, Frawley PJ,Polissar NL. Six- and twelve-month abstinence rates in inpatient alcoholics treated with either faradic aversion or chemical aversion compared with matched inpatients from a treatment registry. *Journal of addictive diseases.* 1997;16(1):5-24. PMID: 9046442

CODES

Codes	Number	Description
CPT	90899	Unlisted psychiatric service or procedure
HCPCS	None	

Date of Origin: *November 2001*

Regence

Medical Policy Manual Behavioral Health, Policy No. 18

Applied Behavior Analysis for the Treatment of Autism Spectrum Disorder

Effective: June 1, 2023

Next Review: April 2024
Last Review: April 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Applied Behavior Analysis (ABA) is an umbrella term describing principles and techniques used in the assessment, treatment, and prevention of challenging behaviors and the promotion of new desired behaviors. The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement.

MEDICAL POLICY CRITERIA

Note: This policy only applies to member contracts that are subject to preauthorization for Applied Behavior Analysis for the Treatment of Autism Spectrum Disorder, as specified by their group plan. Please check the preauthorization website for the member contract to confirm requirements.

I. Initiation of Applied Behavior Analysis (ABA)-based therapy may be considered **medically necessary** when all of the following criteria (A. - C.) are met:

A. An ABA assessment has been documented and all of the following criteria (1. - 3.) are met:

1. The member has a diagnosis of an Autism Spectrum Disorder according to

the DSM (Diagnostic and Statistical Manual of Mental Disorders), either the DSM-IV or DSM-5 (see Policy Guidelines), by a licensed provider experienced in the diagnosis and treatment of autism; and

2. The Autism Spectrum Disorder (ASD) related symptoms and behaviors are impairing the member's communication, social and/or behavioral functioning such that the member is a safety risk to self or others and/or is unable to participate in age-appropriate home or community activities; and
3. ABA therapy must be recommended or prescribed by a licensed provider experienced in the diagnosis and treatment of autism.

B. Based upon the recommendation or prescription from the prescribing provider, a documented individualized treatment plan (ITP) is prepared by the treating provider who is certified to provide ABA therapy. An ITP shall be documented in the medical record; and

C. The individualized treatment plan (ITP) shall include all of the following (1. - 7.):

1. A detailed description of specific behaviors targeted for therapy. Targeted behaviors must be those which prevent the member from participating in age-appropriate home or community activities and/or are presenting a safety risk to self or others; and
2. For each targeted behavior, an objective baseline measurement using standardized instruments that include frequency, intensity and duration; and
3. A detailed description of treatment interventions and techniques specific to each of the targeted behaviors, including the frequency and duration of treatment for each intervention which is designed to improve the member's ability to participate in age-appropriate home or community activities and/or reduce the safety risk to self or others; and
4. Where there was a prior course of ABA therapy, documentation will specify the anticipated benefit of an additional course of treatment; and
5. A description of training and participation of family (parents, legal guardians and/or active caretakers as appropriate) in setting baseline and demonstrating progress toward treatment goals that directly support member's ITP; and
6. Clinical justification for the number of days per week and hours per day of direct ABA services provided to the member and the family, and the hours per week of direct face-to-face supervision of the treatment being delivered and observation of the child in their natural setting; and
7. Individualized and measurable discharge and/or transition criteria.

II. Continuation of ABA-based therapy may be considered **medically necessary** when there has been functional and measurable progress in the ITP goals, demonstrated when all of the following criteria (A. - D.) are met:

A. Member continues to meet Criteria I.B. and I.C. above; and

B. Data on targeted behaviors is documented by the individuals who are delivering the prescribed or recommended ABA therapy to the member during each ABA session. The treating provider who is certified to provide ABA therapy will

routinely collate and evaluate the data from all sessions and conduct a case review and treatment plan review; and

C. Progress toward each of the defined goals in the ITP is assessed and documented for each targeted behavior regarding whether clinically significant improvements are achieved and sustained both during treatment sessions and outside the treatment setting (e.g. home/community). Progress toward the ITP goals is measured using the same indices utilized for baseline measurements in the ITP; and

D. Objective measurements using standardized instruments that include frequency, intensity, and duration and evaluation to occur at a minimum of every six months.

III. Initial or continued ABA-based therapy for all indications is considered **not medically necessary** when the above applicable criteria are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

APPLICABLE BENEFITS

This policy applies to member contracts with applicable benefits subject to the following:

- Washington's Mental Health Parity Act (RCW 48.44); or
- Oregon's Mental Health Parity Act (ORS 743.168) effective August 8, 2014; or
- Idaho's Clarification Regarding Coverage of Treatments for Autism Spectrum Disorder (Bulletin No. 18-02), or
- Utah's Autism Services Amendment, SB 57 (UCA 31A-22-642) effective 2016.

CERTIFIED PROVIDERS

Treating providers who are certified to provide ABA therapy include a qualified Lead Behavior Analysis Therapist (LBAT), and in Idaho, a credentialed provider with a Board-Certified Behavioral Analysis (BCBA) certification issued by the Behavioral Analyst Certification Board.

TREATMENT EXPECTATIONS

At least every three months, the LBAT, or in Idaho, a credentialed provider with a Board Certified Behavioral Analysis (BCBA) certification issued by the Behavioral Analyst Certification Board, should assess the member and update the individualized treatment plan (ITP) as indicated by the member's response to therapy and obtain review by the Prescribing Provider or another licensed provider who has experience in the diagnosis and treatment of autism.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

The following information may be required for review of ABA services:

Initiation

- Documentation of the following from the prescribing provider (Criteria I.A.1. and I.A.2., above):
  - Diagnosis of Autism Spectrum Disorder (ASD)
  - ASD is impairing the member's functioning such that the member is a safety risk and/or is unable to participate in age-appropriate activities
- Written recommendation, clinical order, or prescription for ABA services from the provider (Criteria I.A.3., above)
- Individualized treatment plan (ITP) with the information listed in Criteria I.C.1.-7., above
- List of specific services requested with the number of units/hours requested per specified period of time

Continuation

The following documentation should be submitted within five business days prior to the end of a current authorization:

- Updated ITP with the information listed in Criteria II.A.-C., above

CROSS REFERENCES

1. Applied Behavior Analysis Initial Assessment for the Treatment of Autism Spectrum Disorder, Behavioral Health, Policy No. 33

BACKGROUND

AUTISM SPECTRUM DISORDER

Autism Spectrum Disorder (ASD) is a neurodevelopment disorder characterized by impaired social communication and interaction and atypical interests and behavioral patterns. ASD may be accompanied by other conditions, such as epilepsy and cognitive impairment. As defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), ASD includes:[1]

- Autistic Disorder
- Asperger's Disorder
- Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS)

Diagnostic criteria for ASD as defined by the DSM-5[1], are listed in Appendix 1.

BEHAVIORAL INTERVENTIONS FOR AUTISM SPECTRUM DISORDER

A number of behavioral interventions (e.g., educational, medical, behavioral, complementary, and other allied health interventions) aiming to improve core social, communication and challenging behaviors are available. Several treatments for ASD have been developed based upon different treatment principles, such as applied behavior analysis (ABA) as described below. With the exception of two treatment therapies (UCLA/Lovaas and Early Start Denver Model), most ABA intervention protocols have not been manualized, resulting in the potential for practice and treatment variation.

Applied Behavior Analysis

ABA may be defined as: “the design, implementation and evaluation of environmental modifications, using behavioral interventions for the treatment of autism spectrum disorder. The goal of the therapy is to produce clinically significant improvements in core deficits associated with autism spectrum disorder (i.e. significant issues with communication, social interaction or injurious behaviors). It includes the use of direct observation, measurement and functional analysis of the relationship between the environment and behavior and uses behavioral stimuli and consequences.”

The majority of the research supporting the use of ABA has been conducted in children; although there is some evidence of the effectiveness of ABA in adults (18 years and older), the evidence is less robust and definitive, warranting closer review.[2, 3]

Early Intensive Behavioral Intervention

Early intensive behavioral interventions incorporate principles of ABA but differ in methods and settings. There are two intensive, manualized ABA-based early intervention programs intended to improve the challenging behaviors specifically associated with ASD that include University of California, Los Angeles (UCLA/Lovaas and the Early Start Denver model).

SUMMARY

Applied Behavior Analysis (ABA) is applied in the assessment, treatment, and prevention of challenging behaviors and the promotion of new desired behaviors. This method of treatment is often used for Autism Spectrum Disorder (ASD). Individual states have mandated requirements for the assessment and treatment of ASD, which the policy criteria align with. Therefore, ABA may be considered medically necessary for the initiation and continuation of treatment for ASD when policy criteria are met. When policy criteria are not met, ABA for ASD is considered not medically necessary.

REFERENCES

1. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Arlington VA: American Psychiatric Press.
2. Bishop-Fitzpatrick L, Minshew NJ, Eack SM. A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of autism and developmental disorders.* 2013;43(3):687-94. PMID: 22825929
3. Wong C, Odom SL, Hume KA, et al. Evidence-Based Practices for Children, Youth, and Young Adults with Autism Spectrum Disorder: A Comprehensive Review. *Journal of autism and developmental disorders.* 2015;45(7):1951-66. PMID: 25578338

CODES

Codes	Number	Description
CPT	0362T	Behavior identification supporting assessment, each 15 minutes of technicians' time, face-to-face with a patient, requiring the following components: administration by the physician or other qualified health care professional who is on site; with the assistance of two or more technicians;

Codes	Number	Description
		for a patient who exhibits destructive behavior; completion in an environment that is customized to the patient's behavior.
	0373T	Adaptive behavior treatment with protocol modification, each 15 minutes of technicians' time, face-to-face with a patient, requiring the following components: administration by the physician or other qualified health care professional who is on site; with the assistance of two or more technicians; for a patient who exhibits destructive behavior; completion in an environment that is customized to the patient's behavior
	97151	Behavior identification assessment, administered by a physician or other qualified health care professional, each 15 minutes of the physician's or other qualified health care professional's time face-to-face with patient and/or guardian(s)/caregiver(s) administering assessments and discussing findings and recommendations, and non-face-to-face analyzing past data, scoring/interpreting the assessment, and preparing the report/treatment plan
	97152	Behavior identification-supporting assessment, administered by one technician under the direction of a physician or other qualified health care professional, face-to-face with the patient, each 15 minutes
	97153	Adaptive behavior treatment by protocol, administered by technician under the direction of a physician or other qualified health care professional, face-to-face with one patient, each 15 minutes
	97154	Group adaptive behavior treatment by protocol, administered by technician under the direction of a physician or other qualified health care professional, face-to-face with two or more patients, each 15 minutes
	97155	Adaptive behavior treatment with protocol modification, administered by physician or other qualified health care professional, which may include simultaneous direction of technician, face-to-face with one patient, each 15 minutes
	97156	Family adaptive behavior treatment guidance, administered by physician or other qualified health care professional (with or without the patient present), face-to-face with guardian(s)/caregiver(s), each 15 minutes
	97157	Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present), face-to-face with multiple sets of guardians/caregivers, each 15 minutes
	97158	Group adaptive behavior treatment with protocol modification, administered by physician or other qualified health care professional, face-to-face with multiple patients, each 15 minutes
HCPCS	None	

APPENDIX 1

Diagnostic and Statistical Manual of Mental Disorders, *5th Edition* (DSM-5)

Autism Spectrum Disorder, 299.00 (F84.0)

Diagnostic Criteria

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

APPENDIX 1

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted repetitive patterns of behavior (see Table 1).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 1).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

APPENDIX 1

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

With or without accompanying intellectual impairment

With or without accompanying language impairment

Associated with a known medical or genetic condition or environmental factor

Table 1. Severity levels for autism spectrum disorder

Severity level	Social communication	Restricted, repetitive behaviors
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communizations skills cause severe impairment sin functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behavior, difficulty coping with change or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical	Inflexibility of behavior causes significant interference with functioning in one or more contexts.

APPENDIX 1		
	or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with other fails, and whose attempts to make friends are odd and typically unsuccessful.	Difficulty switching between activities. Problems of organization and planning hamper independence.

Date of Origin: *January 2012*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 25

Eating Disorder Inpatient Treatment

Effective: November 1, 2022

Next Review: January 2023
Last Review: October 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Eating Disorder Inpatient (IP) is a 24-hour acute treatment setting that is licensed as a hospital by the appropriate agency and under the direct supervision of an attending psychiatrist or psychiatric extender.

MEDICAL POLICY CRITERIA

Note: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. An Inpatient Hospitalization (IP) admission for an Eating Disorder provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. - B.) are met:

   A. All of the following intensity of service criteria (1. – 12.) are met:

      1. The hospital or inpatient unit is licensed by the appropriate state agency.
      2. There is an expectation that the member's history and physical examination is completed within 24 hours of admission (unless completed within 72 hours prior to admission or if transferred from an acute inpatient level of care).

3. There is an expectation that drug screens and relevant lab tests (electrolytes, chemistry, CBC, thyroid and ECG, etc.) are completed upon admission and as clinically indicated and documented in the medical record.
4. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 24 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents medical monitoring and evaluation daily. The attending provider must be available 24 hour a day, 7 days per week.
5. There is an expectation that within 24 hours of admission, following a multidisciplinary assessment that includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
6. Treatment programing includes an expectation of at least one individual counseling session weekly or more as clinically indicated, which is documented in the clinical record.
7. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
8. Treatment programing is multidisciplinary and includes clinical services provided daily that comprehensively address the needs identified in the member's treatment plan. In addition, the program is operated with licensed clinical staff who are trained and experienced in the medical and psychiatric treatment of Eating Disorders.
9. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
10. On-site registered nursing care is available 24 hours a day, 7 days a week with full capabilities for all appropriate interventions in medical and behavioral health and emergencies that occur on the unit.
11. On-site, licensed clinical staff is available 24 hours a day, seven days a week adequate to supervise the member's medical and psychological needs.
12. There is an expectation that nutritional planning including target weight range and planned interventions by a registered dietitian is undertaken and documented in the medical record.

B. All of the following severity of illness criteria (1. - 2.) are met:
    1. All the following are met (a. –d.):
        a. The member has been given a severe Eating Disorder diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.
        b. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.
        c. The treatment is not primarily for the convenience of the provider or member (e.g., primarily for lack of housing options, respite care, or custodial needs).
        d. Treatment could not be safely provided at a lower level of care or no safe lower level of care is available.
    2. One or more of the following criteria must be met:
        a. The member presents with medical risks due to one or more the following:
            i. Heart Rate: <40 in Adults; <50 in Child/Adolescent
            ii. Blood Pressure: <90/60 mm Hg in Adults; <80/50 mm Hg in Child/Adolescent
            iii. Orthostatic Pulse Increase: (Lying to standing) Change of more than 20 beats per minute
            iv. Orthostatic Blood Pressure Decrease: (Lying to standing) Change of more than 10 mm Hg
        b. The member presents with one or more of the following abnormal labs resulting from disordered eating and require inpatient stabilization:
            i. Low serum glucose: < 60 mg/dl
            ii. Low Potassium (Hypokalemia): <3.2 mEq/L
            iii. Low Phosphorus (Hypophosphatemia): <2.5 mg/dL
            iv. Low Magnesium (Hypomagnesemia): <1.5 mg/dL
            v. Low Sodium (Hyponatremia): <135 mEq/L
        c. The member presents with medical conditions either secondary to or exacerbated by disordered eating such as: severe dehydration with corresponding lab findings, poor liver function, poor kidney function, cardiac abnormalities, uncontrolled or risky diabetes, etc.
        d. The member meets one of the following biometric criteria:
            i. A body mass index (BMI) less than 16 and requires re-feeding
            ii. BMI is greater than or equal to 16, AND there is evidence of one of the following:

a.) The member has been losing >2 lbs per week resulting in physiological abnormalities that require inpatient stabilization; or

b.) Weight loss associated with medical instability that is not primarily due to a general medical condition.

e. The individual's eating disorder symptoms require around the clock medical/nursing intervention for one or more of the following:

i. For issues of imminent risk of harm to self or others.

ii. There is a need to provide immediate interruption of food restriction, excessive exercise, binging/purging, and/or use of laxatives/diet pills/diuretics because acute medical complications are imminent without intervention.

iii. To avoid impending life-threatening complications due to a co-morbid medical condition (e.g., pregnancy, diabetes, etc.).

iv. Due to the severity of food restriction/malnutrition, medically managed re-feeding is indicated to mitigate risks of Refeeding Syndrome.

II. A continued stay in Inpatient Hospitalization (IP) for an Eating Disorder under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – D.) are met:

A. The individual continues to meet admission criteria (I.A. – B.).

B. There is evidence of active discharge planning.

C. Family participation (see Policy Guidelines):

1. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.

2. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within 48 hours of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.

D. One or more of the following criteria are met:

1. The active treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.

2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.

3. Member is experiencing complications arising from medications or other treatments (such as Electroconvulsive Therapy) with such severity that require further stabilization and 24-hour observation.
4. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Recent lab results
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation
  - MD Notes
  - Treatment Plan/Progress Reports
  - Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
2. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
3. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
4. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
5. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 9/26/2022]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 9/26/2022]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies®*, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	0114	R&B Private, Psychiatric
	0124	R&B Semi-Private, Psychiatric
	0134	R&B Multi-Bed, Psychiatric
	0144	R&B Deluxe Private, Psychiatric
	0154	R&B Ward, Psychiatric
	0204	ICU, Psychiatric

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 26

Eating Disorder Intensive Outpatient

Effective: November 1, 2022

Next Review: January 2023
Last Review: October 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Intensive Outpatient (IOP) is an outpatient program that is licensed as an appropriate facility/agency by the appropriate state agency and is provided under the supervision of a psychiatrist or psychiatric extender. Intensive Outpatient (IOP) is intended to provide treatment on an outpatient basis, does not include boarding/housing and is intended to provide treatment interventions in a structured setting, with patients returning to their home environments each day.

MEDICAL POLICY CRITERIA

Notes: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. An Intensive Outpatient Program (IOP) admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

   A. All of the following intensity of service criteria (1. – 9.) are met:

      1. If required by state statute, the facility is licensed by the appropriate state agency. If state license not required, facility is accredited.

2. There is an expectation that drug screens and relevant lab tests (electrolytes, chemistry, CBC, thyroid and ECG, etc.) are completed upon admission and as clinically indicated and are documented in the clinical record.
3. There is an expectation of evaluation by a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) when clinically necessary. The physician, or physician extender will continue to be available throughout the program as medically indicated for face-to-face evaluations.
4. There is an expectation that within 5 days of admission, following a multidisciplinary assessment which includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
5. Treatment programing includes documentation of at least one individual counseling session weekly or more as clinically indicated.
6. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
7. All treatment is supervised by licensed behavioral health practitioners.
8. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
9. There is an expectation that a multidisciplinary treatment program occurs 3 days per week and provides a minimum of 9 hours of weekly clinical services to comprehensively address the needs identified in the member's treatment plan. In addition, the program is operated with licensed clinical staff who are trained and experienced in the medical and psychiatric treatment of Eating Disorders.

B. All of the following severity of illness criteria (1. – 8.) are met:

1. The member has been given a severe Eating Disorder diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.
2. The member is able to actively participate in and comply with treatment in this level of care.
3. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.

4. Members reporting non-acute safety concerns can develop a safety plan and access crisis intervention so that a more intensive level of care can be avoided.
5. The member's family and/or support system is willing to engage in the treatment process through family therapy as appropriate.
6. The member is experiencing significant disruption in multiple areas of functioning due to disordered eating behaviors (e.g., work, school, social relationships, family relationships).
7. Lack of external supports alone is not sufficient for continued treatment at this level of care.
8. Treatment could not be safely provided at a lower level of care or safe lower level of care is not available.

II. A continued stay in an Intensive Outpatient Program (IOP) provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All the following (1. – 5.) must be met:

1. Member continues to meet admission criteria (I.A. –B.).
2. The member and family are involved to the best of their ability in the treatment and discharge planning process.
3. Continued stay is intended to provide active treatment and is not primarily to provide a safe and supportive environment.
4. Family participation (see Policy Guidelines):
    a. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
    b. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within five days of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.
5. There is evidence of active discharge planning.

B. One or more of the following criteria must be met:

1. The treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.
2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.

3. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

MULTIDISCIPLINARY TREATMENT PROGRAM

The intent of the standard for nine hours of weekly treatment program (groups, activities and psychotherapies) is that they are evidence-based and are explicitly focused on the alleviation of the current condition as opposed to providing general recreation activities, watching videos, etc. and other facility offerings that are not tied back directly to the treatment plan.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Recent lab results
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation
  - MD Notes
  - Treatment Plan/Progress Reports
  - Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
3. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
4. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
5. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31

7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 9/26/2022]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 9/26/2022]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies*®, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	0905	Intensive Outpatient Program, Psychiatric

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 27

Eating Disorder Partial Hospitalization

Effective: November 1, 2022

Next Review: January 2023
Last Review: October 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Partial Hospitalization (PHP) is an outpatient program that is provided under the supervision of an attending psychiatrist or psychiatric extender. Partial Hospitalization (PHP) is intended to provide treatment on an outpatient basis, does not include boarding/housing and is intended to provide treatment interventions in a structured setting, with patients returning to their home environments each day.

MEDICAL POLICY CRITERIA

Note: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. A Partial Hospitalization (PHP) outpatient program admission for an Eating Disorder provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All of the following intensity of service criteria (1. – 12.) are met:

1. If required by state statute, the facility is licensed by the appropriate state agency. If state license not required, facility is accredited.

2. There is an expectation that drug screens and relevant lab tests (electrolytes, chemistry, CBC, thyroid and ECG, etc.) are completed upon admission and as clinically indicated and are documented in the clinical record.
3. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 48 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents monitoring and evaluation as indicated, but no less than weekly.
4. There is an expectation that within 5 days of admission, following a multidisciplinary assessment that includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
5. Treatment programing includes an expectation of at least one individual counseling session weekly or more as clinically indicated, which is documented in the medical record.
6. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
7. All treatment is supervised by licensed behavioral health practitioners.
8. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
9. Treatment programing is multidisciplinary and occurs 5 days per week and provides 25 hours of weekly clinical services to comprehensively address the needs identified in the member's treatment plan. In addition, the program is operated with licensed clinical staff who are trained and experienced in the medical and psychiatric treatment of Eating Disorders.
10. When members are receiving boarding services, during non-program hours the member is allowed the opportunity to:
    a. Function independently.
    b. Develop and practice new recovery skills in the real world to prepare for community re-integration and sustained, community-based recovery.
11. There is an expectation that nutritional planning including target weight range and planned interventions by a registered dietitian is undertaken and documented in the medical record.

12. There is documentation of a safety plan including access for the member and/or family/support system to professional supports outside of program hours.

B. All of the following severity of illness criteria (1. – 2.) are met:

1. All the following are met (a. – h.):

a. The member has been given a severe Eating Disorder diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.

b. The member is able to actively participate in and comply with treatment at this level of care.

c. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.

d. Members reporting non-acute safety concerns can develop a safety plan and access crisis intervention so that a more intensive level of care can be avoided.

e. The member's family and/or support system are willing to participate in the treatment and discharge planning process as appropriate.

f. If member has comorbid medical issues, the issues can be safely managed in a partial hospitalization level of care.

g. Lack of external supports alone is not sufficient for continued treatment at this level of care.

h. Treatment could not be safely provided at a lower level of care or no safe lower level of care is available.

2. One or more of the following are met:

a. The member is demonstrating significant impairments in functioning due to an Eating Disorder not requiring 24-hour monitoring, as evidenced by both (i. – ii.) of the following:

i. The patient's symptoms or behavioral manifestations are of such severity that there is significant interference with one or more of the following:

a.) Family functioning.

b.) Vocational functioning.

c.) Educational functioning.

d.) Other age-appropriate social role functions.

ii. The member is unable to employ the appropriate coping skills outside of a structured setting which puts member at risk of the condition worsening.

b. The member has recently demonstrated non-lethal self-injurious behavior (superficial cutting) or made serious threats of self-harm or harm to others

but does not require 24-hour monitoring.

c. The member's eating disorder is interfering with their ability to manage a serious medical condition which, left unmanaged, could be life-threatening.

II. A continued stay in a Partial Hospitalization (PHP) outpatient program for an Eating Disorder provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All the following (1. – 4.) must be met:

1. Member continues to meet admission criteria (I.A. – B.)
2. The member continues to demonstrate motivation for change, interest in and ability to actively engage in their behavioral health treatment, as evidenced by active participation in groups, cooperation with treatment plan, working on assignments, actively developing discharge plan, and other markers of treatment engagement. If member is not engaged, there are documented interventions by the treatment team to address.
3. Family participation (see Policy Guidelines):
   a. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
   b. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within 72 hours of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.
4. There is evidence of active discharge planning.

B. One or more of the following criteria must be met:

1. The treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.
2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.
3. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

WEEKLY TREATMENT PROGRAM

The intent of the standard for twenty-five hours of weekly treatment program (groups, activities and psychotherapies) is that they are evidence-based and are explicitly focused on the alleviation of the current condition as opposed to providing general recreation activities, watching videos, etc. and other facility offerings that are not tied back directly to the treatment plan.

For child and adolescent programs, accredited schooling comprises a portion of the 25 hours per week.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Recent lab results
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation
  - MD Notes
  - Treatment Plan/Progress Reports
  - Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
4. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
5. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 9/26/2022]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 9/26/2022]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies*®, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	0912	Partial Hospitalization, Low Intensity
	0913	Partial Hospitalization, High Intensity

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 28

Eating Disorder Residential Treatment

Effective: November 1, 2022

Next Review: January 2023
Last Review: October 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Residential treatment (RTC) is a 24-hour sub-acute treatment setting that is licensed as a residential treatment center by the appropriate agency to provide residential treatment and is under 24-hour care with an attending psychiatrist or psychiatric extender available for consultation 24/7.

MEDICAL POLICY CRITERIA

Notes: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. An Eating Disorder Residential Treatment (RTC) program admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

   A. All of the following intensity of service criteria (1. – 12.) are met:

      1. The facility is licensed by the appropriate state agency.

      2. There is an expectation that the member's history and physical examination is completed within 48 hours of admission (unless completed within 72 hours

prior to admission or if the member is transferred from an acute inpatient level of care).

3. There is expectation that drug screens and relevant lab tests (electrolytes, chemistry, CBC, thyroid and ECG, etc.) are completed upon admission and as clinically indicated and are documented in the medical record.
4. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 48 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents monitoring and evaluation at least weekly. The attending provider must be available 24 hours per day, 7 days per week.
5. There is an expectation that within 72 hours of admission, following a multidisciplinary assessment that includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
6. Treatment programming includes an expectation of at least one individual counseling session per week, or more as clinically indicated, which is documented in the medical record.
7. There is an expectation that evaluations of the member by a licensed behavioral health provider are performed daily and are documented in the medical record.
8. Treatment programing is multidisciplinary and includes clinical services provided daily that comprehensively address the needs identified in the member's treatment plan. In addition, the program is operated with licensed clinical staff who are trained and experienced in the medical and psychiatric treatment of Eating Disorders.
9. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
10. On-site registered nursing care available 24 hours a day, 7 days a week with full capabilities for all appropriate interventions in medical and behavioral health and emergencies that occur on the unit.
11. On-site, licensed clinical staff is available 24 hours a day, seven days a week adequate to supervise the member's medical and psychological needs.

12. There is an expectation that nutritional planning including target weight range and planned interventions by a registered dietitian is undertaken and documented in the medical record.

B. All of the following severity of illness criteria (1. – 2.) are met:

1. All the following are met (a. – g.):

a. The member has been given a severe Eating Disorder diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.

b. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.

c. The treatment is not primarily for the convenience of the provider or member (e.g. lack of housing options, respite care or custodial needs)

d. The member has significant functional impairment in more than one area that requires 24-hour monitoring and intervention: Home, School/Work, Health/Medical, maintaining safe behaviors towards self or others, inability to maintain healthy eating and exercise behaviors despite active, recent attempts to self-manage in a less restrictive setting.

e. Member is able to function independently and actively participate in group and individual therapy.

f. Treatment could not be effectively provided at a lower level of care (supported by clinical documentation) OR The member's home environment is not conducive to treatment/recovery, such that treatment at a lower level of care is unlikely to be successful OR no safe lower level of care is available.

g. The family members and/or support system are committed to change through participation in the treatment process as appropriate.

2. One or more of the following:

a. Member requires 24-hour structure and supervision at each meal to prevent disordered eating patterns (food restriction, binging/purging, etc.) that member's family or support system are unable to provide at a less restrictive level of care.

b. Member requires 24-hour observation to interrupt/avoid compensatory behaviors such as: excessive exercise, food restriction, purging, taking laxatives/diuretics/diet pills that would otherwise lead to imminent medical risks, complications or deterioration of a co-morbid medical condition.

c. In addition to a primary eating disorder requiring active treatment, member presents with a co-occurring psychiatric disorder requiring active treatment or risk of harm that requires 24-hour supervision.

II. Continued stay in an Eating Disorder Residential Treatment (RTC) program provided under the supervision of an attending psychiatrist may be indicated when all of the following are met (A. – F.):

A. The member continues to meet admission criteria (I.A. – B.).

B. There is reasonable expectation that continued treatment provided at this level of care will produce improvement that is sustainable after discharge.

C. Family participation (see Policy Guidelines):

1. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.

2. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within 72 hours of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.

D. The individual and family are involved to the best of their ability in the treatment and discharge planning process.

E. The member continues to demonstrate motivation for change, interest in and ability to actively engage in their behavioral health treatment, as evidenced by active participation in groups, cooperation with treatment plan, working on assignments actively developing discharge plan and other markers of treatment engagement. If member is not engaged, there are documented interventions by the treatment team to address.

F. There is evidence of active discharge planning.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

DAYTIME OUTINGS

For purposes of discharge planning and when clinically indicated, members may participate in daytime outings, during non-program hours, of up to eight hours per outing, with family, guardians, authorized representatives or other supportive individuals, to assess current conflicts, skills development and ability to tolerate a return to his/her living environment and other issues relevant to the unique member.

CUSTODIAL CARE

The following definition of custodial care by the Centers for Medicare & Medicaid Services (CMS) is applicable in support of the policy criteria:[11]

> Custodial care serves to assist an individual in the activities of daily living, such as assistance in walking, getting in and out of bed, bathing, dressing, feeding, and using

the toilet, preparation of special diets, and supervision of medication that usually can be self-administered. Custodial care essentially is personal care that does not require the continuing attention of trained medical or paramedical personnel. In determining whether a person is receiving custodial care, [consider] the level of care and medical supervision required and furnished. [The decision is not based] on diagnosis, type of condition, degree of functional limitation, or rehabilitation potential.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Recent lab results
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation
  - MD Notes
  - Treatment Plan/Progress Reports
  - Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
4. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
5. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.

2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 9/26/2022]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 9/26/2022]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 9/26/2022]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 9/26/2022]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies®*, 2013, pp.
11. Medicare Benefit Policy Manual, Chapter 16 - General Exclusions From Coverage, §110 - Custodial Care.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	1001	Residential Treatment, Psychiatric

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 29

Psychiatric Inpatient Hospitalization

Effective: April 1, 2023

Next Review: January 2024
Last Review: February 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Inpatient Psychiatric Hospitalization is a 24-hour acute treatment setting occurring on a locked unit that is licensed as a hospital by the appropriate agency and under the direct supervision of an attending psychiatrist or psychiatric extender.

MEDICAL POLICY CRITERIA

Notes: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. An Inpatient Psychiatric Hospitalization (IP) admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

   A. All of the following intensity of service criteria (1. – 11.) are met:

      1. The hospital or inpatient unit is licensed by the appropriate state agency.

      2. There is an expectation that the member's history and physical examination is completed within 24 hours of admission (unless completed within 72 hours prior to admission or if transferred from an acute inpatient level of care).

3. There is an expectation that drug screens and relevant lab tests are completed upon admission and as clinically indicated and are documented in the medical record.
4. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 24 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents medical monitoring and evaluation daily. The attending provider must be available 24 hour a day, 7 days per week.
5. There is an expectation that within 24 hours of admission, following a multidisciplinary assessment that includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, subjects such as identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, potential need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care, and other issues that affect the likelihood of successful community tenure.
6. Treatment programing includes an expectation of at least one individual counseling session per week, or more as clinically indicated, which is documented in the medical record.
7. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
8. Treatment programing is multidisciplinary and includes clinical services provided daily that comprehensively address the needs identified in the member's treatment plan.
9. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
10. On-site registered nursing care is available 24 hours a day, 7 days a week with full capabilities for all appropriate interventions in medical and behavioral health and emergencies that occur on the unit.
11. On-site, licensed clinical staff is available 24 hours a day, 7 days a week adequate to supervise the member's medical and psychological needs.

B. All of the following severity of illness criteria (1. – 2.) are met:

1. All the following (a. – d.) are met:
    a. The member has been given a severe mental health diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.

b. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.

c. The treatment is not primarily for the convenience of the provider or member (e.g., primarily for lack of housing options, respite care, custodial needs or extended discharge planning).

d. Treatment could not be safely provided at a lower level of care or no safe lower level of care is available.

2. One or more of the following must be met:

a. There is significant evidence that member is an imminent risk of harm to self or to others due to one or more of the following reasons:

i. The member has made a recent and serious attempt to substantially harm self or someone else in a way that was intended to be deadly.

ii. The member is verbalizing intent and plan to harm self or someone else in a way that would either be deadly or cause serious bodily harm.

iii. Recent self-injurious behaviors that are substantial enough to require 24-hour observation and safety planning (example: Cutting self substantially enough to require sutures).

iv. Recent violent, impulsive, and/or agitated behavior that cannot safely be controlled outside of 24-hour monitoring and intervention to prevent serious harm to self or others.

b. The member is experiencing severe deterioration in their ability to care for themself due to the severity of their psychiatric condition. Examples of this level of deterioration are:

i. The member is not taking care of basic tasks such as eating, drinking, caring for hygiene or taking prescribed psychiatric medications which contributes to deterioration.

ii. The member is experiencing a recent onset or exacerbation of psychotic symptoms that are resulting in significant deterioration of functioning that can only be safely managed with 24-hour observation and treatment. (Examples include: delusional thinking with limited to no awareness of reality, auditory and/or visual hallucinations, severe paranoia).

c. Member has a comorbid medical condition in addition to active psychiatric symptoms and requires the resources of an inpatient hospital for safe and appropriate treatment.

II. Continued stay in an Inpatient Psychiatric Hospitalization (IP) provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – D.) are met:

A. The individual continues to meet admission criteria (I.A. – B.).

B. There is evidence of active discharge planning.

C. Family participation (see Policy Guidelines):

1. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
2. For children/adolescents: Family treatment will be provided as part of the treatment plan. If family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within 48 hours of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.

D. One or more of the following criteria must be met:

1. The active treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.
2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.
3. Member is experiencing complications arising from medications or other treatments (such as Electroconvulsive Therapy) with such severity that require further stabilization and 24-hour observation.
4. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- o Pre-Authorization Request Form
- o Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)

- Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)

o Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

o Supporting clinical documentation, including:
- Recent psychiatric evaluation
- MD Notes
- Treatment Plan/Progress Reports
- Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
4. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
5. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32
8. Intensive In-Home Family Intervention, Behavioral Health, Policy No. 34

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 01/30/23]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 01/30/2023]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 01/30/2023]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015.

[cited 01/30/2023]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies*®, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	0114	R&B Private, Psychiatric
	0124	R&B Semi-Private, Psychiatric
	0134	R&B Multi-Bed, Psychiatric
	0144	R&B Deluxe Private, Psychiatric
	0154	R&B Ward, Psychiatric
	0204	ICU, Psychiatric

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 30

Psychiatric Intensive Outpatient

Effective: April 1, 2023

Next Review: January 2024
Last Review: February 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Intensive Outpatient (IOP) is an outpatient program that is licensed as a facility/agency by the appropriate state agency and is provided under the supervision of a psychiatrist or psychiatric extender. Intensive Outpatient (IOP) is intended to provide treatment on an outpatient basis, does not include boarding/housing and is intended to provide treatment interventions in a structured setting, with patients returning to their home environments each day.

MEDICAL POLICY CRITERIA

Note: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. An Intensive Outpatient Program (IOP) admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All of the following intensity of service criteria (1. – 11.) are met:

1. If required by state statute, the facility is licensed by the appropriate state agency. If licensure is not required by state, facility is accredited.

2. There is an expectation that drug screens and relevant lab tests are completed upon admission and as clinically indicated and are documented in the clinical record.
3. There is an expectation of evaluation by a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) when clinically necessary. The physician, or physician extender will continue to be available throughout the program as medically indicated for face-to-face evaluations.
4. There is an expectation that within 5 days of admission, following a multidisciplinary assessment which includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
5. Treatment programming includes documentation of at least one individual counseling session per week or more as clinically indicated.
6. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
7. All treatment is supervised by licensed behavioral health practitioners.
8. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
9. There is an expectation that a multidisciplinary treatment program provides a minimum of 9 hours of weekly clinical services for adults or 6 hours for adolescents to comprehensively address the needs identified in the member's treatment plan (see Policy Guidelines).
10. When members are receiving boarding services, during non-program hours the member is allowed the opportunity to:
    a. Function independently; and
    b. Develop and practice new recovery skills in the real world to prepare for community re-integration and sustained, community-based recovery.
11. There is documentation of a safety plan including access for the member and/or family/support system to professional supports outside of program hours.

B. All of the following severity of illness criteria (1. – 8.) are met:

1. The member has been given a severe mental health diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.
2. The member is able to actively participate in and comply with treatment in this level of care.
3. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.
4. Members reporting non-acute safety concerns can develop a safety plan and access crisis intervention so that a more intensive level of care can be avoided.
5. The member's family and/or support system are willing to participate in the treatment process as appropriate.
6. The member is experiencing significant disruption in multiple areas of functioning due to psychiatric condition (e.g. work, school, social relationships, family relationships).
7. Lack of external supports alone is not sufficient for continued treatment at this level of care.
8. Treatment could not be safely provided at a lower level of care or safe lower level of care is not available.

II. Continued stay in an Intensive Outpatient Program (IOP) provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All the following must be met (1. – 5.):

1. Member continues to meet admission criteria (I.A. – B.)
2. The member and family are involved to the best of their ability in the treatment and discharge planning process.
3. Continued stay is intended to provide active treatment and is not primarily to provide a safe and supportive environment.
4. Family participation (see Policy Guidelines):
    a. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
    b. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within five days of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly or more often if clinically indicated.
5. There is evidence of active discharge planning.

B. One or more of the following must be met:

1. The treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.
2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.
3. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

MULTIDISCIPLINARY TREATMENT PROGRAM

The intent of the standard for hours (nine for adults and six for adolescents) of weekly treatment program (groups, activities and psychotherapies) is that they are evidence-based and are explicitly focused on the alleviation of the current condition as opposed to providing general recreation activities, watching videos, etc. and other facility offerings that are not tied back directly to the treatment plan.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Request for Extension/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation

- MD Notes
- Treatment Plan/Progress Reports
- Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
4. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
5. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
6. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32
8. Intensive In-Home Family Intervention, Behavioral Health, Policy No. 34

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 01/30/23]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 01/30/2023]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 01/30/2023]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 01/30/2023]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies*®, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Code	0905	Intensive Outpatient Program, Psychiatric

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 31

Psychiatric Partial Hospitalization

Effective: April 1, 2023

Next Review: January 2024
Last Review: February 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Partial Hospitalization (PHP) is an outpatient program that is provided under the supervision of an attending psychiatrist or psychiatric extender. Partial Hospitalization (PHP) is intended to provide treatment on an outpatient basis, does not include boarding/housing and is intended to provide treatment interventions in a structured setting, with patients returning to their home environments each day.

MEDICAL POLICY CRITERIA

Note: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. A Partial Hospitalization (PHP) outpatient program admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All of the following intensity of service criteria (1. - 11.) are met:

1. If required by state statute, the facility is licensed by the appropriate state agency. If state license is not required, facility is accredited.

2. There is an expectation that drug screens and relevant lab tests are completed upon admission and as clinically indicated and are documented in the medical record.
3. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 48 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents monitoring and evaluation as indicated, but no less than weekly.
4. There is an expectation that within 5 days of admission, following a multidisciplinary assessment which includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
5. Treatment programming includes an expectation of at least one individual counseling session weekly, or more as clinically indicated, which is documented in the medical record.
6. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
7. All treatment is supervised by licensed behavioral health practitioners.
8. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
9. Treatment programing is multidisciplinary and includes 20 hours of clinical services per week to comprehensively address the needs identified in the member's treatment plan.
10. When a member receives boarding services, during non-program hours the member is supported in and allowed the opportunity to:
    a. Function independently.
    b. Develop and practice new recovery skills in the real world to prepare for community re-integration and sustained, community-based recovery.
11. There is documentation of a safety plan including access for the member and/or family or other support system to professional supports outside of program hours.

B. All of the following severity of illness criteria (1. – 2.) are met:

1. All the following (a. – h.) must be met:
    a. The member has been given a severe mental health diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.
    b. The member is able to actively participate in and comply with treatment at this level of care.
    c. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.
    d. Members reporting non-acute safety concerns can develop a safety plan and access crisis intervention so that a more intensive level of care can be avoided.
    e. The member's family and/or support system are willing to participate in the treatment process and discharge planning as appropriate.
    f. If member has comorbid medical issues, they can be safely managed in a partial hospital level of care.
    g. Lack of external supports alone is not sufficient for continued treatment at this level of care.
    h. Treatment could not be safely provided at a lower level of care or no safe lower level of care is available.
2. One or more of the following must be met:
    a. The member is demonstrating significant impairments in functioning due to a psychiatric disorder not requiring 24-hour monitoring, as evidenced by both of the following (i. – ii.):
        i. The patient's symptoms or behavioral manifestations are of such severity that there is significant interference with one or more of the following:
            a.) Family functioning.
            b.) Vocational functioning.
            c.) Educational functioning.
            d.) Other age appropriate social role functions.
        ii. The member is unable to employ the appropriate coping skills outside of a structured setting which puts member at risk of the condition worsening.
    b. The member has recently demonstrated non-lethal self-injurious behavior (example: superficial cutting) or made serious threats of self-harm or harm to others but does not require 24-hour monitoring.
    c. The member's psychiatric condition is interfering with their ability to manage a serious medical condition which, left unmanaged, could be life-threatening.

II. A continued stay in a Partial Hospitalization (PHP) outpatient program provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All the following (1. – 4.) are met:

1. Member continues to meet admission criteria (I.A. - B.).
2. The member continues to demonstrate motivation for change, interest in and ability to actively engage in their behavioral health treatment, as evidenced by active participation in groups, cooperation with treatment plan, working on assignments, actively developing discharge plan and other markers of treatment engagement. If member is not engaged, there are documented interventions by the treatment team to address.
3. Family participation (see Policy Guidelines):
    a. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
    b. For children/adolescents: Family treatment will be provided as part of the treatment plan. If Family treatment is not rendered, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within five days of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care. Family sessions will occur at least weekly.
4. There is evidence of active discharge planning.

B. One or more of the following criteria must be met:

1. The treatment being provided to the member is demonstrating meaningful improvements in the member's clinical status and appears to be helping the member reach a level of stability that step-down to a lower level of care will be possible.
2. If the active treatment being provided to member does not appear to result in clinical improvements (or the member's condition has deteriorated further), the treatment team is actively re-evaluating the treatment plan and adjusting as needed to produce positive outcomes.
3. The member has developed new symptoms and/or behaviors that require this intensity of service for safe and effective treatment.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

MULTIDISCIPLINARY TREATMENT PROGRAM

The intent of the standard for 20 hours of weekly treatment program (groups, activities and psychotherapies) is that they are evidence-based and are explicitly focused on the alleviation of the current condition as opposed to providing general recreation activities, watching videos, etc. and other facility offerings that are not tied back directly to the treatment plan.

For children and adolescent programs, accredited schooling comprises a portion of the 20 hours of programming.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Pre-Authorization Request Form
- Supporting clinical documentation, including:
  - Initial Psychiatric Evaluation/Intake Assessment
  - Nursing Assessment/ History & Physical (if available)
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Continued Stay/Concurrent Review:

- Supporting clinical documentation, including:
  - Most recent psychiatric evaluation
  - MD Notes
  - Individualized Treatment Plan/Progress Reports

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
4. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
5. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
6. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
7. Psychiatric Residential Treatment, Behavioral Health, Policy No. 32
8. Intensive In-Home Family Intervention, Behavioral Health, Policy No. 34

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 01/30/23]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
2. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 01/30/2023]. 'Available from:'

https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
3. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 01/30/2023]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
4. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
5. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
6. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
7. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
8. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 01/30/2023]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
9. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
10. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies®*, 2013, pp.

CODES

Codes	Number	Description
CPT	None	
HCPCS	None	
Revenue Codes	0912	Partial Hospitalization, Low Intensity
	0913	Partial Hospitalization, High Intensity

Date of Origin: *January 2019*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Behavioral Health, Policy No. 32

Psychiatric Residential Treatment

Effective: April 1, 2023

Next Review: January 2024
Last Review: February 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Residential treatment (RTC) is a 24-hour sub-acute treatment setting that is licensed as a residential treatment center by the appropriate agency to provide residential treatment and is under 24-hour care with an attending psychiatrist or psychiatric extender available for consultation 24/7.

MEDICAL POLICY CRITERIA

Note: Submission of a behavioral health intake form is required for initial intake, concurrent review, stepdown request to a lower level of care, and discharge confirmation.

I. Admission to a Psychiatric Residential Treatment (RTC) program admission provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – B.) are met:

A. All of the following intensity of service criteria (1. – 11.) are met:

1. The facility is licensed by the appropriate state agency.
2. There is an expectation that the member's history and physical examination is completed within 48 hours of admission (unless completed within 72 hours

prior to admission or if the member is transferred from an acute inpatient level of care).

3. There is an expectation that drug screens and relevant lab tests are completed upon admission and as clinically indicated and are documented in the medical record.
4. The attending provider is a psychiatrist, a licensed psychiatric nurse practitioner, or physician assistant with formal practice agreement with a psychiatrist (when permitted by state laws) who is responsible for diagnostic evaluation within 48 hours of admission. After the initial diagnostic evaluation, there is an expectation that the physician, or physician extender provides and documents monitoring and evaluation at least weekly. The attending provider must be available 24 hours per day, 7 days per week.
5. There is an expectation that within 72 hours of admission, following a multidisciplinary assessment that includes input from recent treating providers, an individualized treatment plan (ITP) is developed and documented in the medical record. The ITP should use evidence-based concepts, where applicable, and be amended as needed for changes in the individual's clinical condition. The ITP should include, but is not limited to, identification of key precipitants to current episode of treatment, assessment of psychosocial supports available after discharge, availability of aftercare services in member's home geographic area, need for supportive living placement to continue recovery, need for services for comorbid medical or substance use conditions, contact with aftercare providers to facilitate an effective transition to lower levels of care and other issues that affect the likelihood of successful community tenure.
6. Treatment programming includes an expectation of at least one individual counseling session per week, or more as clinically indicated, which is documented in the medical record.
7. There is an expectation that evaluations of the member are performed daily by a licensed behavioral health provider and are documented in the medical record.
8. Treatment programing is multidisciplinary and includes clinical services provided daily that comprehensively address the needs identified in the member's treatment plan.
9. Mental health and medical services are available on-site (or off-site by arrangement) 24 hours per day, 7 days per week.
10. On-site nursing (e.g., LPNs) is available a minimum of 8 hours a day, 5 days a week. RNs are available 24 hours a day and respond to significant clinical events within one hour.
11. On-site, licensed clinical staff is available 24 hours a day, 7 days a week adequate to supervise the member's medical and psychological needs.

B. All of the following criteria (1. – 7.) are met:

1. The member has been given a severe mental health diagnosis according to the most recent DSM criteria which will be the primary focus of daily active treatment.
2. The member is able to function independently and actively participate in group and individual therapy.
3. There is reasonable expectation that treatment at this level of care will meaningfully impact the presenting symptoms/behaviors leading to the admission.
4. The treatment is not primarily for the convenience of the provider or member (e.g. primarily for lack of housing options, respite care or custodial needs).
5. The member has significant functional impairment in more than one area that requires 24-hour monitoring and intervention: Home, School/Work, Health/Medical, maintaining safe behaviors towards self or others.
6. Treatment could not be effectively provided at a lower level of care (supported by clinical documentation) OR The member's home environment is not conducive to treatment/recovery, such that treatment at a lower level of care is unlikely to be successful OR no safe lower level of care is available.
7. The family members and/or support system are committed to change through participation in the treatment process as appropriate.

II. Continued stay in a Psychiatric Residential Treatment (RTC) program provided under the supervision of an attending psychiatrist or psychiatric extender may be indicated when all of the following (A. – F.) are met:

A. Member continues to meet admission criteria (I.A. – B.)

B. There is reasonable expectation that continued treatment provided at this level of care will produce improvement that is sustainable after discharge.

C. The individual and family are involved to the best of their ability in the treatment and discharge planning process.

D. The member continues to demonstrate motivation for change, interest in and ability to actively engage in their behavioral health treatment, as evidenced by active participation in groups, cooperation with treatment plan, working on assignments actively developing discharge plan and other markers of treatment engagement. If member is not engaged, there are documented interventions by the treatment team to address.

E. Family participation (see Policy Guidelines):

1. For Adults: Family treatment is encouraged when clinically appropriate. Family treatment is available to be provided at an appropriate frequency when clinically warranted.
2. For children/adolescents: Family treatment is being provided at least weekly or more often if clinically indicated. If Family treatment is not provided, the facility/provider specifically lists the contraindications to Family Therapy. The family/support system assessment will be completed within 72 hours of admission with the expectation that family is involved in treatment decisions and discharge planning throughout the course of care.

F. There is evidence of active discharge planning.

POLICY GUIDELINES

FAMILY PARTICIPATION

Family participation may be conducted via telephonic sessions when there is a significant geographic or other limitation.

Custodial Care

The following definition of custodial care by the Centers for Medicare & Medicaid Services (CMS) is applicable in support of the policy criteria:[1]

> Custodial care serves to assist an individual in the activities of daily living, such as assistance in walking, getting in and out of bed, bathing, dressing, feeding, and using the toilet, preparation of special diets, and supervision of medication that usually can be self-administered. Custodial care essentially is personal care that does not require the continuing attention of trained medical or paramedical personnel. In determining whether a person is receiving custodial care, [consider] the level of care and medical supervision required and furnished. [The decision is not based] on diagnosis, type of condition, degree of functional limitation, or rehabilitation potential.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Initial Request:

- Prior Authorization Form
- Initial Psychiatric Evaluation/Intake Assessment
- Other supporting clinical documentation, such as:
  - Nursing Assessment/ History & Physical (if available)
  - Any additional supporting clinical evidence, if available (example: letters from outpatient providers supporting this level of care)
- Preliminary Individualized Treatment Plan

Continued Stay/Concurrent Review:

- Supporting clinical documentation, including:
  - Recent psychiatric evaluation
  - MD Notes
  - Treatment Plan/Progress Reports
  - Any other supporting clinical evidence

CROSS REFERENCES

1. Eating Disorder Inpatient Treatment, Behavioral Health, Policy No. 25
2. Eating Disorder Intensive Outpatient, Behavioral Health, Policy No. 26
3. Eating Disorder Partial Hospitalization, Behavioral Health, Policy No. 27
4. Eating Disorder Residential Treatment, Behavioral Health, Policy No. 28
5. Psychiatric Inpatient Hospitalization, Behavioral Health, Policy No. 29
6. Psychiatric Intensive Outpatient, Behavioral Health, Policy No. 30
7. Psychiatric Partial Hospitalization, Behavioral Health, Policy No. 31
8. Intensive In-Home Family Intervention, Behavioral Health, Policy No. 34

REFERENCES

1. Medicare Benefit Policy Manual, Chapter 16 - General Exclusions From Coverage, §110 - Custodial Care.
2. American Academy of Child and Adolescent Psychiatry. Principles of Care for Treatment of Children and Adolescents with Mental Illnesses in Residential Treatment Centers. 2010. [cited 01/30/23]. 'Available from:' https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/principles_of_care_for_children_in_residential_treatment_centers.pdf.
3. American Academy of Child and Adolescent Psychiatry, Practice Parameters, Washington, DC. [cited 01/30/2023]. 'Available from:' https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx.
4. American Psychiatric Association Practice Guidelines, American Psychiatric Association Publishing, Arlington, VA, 2003-2018. [cited 01/30/2023]. 'Available from:' http://psychiatryonline.org/guidelines.aspx.
5. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5), American Psychiatric Publishing, Arlington, VA, May 2013*, pp.
6. Association for Ambulatory Behavioral Healthcare: Partial hospitalization programs [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
7. Association for Ambulatory Behavioral Healthcare: Intensive Outpatient Program. [cited 01/30/2023]. 'Available from:' https://aabh.org/standards-guidelines/.
8. *Medicare Benefit Policy, Outpatient Hospital Psychiatric Services, Manual, Chapter 6, Section 70 - Hospital Services Covered Under Part B, A3-3112.7, HO-230.5 (Rev. 157, 06-08-12)*, pp.
9. Mental Health America, Position Statement 44: Residential Treatment for Children and Adolescents with Serious Mental Health and Substance Use Conditions, June 2015. [cited 01/30/2023]. 'Available from:' https://www.mhanational.org/issues/position-statement-44-residential-treatment-children-and-adolescents-serious-mental-health.
10. Harrington BC, Jimerson M, Haxton C, et al. Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. *Am Fam Physician.* 2015;91(1):46-52. PMID: 25591200
11. Mee-Lee D SG, Fishman MJ, Gasfriend DR, Miller MM, eds. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, 3rd ed. Carson City, NV: The Shange Companies®*, 2013, pp.

CODES

Codes	Number	Description
CPT	None	

Codes	Number	Description
HCPCS	None	
Revenue Code	1001	Residential Treatment, Psychiatric

Date of Origin: *January 2019*

Regence

Regence BlueShield serves select counties in the state of Washington and is an Independent Licensee of the Blue Cross and Blue Shield Association

Pre-authorization Request Form
Behavioral Health
Fax: 1 (888) 496-1540
Mail to: PO Box 1271, WW5-53
Portland, OR 97207-1271

Instructions: This form should be completed and filled out by the requesting provider. Prior to completing this form, please confirm the patient's benefits, eligibility and whether pre-authorization is required.

Is this for a Medicare Preservice Benefit Organization Determination Request? ☐ Yes ☐ No

Expedited request. I attest that this request meets the definition indicated below by checking the expedited request box. ☐ Fax to 1 (855) 240-6498.

Expedited is defined as: When the member or his/her provider believes that waiting for a decision within the standard timeframe could place the member's life, health or ability to regain maximum function in serious jeopardy.

SECTION 1 – PATIENT INFORMATION

Patient Name (Last)	First	MI	Patient's Phone #

Patient's Regence Member ID #	Group #	Date of Birth

SECTION 2 – PROVIDER INFORMATION

Please check one: ☐ Requesting/Prescribing Provider ☐ Rendering/Treating Provider

Provider Name		Tax ID #	
NPI #	Office Phone #	Confidential Voice Mail ☐ Yes ☐ No	Fax #
Mailing Address		City	State / ZIP Code
Provider Specialty		Email Address	

Who should we contact if we require additional information?

Name	Phone # Ext.	Confidential Voice Mail ☐ Yes ☐ No	Fax #

If a physician reviewer needs a peer to peer discussion before a determination, please provide the treating provider's direct phone number and availability for the next 3 to 5 days.

Phone #: Ext:	Date: Time:	Date: Time:	Date: Time:

Facility Name		Tax ID #	NPI #
Mailing Address		Fax #	
City / State / ZIP Code		Phone # Ext.	Confidential Voice Mail ☐ Yes ☐ No
Facility Type: ☐ Freestanding ☐ Acute		Email Address	

SECTION 3 – PREAUTHORIZATION REQUEST

Date of Services/Anticipated Admission _____

Substance Use Disorders: ASAM Level of Care Requested: ☐ 2.0/2.1 ☐ 2.5 ☐ 3.5 ☐ 3.7 ☐ 4.0

Mental Health Care Requested:

☐ Inpatient ☐ Residential Treatment ☐ Partial Hospitalization
☐ Intensive Outpatient ☐ Other, please specify _____

Note: This form does not serve as a notification of admission. Please reference our provider website for instructions about how to notify us of an admission.

Please provide all diagnosis, CPT or HCPCS codes and their descriptions.

Diagnosis code(s) and description(s)	CPT or HCPCS code(s) and description(s)
Primary:	
Second:	
Third:	

SECTION 4 – DOCUMENTATION SUBMISSION

Please submit the following documentation, as appropriate for this request:

Psychiatric or substance use disorder evaluation or intake assessment including:

- Family history
- Medical, psychiatric and substance use history
- Mental status exam
- Personal and social history (psychosocial)
- History of current complaint/clinical status
- Member's current complaint/clinical status

History and physical/nursing assessment (if available) including:

- Current vitals
- Current medical concerns/risks

Substance use disorders only:

- Clinical Institute Withdrawal Assessment (CIWA) or
- Clinical Opiate Withdrawal Scale (COWS) score or
- Description of active withdrawal symptoms

Any other supporting documents you would like considered, such as letters from outpatient providers, etc.

SAMPLE COVER LETTER

CHILD was formally evaluated on DATE at SITE OF EXAM by PROVIDER. CHILD demonstrated impairments in social interaction, social communication and atypical behavior consistent with an Autism Spectrum Disorder. CHILD's behaviors and/or impairments are having an adverse impact on development and/or communication as documented on DATE by the presence of severe behaviors and/or functional impairments that interfere with CHILD's ability to participate adequately in their home, school or community environments and/or the health and safety of CHILD or others are at significant safety risk. Please see the attached report/COE report/treatment plan and DSM-IV-TR checklist for details.

Applied behavioral analysis services are recommended given the adverse impact of CHILD's behaviors and/or core impairments. CHOOSE HERE [Less intensive behavioral treatment or other therapy has been tried and not been successful, or it is not accessible, or there is no equally effective alternative available for reducing severe interfering or disruptive behaviors, increasing pro-social behaviors, or achieving desired behaviors]; and Applied Behavioral analysis services are reasonably expected to result in a measureable improvement in CHILD's skills and behaviors.

Effective November 21, 2016

Uniform Medical Plan ABA Therapy Clinical Considerations

ABA Therapy hours of service should reflect the number of and type of behavioral targets and key functional skills to be addressed and include a clinical summary justifying the hours requested for each behavioral target. The total hours of ABA Therapy requested should be comprised of fewer than 40 hours per week.

Any requests for greater than 40 hours per week should show documentation as to why more than 40 hours of therapy is medically necessary.

ABA therapy documentation should show the following:

- The client‘s response to ABA therapy services and progress being made
- Meaningful, measurable, and functional improvement, changes, or progress
    - Meaningful changes should be demonstrated by:
        - Data confirming the changes or progress
        - Documentation in charts and graphs
        - Durability over time beyond the end of the actual treatment session
        - Generalizable outside the treatment setting to the client’s residence or the community within which the client resides
- Compliance with treatment plan, including keeping appointments, attending and participating in treatment and family training sessions, completion of homework assignments, and family application of training techniques as directed by the therapy assistant or LBAT.

Regence

Medical Policy Manual Allied Health, Policy No. 32

Biofeedback

Effective: February 1, 2024

Next Review: August 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Biofeedback is intended to increase awareness and control of certain body functions normally considered to be outside conscious control.

MEDICAL POLICY CRITERIA

Note: This policy does not cover biofeedback devices for post-traumatic stress disorder or panic attacks.

I. Biofeedback as part of the overall treatment plan may be **medically necessary** for one or more of the following indications:

   A. Migraine or tension headaches

   B. Stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT)

   C. Dyssynergia-type constipation in adults when all of the following criteria (1.-3.) are met:

      1. Symptoms of functional constipation that meet <u>all</u> of the following ROME IV criteria (see Policy Guidelines)

2. Objective physiologic evidence of pelvic floor dyssynergia when one or both of the following criteria are met:
    a. Inappropriate contraction of the pelvic floor muscles
    b. Less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
3. Failed 3-month trial of standard treatments for constipation including laxatives, dietary changes, and pelvic floor exercises

II. Unsupervised biofeedback in the home setting is considered **investigational** for all indications.

III. Biofeedback is considered **investigational** for all other indications, including but not limited to the following: chronic pain, fecal incontinence, encopresis, and constipation other than dyssynergia type in adults, fibromyalgia, headaches other than migraine and tension (e.g., cluster headaches), myalgia or muscle pain, neck pain, orofacial pain, shoulder pain, temporomandibular joint disorders, and urinary disorders not meeting criteria, including but not limited to: post- prostatectomy urinary dysfunction, urinary incontinence not administered in conjunction with pelvic floor muscle training (PFMT), urinary retention, vesicoureteral reflux and voiding dysfunction.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Rome IV diagnostic criteria for functional constipation are as follows:[1]

1. Must include 2 or more of the following:
    a. Straining during more than one-fourth (25%) of defecations
    b. Lumpy or hard stools (Bristol Stool Form Scale1-2) for more than one-fourth (25%) of defecations
    c. Sensation of incomplete evacuation for more than one-fourth (25%) of defecations
    d. Sensation of anorectal obstruction/blockage for more than one-fourth (25%) of defecations
    e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
    f. Fewer than 3 spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical documenting symptoms and treatment specific to policy criteria
- If for constipation, three months of chart note documentation. Indicate if symptom onset is at least six months prior to diagnosis (please include dates).

- Clinical documentation with physiologic evidence of pelvic floor dyssynergia

CROSS REFERENCES

1. Neurofeedback, Medicine, Policy No. 65
2. Digital Therapeutic Products for PTSD and Panic Disorder, Medicine, Policy No. 175.05
3. Sphenopalatine Ganglion Block for Headache and Pain, Medicine, Policy No. 160
4. Percutaneous Neuromodulation Therapy (PNT), Surgery, Policy No. 44

BACKGROUND

Biofeedback is a technique intended to teach patients self-regulation of certain physiologic processes not normally considered to be under voluntary control. The technique involves the feedback of a variety of types of information not normally available to the patient, followed by a concerted effort on the part of the patient to use this feedback to help alter the physiological process in some specific way. Biofeedback training is done either in individual or group sessions, alone, or in combination with other behavioral therapies designed to teach relaxation. A typical program consists of 10 to 20 training sessions of 30 minutes each. Training sessions are performed in a quiet, non-arousing environment. Subjects are instructed to use mental techniques to affect the physiologic variable monitored, and feedback is provided for successful alteration of that physiologic parameter. The feedback may be in the form of lights or tone, verbal praise, or other auditory or visual stimuli.

REGULATORY STATUS

A variety of biofeedback devices are cleared for marketing though the Food and Drug Administration's (FDA) 510(k) process. The FDA defines a biofeedback device as "an instrument that provides a visual or auditory signal corresponding to the status of one or more of a patient's physiological parameters (e.g., brain alpha wave activity, muscle activity, skin temperature, etc.) so that the patient can control voluntarily these physiological parameters."

EVIDENCE SUMMARY

There are several methodologic challenges that arise in assessing biofeedback for any indication. For example, most interventions that include biofeedback are multimodal and include relaxation and behavioral instruction which may have effects separate from those that may occur due to biofeedback. While studies may report a beneficial effect of multimodality treatment, without appropriate control conditions, it is difficult to isolate the specific contribution of biofeedback to the overall treatment effect. In addition, behavioral therapies (non-drug treatments including biofeedback) result in both nonspecific and specific therapeutic effects. Nonspecific effects, sometimes called the placebo effect, occur as a result of therapist contact, positive expectancies on the part of the patient and therapist, and other beneficial effects that occur as a result of being a patient in a therapeutic environment. Specific effects are those that occur only because of the active treatment, above any nonspecific effects that may be present.

In order to isolate the independent contribution of biofeedback on health outcomes (specific effects) and properly control for nonspecific treatment effects, well-designed randomized controlled trials (RCT) with the following attributes are necessary:

- Randomization helps to achieve equal distribution of individual differences by randomly assigning patients to either biofeedback or sham-biofeedback treatment groups. This promotes the equal distribution of patient characteristics across the two study groups.

Consequently, any observed differences in the outcome may, with reasonable assuredness, be attributed to the treatment under investigation.

- A comparable sham control group helps control for expected high placebo effects as well as for the variable natural history of the condition being treated.
- Blinding of study participants, caregivers, and investigators to active or sham assignments helps control for bias for or against the treatment. Blinding assures that placebo effects do not get interpreted as true treatment effects.
- Small studies limit the ability to rule out chance as an explanation of study findings.
- Follow-up periods must be long enough to determine the durability of any treatment effects.

Therefore, the focus of the evidence review for biofeedback for all indications is on RCTs with the attributes noted above.

ASTHMA

SYSTEMATIC REVIEWS

Yorke (2015) published a SR of studies evaluating nonpharmacologic interventions for the treatment of adults with asthma.[2] The literature search, conducted through May 2014, identified 23 studies for inclusion. The nonpharmacologic interventions were organized into groups: relaxation-based therapies (n=9 studies); cognitive behavioral therapies (n=5 studies); biofeedback techniques (n=3 studies); and mindfulness (n=1 study). Five studies incorporated multicomponent interventions. The three biofeedback RCTs used different techniques: exhaled carbon dioxide capnography (pooled n=12)[3]; HRV using a physiograph (pooled n=94 patients)[4]; and respiratory sinus arrhythmia by electrocardiographic feedback and muscle tension by electromyography (EMG; pooled n=17 patients).[5] Common outcomes in the 3 studies included peak expiratory flow and respiratory impedance. Two of the trials reported on medication use. While differences were detected in exhaled carbon dioxide, HRV, and muscle tension, no changes in forced expiratory volume in one second (FEV_1) were found and medication use decreased in only one trial. Reviewers concluded that larger sample sizes were needed to demonstrate effects and that, while certain parameters that patients received biofeedback on may have differed between treatment groups, those differences did not translate into meaningful clinical benefits.

RANDOMIZED CONTROLLED TRIALS

Lehrer (2004)[4] reported the results of a study in which 94 asthma patients were randomized to one of the following four groups: “Full protocol” including heart rate variability (HRV) biofeedback and training in pursed-lips abdominal breathing with prolonged exhalation; HRV biofeedback alone; Placebo biofeedback involving bogus “subliminal suggestions designed to help asthma”, with no other details provided and no actual suggestions given plus biofeedback training to alternately increase and decrease frontal EEG alpha rhythms; and waiting list control group. Although reported improvement was greater in the two treatment groups, scientific conclusions cannot be drawn from this data due to several limitations, including possible selection bias due to lack of randomization, short study duration, lack of follow-up to assess long-term effects, and differences between groups in task involvement and assessment

frequency. The authors concluded that further research is needed. They advise caution in the use biofeedback for the treatment of asthma until the mechanisms of action are better understood and the long-term effects have been documented.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with asthma. Additional evidence is needed from well-designed comparative studies.

AUTISM SPECTRUM DISORDER

Autism Spectrum Disorders (ASD) can vary in severity of disease and therefore treatments utilized to treat the disease, making it difficult to isolate outcomes associated with biofeedback. The following literature review for biofeedback as a treatment of ASD focuses on SRs and RCTs.

SYSTEMATIC REVIEW

Coben and Myers (2010) reviewed the literature on EEG biofeedback for ASDs.[6] The authors identified two published small, non-RCTs evaluating EEG biofeedback in the treatment of ASDs. As described in the review, a study published by Jarusiewicz and colleagues in 2002 compared treatment with 20 to 69 sessions of biofeedback in 12 autistic children to a matched control group that did not receive biofeedback. Mean reduction in autistic symptoms, as measured by the Autism Treatment Evaluation Checklist (ATEC), was 26% in the biofeedback group and 3% in the comparison group; this difference was statistically significant. The other study was published by Coben and Padolsky in 2007. It compared 20 sessions of EEG biofeedback in 37 patients to a waiting-list control group. After treatment, parents reported reduction in symptoms in 89% of the treatment group compared to 17% of the control group (p-value not reported). Studies differed in their biofeedback protocols and number of sessions. The review article concluded that RCTs are needed to determine the effectiveness of biofeedback to treat ASDs.

RANDOMIZED CONTROLLED TRIALS

Yang (2015) conducted a RCT to explore the effects of visual condition and target size during four reach-to-grasp tasks between 20 autistic and 20 matched control children subjects.[7] The autistic children showed longer movement time, larger normalized jerk score, more movement when compared to controls, especially in non-visual feedback and small target blocks. This study is limited by the small sample size and other methodological considerations making it hard to determine the efficacy of visual effects for autism.

Kouijzer (2013) published a RCT evaluating electroencephalography (EEG) biofeedback as a treatment for ASD.[8] The trial included 35 teenagers between 12 and 18 years-old with confirmed diagnoses of ASD. Participants were randomly assigned to receive EEG biofeedback (n=13), skin conductance biofeedback (n=12), or a waiting-list control group (n=13). The biofeedback interventions included 40 sessions provided twice a week. Patients and parents in the biofeedback groups but not on the waiting-list were blinded to treatment allocation. The primary outcome measure was change in symptoms at three months as measured by the total score on the Social Communication Questionnaire (SCQ) which has a potential range of 0 to 36. In the primary analysis, the investigators only included participants

who successfully influenced their EEG activity (called “EEG-regulators”) in the primary analysis. The justification for this was to be able to identify the specific effects of biofeedback on symptoms. Among the 19 of 35 (54%) regulators, there was no statistically significant difference in the SCQ scores between participants treated with EEG- or skin-conductance biofeedback. The investigators evaluated non-specific effects of EEG biofeedback by examining the SCQ scores among EEG-non-regulators as rated by the parents. There was no statistically significant difference in scores among participants in the EEG biofeedback group, the skin conductance biofeedback group and the control group.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with ASDs. The scientific evidence on the effectiveness of biofeedback for treatment of autism consists of one small RCT and a limited number of small, non-randomized studies. The RCT did not report a significant benefit of biofeedback on autism-related symptoms.

BELL’S PALSY (IDIOPATHIC FACIAL PARALYSIS)

SYSTEMATIC REVIEWS

A 2011 Cochrane SR of physical therapy modalities for the treatment of Bell’s palsy.[9] The authors identified two case series and one small RCT. However, no analysis of these studies was performed because they did not meet the minimum methodological quality to be included in the review.

Cardoso (2008) examined the effects of facial exercises associated either with mirror or EMG biofeedback with respect to complications of delayed recovery in Bell's palsy.[10] Patients with unilateral idiopathic facial palsy treated with facial exercises associated with mirror and/or EMG biofeedback were included in this review. Four studies (n=132) met the eligibility criteria. The studies described mime therapy versus control (n=50), mirror biofeedback exercise versus control (n=27), "small" mirror movements versus conventional neuromuscular retraining (n=10), and EMG biofeedback plus mirror training versus mirror training alone. The treatment length varied from one to twelve months. The authors concluded that “…because of the small number of RCTs, it was not possible to analyze if the exercises, associated either with mirror or EMG biofeedback, were effective. In summary, the available evidence from ran RCTs is not yet strong enough to become integrated into clinical practice.”

RANDOMIZED CONTROLLED TRIALS

No RCTs identified after the above SRs.

SECTION SUMMARY

Current evidence from small RCTs with variable biofeedback protocols and type of comparison interventions is insufficient to permit conclusions on the impact of biofeedback on Bell’s palsy.

BRUXISM AND SLEEP BRUXISM

SYSTEMATIC REVIEWS

Manfredini (2015) published a SR which included 14 studies, 12 of the studies were RCTs.[11] Two of the studies evaluated bruxism. The authors concluded that the potential benefit of biofeedback (BF) and cognitive-behavioral (CB) approaches to sleep bruxism management is not fully supported.

Wang (2013) published a SR of RCT and non-RCTs on biofeedback treatment for sleep bruxism.[12] The full text of 17 articles was reviewed and seven studies with a total of 240 participants met the inclusion criteria. Studies were generally small; onlytwo included more than 50 participants. Four studies used audio biofeedback, two used contingent electrical stimulation and 1 used visual biofeedback. Treatment duration ranged from one night to six weeks. In four of the studies, the duration of treatment was two weeks. Three of the studies were considered to be at moderate risk of bias and the other four were considered to be at high-risk of bias. The primary outcome of the analysis was the number of sleep bruxism episodes per hour detected by EMG recording. Only two studies (total n=27) reported this outcome and had data suitable for meta-analysis. A pooled analysis did not find a statistically significant difference between the biofeedback and control groups; mean difference: -4.47 (95% CI: -12.33 to 3.38). Findings were not pooled for any other outcomes.

RANDOMIZED CONTROLLED TRIALS

Sato (2015) published a RCT limited in size on the use of EMG biofeedback training for daytime clenching and its effect on sleep bruxism.[13] Patients were monitored for five hours of daytime and night time and were randomized to EMG biofeedback (n=7) or to a control group (n=5). Patients in the biofeedback group received a small auditory signal in the daytime when clenching activity was detected. There were significant decreases in EMG events during weeks two and three in the biofeedback group during the daytime, and the decreases in events carried over into the night time. There were no decreases in EMG events in the control group.

SECTION SUMMARY

There is insufficient evidence from SRs and RCTs that biofeedback improves outcomes in individuals with bruxism. Additional evidence is needed from well-designed comparative studies.

CHRONIC PAIN (NON-HEADACHE)

As discussed in the Background section above, the focus of the evidence review was on RCTs. This study design is particularly important when studying treatments for pain. The most clinically relevant outcomes of therapy for pain are improvement in symptoms, function, and quality of life. These outcomes are subjective and can be influenced by nonspecific effects such as placebo response and the natural history of the disease. Randomized treatment allocation and the inclusion of a control group are needed to isolate the effect of biofeedback therapy.

GENERAL NON-HEADACHE PAIN

Systematic Reviews

A Cochrane SR by Williams on psychological therapies (cognitive-behavioral therapy [CBT] and behavioral therapy, including biofeedback) for chronic non-headache pain in adults was updated in 2012.[14] Forty-two trials provided analyzable data, thirteen of which had not been included in previous updates of this review. The SR found that although the quality of trial

design had improved over time, the quality of treatments, reporting, or both had not improved. CBT (not behavioral therapy) had weak effects in improving pain, but only immediately following treatment. CBT also had small effects on pain-related disability, altering mood, and catastrophizing outcomes compared with usual treatment or waiting list patients, with some maintenance at six months follow-up. However, it was not possible to isolate the results for the individual components of CBT, including biofeedback. Behavioral therapy had no effect on mood but showed an effect on catastrophizing immediately post-treatment. The authors recommended against future general RCTs, recommending instead, studies to identify which components of CBT work for which type of patient.

Another Cochrane SR review by Eccleston and colleagues evaluated psychological therapies for the management of chronic and recurrent pain in children and adolescents. Included studies were RCTs with at least 10 participants in each arm. Although psychological therapies were found to improve pain, only one of the five studies on non-headache pain evaluated biofeedback.

Polermo conducted an SR of RCTs to update previously published SRs on psychological therapies for management of chronic non-headache pain in children and adolescents was published by Palermo and colleagues in 2010.[15] RCTs included in previous SRs were automatically eligible for inclusion in this SR. The review did not identify any new RCTs that had not been included in previous SRs. It was not possible to isolate the results of the individual components of the psychological therapies, including biofeedback.

Randomized Controlled Trials

No RCTs were identified that were published after the above SRs.

ARTHRITIS

Systematic Reviews

Richards (2017) published a SR evaluating the application of real-time biofeedback to reduce knee adduction movement (KAM) during gait training, for patients with knee osteoarthritis (KOA).[16] Twelve studies met the inclusion criteria. The authors concluded there are limited controlled studies, but found value for further research in the outcomes of biofeedback to reduce KAM.

In a SR with meta-analysis of psychological interventions for rheumatoid arthritis including relaxation, biofeedback, and cognitive-behavioral therapy, Astin and colleagues concluded that psychological interventions may be important adjunctive therapies in rheumatoid arthritis treatment.[17] In the 25 studies analyzed, significant pooled effect sizes were found for pain after an intervention. However, the same effect was not seen long term, and the meta-analysis did not isolate biofeedback from other psychological interventions. Therefore, the specific effects of biofeedback, as discussed in the Background section above, could not be isolated.

Randomized Controlled Trials

Eid (2016) published a RCT that evaluated the outcomes of electromyographic (EMG) biofeedback training on pain, quadriceps strength and functional ability for 11 boys and 25 girls with polyarticular juvenile rheumatoid arthritis (JRA).[18] Children were assigned to the EMG biofeedback group (n=18) or the control group (n=18). Treatments occurred over 12 weeks,

with evaluation at six and 12 weeks. Both groups showed significant improvement at 12 weeks.

FIBROMYALGIA

Systematic Reviews

In 2015 a Cochrane SR was published by Theodom examining mind and body therapy for fibromyalgia. Sixty-one trails were included in the review.[19] The study participants were predominately women and their nature of fibromyalgia varied from mild to severe across the study population. No adverse events were reported. The authors found there was very low quality evidence that biofeedback in comparison to usual care controls had an effect on physical functioning, (SMD -0.1,95% CI-0.4 to 0.3, - 1.2% absolute change, 1 oint shift on a 0-100 scale) pain(SMD -2.6, 95% CI -91.3 to 86.1, -2.6% absolute change, and mood ((SMD 0.1, 95% CI -0.3 to 0.5, 1.9% absolute change, less than 1 point shift on a 0 to 90 scale) post-intervention. Due to the very low-quality evidence, it is unclear what role biofeedback has fibromyalgia.

In 2013 Glombiewski published the results of a meta-analysis that included three studies on EEG-biofeedback (neurofeedback) and four studies on EMG-biofeedback for fibromyalgia (N=321).[20] Studies in which biofeedback was evaluated only as part of multicomponent interventions were excluded from the review. A sham intervention was used as a control condition in four studies, two using EEG biofeedback and two using EMG- biofeedback. A pooled analysis was conducted for each therapy. EMG-biofeedback was reported to have significantly reduced pain intensity compared to control groups (effect size, Hedges *g*: 0.86, 95% CI, 0.11 to 0.62). Pooled analyses of studies of EMG and EEG biofeedback did not find a significant benefit of the intervention on other outcomes including sleep problems, depression and health-related quality of life. None of the studies included in this review were high quality, with risk of bias assigned by the authors as either unclear or high for all included studies. In addition, all of the studies reported on short-term outcomes, resulting in a lack of evidence on whether longer-term outcomes are improved. The authors recommended further research focused on long-term effects and predictors of treatment response.

Randomized Controlled Trials

No RCTs identified after the SR above.

KNEE PAIN

Systematic Reviews

A number of SRs have been published that included trials of biofeedback in the treatment of anterior knee pain[21], patellofemoral pain syndrome,[22] and in post-meniscal repair rehabilitation.[22] Mixed results have been reported by the SRs, but no standardized treatment protocols or patient selection criteria have been established for biofeedback for knee pain of any etiology.

Randomized Controlled Trials

No RCTs were published after the above SR.

LOW BACK PAIN

Systematic Review

Sielski (2017) published a SR evaluating the impact of biofeedback for chronic back pain.[23] Twenty-one studies met all inclusion criteria, one of which had to be biofeedback at least 25% of the time. Outcomes were determined for pain, disability, depression, reduced muscle tension, and coping skills. The authors concluded that although the outcomes of biofeedback are promising, the SR had limitations including heterogeneity of how biofeedback and back pain were defined and the positive results should be interpreted with caution.

Qaseem (2017) published a guideline from the American College of Physicians (ACP) that by using the ACP was based on a SR of RCTs and SRs published through April 2015.[24] For patients with acute or sub-acute low back pain, biofeedback was not mentioned. For patients with chronic low back pain the recommendation was to initially try nonpharmacological treatments including biofeedback based on “low quality evidence”. For patients with chronic low back pain who have not responded to nonpharmacological treatments, pharmacological treatment may be considered.

Haines (2017) published an economic evaluation that was done alongside a pilot randomized trial that evaluated motion-sensor biofeedback for sub-acute and chronic low back pain over 12 months.[25] Patients received motion-sensor biofeedback with guideline based care (n=38) or guideline based care alone (n=45) over ten weeks and completed a three, six, and 12 month assessment. The authors concluded that motion-sensor biofeedback is both clinically and economically effective, but more studies are needed.

Daffada (2015) conducted a SR to identify and assess the current evidence regarding the effectiveness of interventions (i.e. graded motor imagery and mirror visual feedback) which target cortical remapping in the management of chronic low back pain (CLBP).[26] Five articles were included in the review, which were comprised of three RCTs, one randomized cross-over study, and one multiple case study design. Although the authors report these interventions, including visual feedback, could be effective, the paucity of literature, small sample sizes, and methodological constraints of the studies included in the review make it difficult to determine the effectiveness of the interventions in the management of CLBP.

A 2010 Cochrane review[27] on behavioral treatments for chronic low-back pain included a meta-analysis of three small RCTs[28-31] comparing electromyography (EMG) biofeedback to a waiting-list control group. These studies were graded as low to very low quality due to methodological limitations and imprecision. In the pooled analysis there were a total of 34 patients in the intervention group and 30 patients in the control group. The standard mean difference in short-term pain was -0.80 (95% confidence interval [CI]:-1.32 to -0.28); this difference was statistically significant favoring the biofeedback group. One additional RCT was not included in the pooled analysis due to differences in reporting.[28] This small RCT (N=44) was determined to have a low risk of bias and reported no significant differences in outcomes between groups. The Cochrane review did not conduct meta-analyses of trials comparing biofeedback to sham biofeedback.

Randomized Controlled Trials

Kent (2023) compared the effectiveness and economic efficiency of Cognitive Functional Therapy (CFT), delivered with or without movement sensor biofeedback, with usual care for patients with chronic, disabling low back pain in a three-arm, unblinded, RCT as part of the (RESTORE) trial.[32] Participants (N=492) were randomly assigned (1:1:1) via a centralized

adaptive schedule to usual care (N=165), CFT only (N=164), or CFT plus biofeedback (N=165). Both interventions were more effective than usual care (CFT only mean difference -4·6 [95% CI -5·9 to -3·4] and CFT plus biofeedback mean difference -4·6 [-5·8 to -3·3]) for activity limitation at 13 weeks (primary endpoint). Effect sizes were similar at 52 weeks.

Tan (2015) conducted a four arm RCT of hypnosis compared with biofeedback for 100 veterans adults with chronic low back pain (CLBP).[33] Group one included an eight-session self-hypnosis training intervention without audio recordings for home practice; group two consisted of an eight-session self-hypnosis training intervention with recordings; group three had a two-session self-hypnosis training intervention with recordings and brief weekly reminder telephone calls; and group four had an eight-session active biofeedback control intervention. All four groups reported significant pre-to post-treatment improvements in pain intensity, pain interference, and sleep quality. This study was limited by the small sample size and other methodological constraints making it hard to determine the efficacy of biofeedback for adults with CLBP.

In a 2010 study published after the above Cochrane SR, Kapitza compared the efficacy of respiratory biofeedback to sham biofeedback in 42 patients with lower back pain.[34] All participants were instructed to perform daily breathing exercises with a portable respiratory feedback machine; exercises were performed for 30 minutes on 15 consecutive days. Patients were randomized to an intervention group that received visual and auditory feedback of their breathing exercises or a control group that received a proxy signal imitating breathing biofeedback. Patients recorded pain levels in a diary three times a day, measuring pain on a visual analogue scale (VAS). Both groups showed reduction in pain levels at the end of the intervention period and at the three month follow-up, but there were no significant differences in pain between groups. For example, the mean change in pain with activity three months after the intervention was a reduction in 1.12 points on a 10-point VAS scale in the intervention group and 0.96 points in the sham control group; $p>0.05$. The mean change in pain at rest after three months was a reduction of 0.79 points in the intervention group and 0.49 points in the control group; $p>0.05$.

Another 2010 RCT, by Glombiewski, assessed whether the addition of EMG biofeedback to CBT improved outcomes in 128 patients with lower back pain.[35] Patients with musculoskeletal pain of the low, mid, or upper back, with pain duration of at least six months on most days of the week, were randomized to CBT, CBT plus biofeedback, or a waiting-list control; 116 patients began the 1-hour weekly sessions (17-25 treatments) and were included in the final analysis. CBT alone included breathing exercises and progressive muscle relaxation; biofeedback was used for 40% of the CBT treatment time in the combined treatment condition. Both treatments were found to improve outcomes including pain intensity compared to a waiting-list control (moderate effect size of 0.66 for pain intensity in the CBT plus biofeedback group). However, the addition of biofeedback did not improve outcomes over CBT alone.

NECK AND SHOULDER PAIN

Systematic Reviews

Campo (2021) published a systematic review and meta-analysis that evaluated the effectiveness of biofeedback for improving pain, disability, and work ability in adults with neck pain.[36] The review included 15 RCTs with eight studies utilizing EMG biofeedback and seven studies pressure biofeedback. There was no restriction on the control intervention (eg, no treatment, placebo, active treatment) or co-intervention, provided the independent effects of

biofeedback could be elucidated. Results suggest that biofeedback has a moderate effect on reducing short-term disability and a small effect on reducing intermediate-term disability with no effect on pain or work ability in the short- and intermediate-term. Of note, there were a variety of control interventions across included studies (eg, exercise, electroacupuncture, electrotherapy, education) with few studies directly comparing biofeedback to no treatment or placebo.

Kamonseki (2021) completed a systematic review and meta-analysis of 5 RCTs (N=272) that examined the effects of EMG biofeedback for shoulder pain and function.[37] Very-low quality of evidence found that electromyographic biofeedback was not superior to control for reducing shoulder pain (standardized mean differences = -0.21, 95% confidence interval: -0.67 to 0.24, p=0.36) or shoulder function (standardized mean differences = -0.11, 95% confidence interval: -0.41 to 0.19, p=0.48). The authors state the very low quality of evidence does not permit a definitive recommendation regarding EMG biofeedback in the treatment of shoulder pain.

Shearer (2016) published a SR evaluating the impact of psychological interventions, one of which was biofeedback for neck pain and associated disorders (NAD) and whiplash disorders.[38] The SR included RCTs, cohort and case control studies. No clear positive effects were seen for biofeedback and the authors noted more sound methodological research is needed.

Hesselstrand (2015) published a SR of 19 studies called Occupational Therapy Interventions in Chronic Pain-A SR.[39] One RCT addressed surface EMG biofeedback training for persons with neck and shoulder complaints after whiplash-associated disorders, concerning activities of daily living and pain. The SR concluded that no support exists for the effectiveness of electromyographic biofeedback training as a supplement and that more studies are needed to confirm this result.

Randomized Controlled Trial

de Oliveira (2022) conducted an RCT in 24 patients with subacromial pain syndrome who received exercise or exercise plus EMG biofeedback for 8 weeks.[40] The primary outcomes were pain and shoulder function. At 8 weeks, pain was better in the exercise-only group (mean numeric pain rating, 0.5 vs 2 with exercise plus biofeedback; p=.01); however, this outcome was not different between groups at other time points. The only other significant finding was forward rotation of the scapula, which was better in the biofeedback group at 12 weeks (p=.006). All other outcomes were similar between groups.

Ma (2011) published an RCT that included 72 patients with chronic (at least three months) computer work-related neck and shoulder pain.[41] Patients were randomized to one of four six-week interventions: Biofeedback, exercise, passive treatment (e.g., hot packs), or a control group receiving only an educational pamphlet. Members of the biofeedback group were given a portable EMG biofeedback machine and were instructed to use it for two hours daily while performing computer work. The active exercise group was given an exercise routine to perform on their own for no longer than 20 minutes, four times a day. Sixty of 72 (83%) participants were available for the post-intervention follow-up assessment (n=15 per group). At the end of the intervention, the average VAS score and neck disability index (NDI) scores were significantly lower in the biofeedback group than in the other three groups. For example, the mean VAS post-intervention was 1.87 (standard deviation [SD]: 0.74) in the biofeedback group and 2.10 (SD: 1.34) in the active exercise group (p< 0.05).

This study found a short-term benefit of a biofeedback intervention, but the magnitude of difference in the VAS scores and the NDI index was small and of uncertain clinical significance. In addition, there were several methodologic limitations. The study was of small size and had a substantial number of dropouts; data were available on only 39 of 72 (54%) participants at six months. The interventions were not balanced in intensity, as the biofeedback intervention was more intensive (two hours per day) than the other interventions, such as the passive treatment arm, which received two 15-minute sessions per week. Long-term data were not available due to the low follow-up rate, which at six months was too small for meaningful analysis.

OROFACIAL PAIN (INCLUDING TEMPOROMANDIBULAR JOINT DISORDER)

Systematic Reviews

A 2011 Cochrane SR identified 17 trials evaluating non-pharmacological psychological interventions for adults with chronic orofacial pain (e.g., temporomandibular joint (TMJ) disorder).[42] For the outcome short-term pain relief (three months or less), there was a significantly greater reduction in pain with interventions that combined CBT and biofeedback compared to usual care (two studies). However, there was not a significant benefit of a combined CBT/biofeedback on longer-term i.e., six-month pain relief, and there were no studies that compared CBT alone to CBT combined with biofeedback. For biofeedback-only interventions, a pooled analysis of two studies on short-term pain relief did not find a significant benefit compared to usual care. There was only one study reporting long-term pain relief after a biofeedback-only intervention, so a pooled analysis could not be conducted. The authors concluded that there is weak evidence to support psychosocial interventions for managing chronic orofacial pain and the most promising evidence is for CBT, with or without biofeedback. They noted that the trials in the review were few in number and had a high risk of bias, and they recommended additional high-quality trials.

The conclusions of the Cochrane review are similar to previous SRs on treatment of TMJ disorder. The reviews also concluded that there is weak evidence that psychosocial/physical therapy interventions, including biofeedback among others, are beneficial for treating TMJ but that there were few studies and they tended to be of poor methodologic quality. For example, Medlicott and colleagues recommended caution in interpreting results due to heterogeneity in study design and interventions used.[43] Since biofeedback was not isolated from other therapies, no conclusions could be reached for biofeedback alone. Based on two poor-quality RCTs, McNeely and colleagues concluded that biofeedback did not reduce pain more than relaxation or occlusal splint therapy for TMJ, but did improve oral opening when compared with occlusal splints.[44]

Randomized Controlled Trials

No RCTs identified after the above SR.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systematic Reviews

No SRs were identified for biofeedback for the treatment of SLE.

Randomized Controlled Trial

In an RCT of 92 patients with Systemic Lupus Erythematosus (SLE), Greco and colleagues reported that patients treated with six sessions of biofeedback-assisted cognitive-behavioral treatment for stress reduction had a statistically significant greater improvement in pain post treatment than a symptom-monitoring support group (p=0.044) and a usual care group (p=0.028).[45] However, these improvements in pain were not sustained at a nine-month follow-up and further studies are needed to determine the incremental benefits of biofeedback-assisted cognitive-behavioral treatment over other interventions in SLE patients.

RECURRENT ABDOMINAL PAIN

Systematic Reviews

No SRs were identified using biofeedback for the treatment of recurrent abdominal pain.

Randomized Controlled Trial

Humphrey's and Everts randomly assigned 64 patients with recurrent abdominal pain to groups treated with: 1) increased dietary fiber; 2) fiber and biofeedback; 3) fiber, biofeedback, and cognitive-behavioral therapy; and 4) fiber, biofeedback, cognitive-behavioral therapy, and parental support.[46] The three multi-component treatment groups were similar and had better pain reduction than the fiber-only group. This study does not address placebo effects. In a SR of recurrent abdominal pain therapies in children, Weider and colleagues concluded that behavioral interventions (cognitive-behavioral therapy and biofeedback) had a general positive effect on nonspecific recurrent abdominal pain and were safe.[47] However, the specific effects of biofeedback were not isolated in this SR.

VESTIBULODYNIA/VULVODYNIA/VULVAR VESTIBULITIS

Systematic Reviews

Morin published a SR to evaluate the outcomes of different physical therapies, one of which was biofeedback for women with provoked vestibulodynia.[48] The SR included RCTs, prospective and retrospective studies, case reports and study protocols, most of which had methodological limitations. The authors concluded more well designed RCTs are needed.

Randomized Controlled Trial

An RCT by Bergeron of 78 patients with vulvar vestibulitis compared biofeedback, surgery and cognitive-behavioral therapy.[49] Surgery patients had significantly better pain scores than patients who received biofeedback or cognitive-behavioral therapy. No placebo treatment was used.

OTHER CHRONIC PAIN

Other pain for which there are no publications sufficient to demonstrate the effectiveness of biofeedback include muscle pain or myalgia.

SECTION SUMMARY

The current evidence base is insufficient to allow scientific conclusions concerning the contribution of biofeedback to improvements in health outcomes for the treatment of chronic non-headache pain. [Headache is discussed separately below]

DEPRESSION, ANXIETY, AND POST-TRAUMATIC STRESS DISORDERS

Systematic Reviews and Technology Assessments

In 2018, the Canadian Agency for Drugs and Technology in Health (CADTH) published an updated "Post-Traumatic Stress Disorder: Summary of Evidence of the Clinical Effectiveness of Treatments".[50] They reviewed 26 treatments, one of which was biofeedback. They continued their stance that there is no evidence-based guidelines for the treatment of any mood or anxiety disorders. Additional well-designed, controlled clinical studies are needed to determine the clinical effectiveness of biofeedback on PTSD.

A 2017 CADTH evidence report on biofeedback for mood and anxiety disorders states the following:[51]

> Evidence from single randomized controlled trials suggests that compared with no treatment there is a statistically significant improvement in symptoms with neurofeedback treatment in patients with post-traumatic stress disorder (PTSD) or generalized anxiety disorder (GAD).
>
> A single randomized controlled trial (RCT) showed that for patients with PTSD there was improvement in symptoms with biofeedback (BF) plus treatment as usual (TAU) and also with TAU alone but the improvement occurred faster in the BF plus TAU group.
>
> A single RCT showed that for patients with PTSD there were no between group differences for BF and various mindfulness related treatment modalities. A single RCT showed that for patients with major depressive disorder, there was a statistically significant improvement in depression with BF plus TAU.
>
> Results need to be interpreted in the light of limitations (such as small sample size, lack of randomization details, lack of reporting of adverse events, lack of long-term data).
>
> No relevant studies on the clinical effectiveness of biofeedback using home equipment for treatment of PTSD, GAD, or depression without continued support from health professionals were identified.
>
> No relevant evidence based guidelines regarding the use of neurofeedback or biofeedback for the treatment of PTSD, GAD, or depression were identified.

Goessl (2017) published a SR on the effect of heart rate variability (HRV) biofeedback training in patients with stress and anxiety.[52] HRV is a measure of cardiac vagal tone. Low HRV is associated with certain psychological states such as anxiety. The literature search identified 24 studies (total N=484 patients), published between 1976 and 2015, for inclusion. Sample sizes ranged from five to 106 patients (median, 14 patients). The Cochrane risk of bias tool was used to assess study quality. Many studies had high or unclear risk of bias due to the following factors: inadequate randomization descriptions, improper randomization, undescribed allocation concealment, and missing data that was either not described or mishandled; 13 studies included a comparison group (six waitlist, three standard of care, two sham, one daily thought record, one progressive muscle relaxation). The average within-group effect size among the 24 studies, measured by Hedges' *g*, was 0.81, indicating a large effect on anxiety. The average between-group effect size among the 13 studies with comparators, also measured by Hedges' *g*, was 0.83, indicating HRV had a larger effect on anxiety than the comparators.

Schoenberg and David (2014) published a systematic review (SR) on biofeedback for psychiatric disorders, one of which was anxiety.[53] They identified 227 articles and 63 met the criteria for review. The authors concluded that development of standardized controlled methodology protocols tailored for specific disorders and guidelines are needed to determine the benefit of biofeedback on health outcomes for those with anxiety.

Randomized Controlled Trials

In addition to those included in the systematic reviews, the following RCTs have been published:

Maynart (2021) compared respiratory and heart rate biofeedback plus usual care to usual care alone in 36 patients with moderate to severe depression or dysthymia.[54] After six weeks (six sessions of biofeedback training), the biofeedback plus usual care group had less severe depression as measured by the Beck Depression Inventory (BDI) than the usual care alone group.

A preliminary open-label RCT by Park and Jung (2020) compared respiratory sinus arrhythmia biofeedback plus usual care to usual care alone in 30 patients with major depressive disorder.[55] After four weeks (six sessions of biofeedback), the biofeedback plus usual care group had greater improvements in Hamilton Depression Rating Scale (HAM-D) scores compared to the group receiving usual care alone. Improvements in other clinical measures, including the BDI, were not significantly different between groups.

Chen (2016) published an RCT comparing diaphragmatic breathing relaxation (DBR) with routine respiration activities in the treatment of 46 patients with anxiety.[56] DBR is a technique that uses diaphragm muscle contractions to force air downward into the body, increasing diaphragm length and breathing efficiency. Outcomes were anxiety level, measured by Beck Anxiety Inventory, and four physiological measures (skin conductivity, peripheral blood flow, heart rate, breathing rate). All patients participated in an individualized eight-week course in breathing relaxation, but only 30 completed it. Fifteen were randomized to DBR training and 15 to routine breathing relaxation training. Researchers and patients were blinded to randomization, with only the trainer being aware of group allocation. After eight weeks, the DBR group experienced statistically significant decreases in Beck Anxiety Inventory scores compared with baseline, while the control group did not experience significant decreases from baseline. The DBR group also experienced significant improvements in all four physiological measurements, while the control group did not. The authors noted this therapy is promising, but more well-controlled studies are needed.

FECAL INCONTINENCE AND CONSTIPATION

The relevant clinical outcome in studies of biofeedback as a treatment of fecal incontinence, encopresis, and constipation should be the overall change in the bowel symptoms. Reduction in episodes of fecal incontinence, encopresis, and constipation, and an increase in voluntary bowel movements as a result of biofeedback are the primary clinical outcomes of interest. Patient symptoms are usually assessed through diary, questionnaire, or interview. However, changes in anorectal physiological assessment (e.g., anal pressure, sensory threshold) often do not correlate with symptom relief (i.e., clinical outcomes).

FECAL INCONTINENCE IN ADULTS

Systematic Reviews

A 2014 Cochrane SR of RCTs compared one method of biofeedback to sham-biofeedback, no treatment, or another method of biofeedback in adults (> 18 years of age) with chronic idiopathic (functional) constipation.[57] Seventeen RCTs (25 individual reports) were included (N=931); biofeedback was compared to conventional nonsurgical treatment in 7 studies[58-64], to different methods of biofeedback in six studies[65-70], to surgical intervention in two studies[71, 72], to sham treatment in one study[73] and to electrical stimulation in one crossover study[74, 75]. No studies compared biofeedback to no treatment. Meta-analysis was not possible due to between-study heterogeneity and evidence was rated as low or very low quality due poor methodological quality with high risk of bias. The length of follow-up was determined to be inadequate in many RCTs. There was significant heterogeneity between groups and between studies that precluded meta-analysis. These included between-group differences at baseline, between-study differences in symptoms measured, symptom measurement tools used, and difference in protocols for biofeedback including the type of biofeedback, the number, frequency, and duration of sessions, and patient education (e.g., diet, normal bowel function, lifestyle advice). In addition, the review noted that many of the included RCTs were likely to be underpowered to detect between-group differences. The authors concluded that there is insufficient evidence to allow conclusions on the efficacy and safety of biofeedback for chronic constipation.

This Cochrane SR also reviewed four prior SRs[76-79] of RCTs that included systematic literature searches. The review reported methodological limitations in all four of these SRs including incomplete reporting of review methods, limited or non-comprehensive literature search strategies, failure to exclude non-SRs, and meta-analyses of heterogeneous studies. These reviews all reported generally poor quality evidence and the need for further research.

A 2013 SR by Vonthein et al. identified 13 RCTS on biofeedback, electrical stimulation, or the combination for treatment of fecal incontinence.[80] Ten RCTs included comparisons of biofeedback and an alternative treatment; some of the biofeedback interventions also involved other components such as sensory training and pelvic floor exercises. A meta-analysis of studies comparing biofeedback to a control intervention significantly favored biofeedback (relative risk, 2.12; 95% CI, 1.42 to 3.16). This study did not attempt to isolate the effect of biofeedback in multicomponent interventions that included pelvic floor exercise or other treatments.

In 2012, an updated Cochrane SR of randomized and quasi-randomized trials for biofeedback and/or sphincter exercises for the treatment of fecal incontinence in adults was published.[81] Almost half of the 21 trials were considered low risk for bias. Due to the variety of different treatment combinations, treatment delivery techniques, and outcome measures, comparison between studies was difficult. In addition, most studies reported immediate post-treatment outcomes with follow-up of only a few weeks. The authors reached the following conclusions:

- Biofeedback or electrical stimulation “may offer an advantage over exercises alone” in patients who have failed conservative management (e.g., diet changes, medications).
- Biofeedback following surgical sphincter repair does not improve health outcomes.
- The evidence does not permit conclusions about best practices in the clinical setting, including but not limited to the technique for biofeedback delivery and which patients are suitable for and most likely to benefit from biofeedback.

- Biofeedback is unlikely to cause harm as no study has reported any adverse events or worsening of symptoms.
- There is a need for large, long-term, well-designed RCTs that use validated outcome measures to compare outcomes of biofeedback with other treatments.

Randomized Controlled Trials

One new RCT was published after the above SRs. Damon randomized 157 patients with fecal incontinence to either a treatment group (n=77) receiving perineal retraining including biofeedback and standard conservative treatment, or a control group (n=80) receiving standard conservative treatment.[82] This RCT reported only short-term outcomes, with a follow-up of four months. The perineal retraining group had a significantly higher success rate than the control group for daily stool frequency, leakage, and urgency (57% versus 37%, respectively; $p<0.021$). However, there was no significant difference in quality of life scores between the two groups.

FECAL INCONTINENCE IN CHILDREN

Systematic Reviews

A 2011 updated Cochrane SR[83] combined the results of nine trials that compared conventional treatment (i.e., laxatives, toilet training, and dietary advice) with versus without biofeedback in children with fecal incontinence.[84-92] The majority of the trials included fewer than 50 participants. Pooling of data was difficult due to the variety of outcome measures; the only outcome reported by all nine trials was the number of children not cured or improved. Combined results of nine trials showed higher rather than lower rates of persisting symptoms of fecal incontinence up to 12 months when biofeedback was added to conventional treatment. In addition, any short-term benefit from biofeedback training did not correspond with later treatment success. The authors concluded that there is no evidence that biofeedback training added any benefit to conventional treatment in the management of functional fecal incontinence in children.

These results confirm the conclusions of prior versions of this Cochrane SR and other SRs.[93-95]

Randomized Controlled Trials

Since the above SRs, one additional randomized trial was published in which the authors reported that the results at six-months follow-up did not differ between biofeedback and customary care.[84]

CONSTIPATION IN ADULTS

Systematic Review

For the treatment of constipation, a SR of 11 RCTs found a benefit of biofeedback as a treatment of constipation in adults.[76] Conclusions of the SR were limited by variability in patient populations, comparison treatments, and outcomes measures. However, detailed examination of several well-conducted RCTs focusing on patients with dyssynergia-type constipation suggested benefits in a sub-group of patients who met criteria similar to trial participants.[59, 60, 73] Studies for other types of constipation were limited to poorly-designed

RCTs and case series. These unreliable studies do not permit conclusions on the effect of biofeedback on other types of constipation in adults.

Randomized Controlled Trials

Hart (2012) published an RCT that studied anorectal biofeedback (AB) for constipation. Twenty-one patients with pelvic floor dyssynergia were randomized into two groups.[60] One group learned to isolate the anal sphincter using an electromyography probe and the other learned to relax trapezius or temporalis muscles with EMG feedback. The authors concluded that although the sample size was statistically underpowered, AB produced clinical improvements in the severity of constipation. The authors also noted there were several study limitations, including patient selection and long-term follow-up; thus, the evaluation of long-term effects on health outcomes needs to be determined in future studies.

CONSTIPATION IN CHILDREN

Systematic Reviews

A systematic review conducted by Wegh (2021) assessed the effectiveness of nonpharmacological interventions for functional constipation in children.[96] Studies included in the review were RCTs that enrolled children aged 0 to 18 years with functional constipation as defined by Rome III or IV criteria and reported defecation outcomes and/or QOL outcomes. The review included three RCTs comparing biofeedback alone with biofeedback in conjunction with laxative use. The trials were all assessed as having a high risk of bias. Meta-analysis found no difference between groups in study-defined treatment success (risk difference, 0.23; 95% CI, -0.08 to 0.54) and heterogeneity was high (I^2=86%). Other clinical outcomes and harms of treatment were not reported.

Randomized Controlled Trials

A RCT conducted by Van Ginkel (2001) evaluated biofeedback in the treatment of constipation in children.[97] Groups included standard treatment i.e., education, laxatives (n=111) or standard treatment plus two sessions of anorectal manometry (n=91). Manometry measurements were viewed by the child and parent during measurement sessions and the data discussed after each session with instructions in home exercises. At six weeks follow-up, there was no significant different in success between the standard treatment group (4%) and the biofeedback group (7%). At the final 104 week follow-up, 43%of the standard treatment group and 35% of the biofeedback group were considered treatment successes. This difference was not significant. The authors noted that 30% of the randomized patients were missing at the final follow-up.

Section Summary

The current evidence from several well-designed, well-conducted RCTs is sufficient to determine that biofeedback as a treatment of dyssynergia-type constipation may be beneficial in adult patients who meet the policy criteria.

The evidence base is insufficient to draw conclusions or demonstrate a significant health benefit as a result of biofeedback treatments for the treatment of incontinence or constipation other than dyssynergia-type constipation in adults. The evidence is limited to data from studies with significant methodological limitations including inadequate randomization, lack of a

placebo control group, heterogeneity between patient groups and between study protocols, and short-term follow-up periods.

HEADACHE

TENSION AND MIGRAINE HEADACHE

Systematic Reviews

Sullivan (2016) published a SR to evaluate the outcomes of psychological interventions, one of which was biofeedback for migraines.[98] Twenty-four studies were reviewed. The authors noted there were methodological limitations from the study review and that biofeedback was not superior to relaxation training or cognitive behavioral therapy.

A number of other SRs, including two Cochrane SRs, have reported small beneficial effects in children and medium to large beneficial effects in adults when biofeedback is used in conjunction with other prevention measures such as relaxation techniques.[15, 99-105]

Randomized Controlled Trials

Despite the poor quality of case series and RCTs, biofeedback has evolved into a standard of care as part of comprehensive regimens, including medication and relaxation techniques, for treatment and prevention of tension-type headaches, and the prevention of migraine headaches.

Data from case series and RCTs is difficult to interpret due to poor study design, high drop-out rates, and inconsistent outcomes.[106-111]

OTHER HEADACHE

The evidence is insufficient to determine the effect of biofeedback for the prevention or treatment of headaches other than migraine and tension headaches, including but not limited to cluster headaches.

SECTION SUMMARY

Despite the poor quality of studies, biofeedback has evolved into a standard of care as part of comprehensive regimens, including medication and relaxation techniques, for treatment and prevention of tension-type headaches and the prevention of migraine headaches.

There is not enough research to show that biofeedback improves outcomes in patients with headaches other than migraine and tension headaches.

HYPERTENSION

SYSTEMATIC REVIEWS

Nagele (2014) published a SR with meta-analysis on stress-reduction techniques in adults with essential hypertension.[112] The review included SRs and RCTs with a no-treatment control group and at least 24 weeks follow-up that were published through September 2012. Outcomes of interest were mortality, cardiovascular morbidity/mortality, end-stage renal disease, health related quality of life, adverse events, change in blood pressure, and changes in antihypertensive medication. Biofeedback was one of a number of the stress-reduction

techniques included in the review. The review found that data were not reported for most of the patient-relevant outcomes. No benefit was found for use of antihypertensives. Some beneficial effect was found for lowering blood pressure; however, studies were limited by methodological limitations such as heterogeneity between studies, short-term follow-up. The authors concluded that a beneficial effect of stress-reduction techniques on hypertension remains unproven.

In a 2010 SR, Greenhalgh concluded, "…we found no convincing evidence that consistently demonstrates the effectiveness of the use of any particular biofeedback treatment in the control of essential hypertension when compared with pharmacotherapy, placebo, no intervention or other behavioral therapies."[113] Trials generally had small sample sizes; only four included more than 100 patients. Trials included a variety of biofeedback techniques, and some included more than one modality. Results were not pooled due to differences in interventions and outcomes and the generally poor quality of the studies. Only one trial was identified that compared a biofeedback combination intervention to sham biofeedback, and this study did not find a significant difference in the efficacy of the two interventions. Only four studies on biofeedback alone and four on a combined biofeedback intervention reported data beyond six months; most of these found no significant differences in efficacy between the biofeedback and control groups.

Rainforth reviewed RCTs and all previous meta-analyses related to stress reduction programs including biofeedback.[114] Each type of therapy was analyzed separately. No significant reduction in blood pressure was achieved using biofeedback alone or biofeedback combined with relaxation training.

RANDOMIZED CONTROLLED TRIALS

Wang (2016) published an RCT evaluating the effect of direct blood pressure biofeedback on patients with prehypertension or stage I hypertension.[115] A trained nurse instructed patients in blood pressure self-regulation by using slow diaphragmatic breathing and passive attitude. During the eight-week training (one session per week), patients in the treatment group received real-time blood pressure feedback signals (n=29) and controls received pseudo-feedback signals (n=28). Outcomes were systolic and diastolic blood pressure, measured at baseline and one and eight weeks after training. Both groups significantly decreased blood pressure following training. The decreases were equal in magnitude, suggesting that blood pressure self-regulation training can effectively lower blood pressure, regardless of the type of feedback signal.

Landman (2013) conducted a randomized, double-blind, sham-controlled trial comparing the effects on blood pressure of lowering breathing frequency in patients with type two diabetes and hypertension using active (n=21) and sham (n=24) biofeedback.[116] The changes in systolic blood pressure from baseline favored the control group while differences in diastolic blood pressure favored the intervention group. However, these differences from baseline, and the differences between the two groups were not statistically significant.

SECTION SUMMARY

Although there are RCTs evaluating biofeedback for treating hypertension, evidence is insufficient due to the shortage of studies isolating the effect of biofeedback, the generally poor quality of the trials, and the variability among interventions.

INSOMNIA

SYSTEMATIC REVIEWS

No SRs were identified using biofeedback for the treatment of insomnia.

RANDOMIZED CONTROLLED TRIALS

No RCTs were identified using biofeedback for the treatment of insomnia.

MOTOR FUNCTION AFTER INJURY OR ORTHOPEDIC SURGERY

SYSTEMATIC REVIEWS

Several SRs have been published; none of these conducted quantitative pooling of results due to heterogeneity among study populations, interventions, and outcome measures.

A 2010 SR by Silkman evaluated the effectiveness of electromyography (EMG) biofeedback for improving muscle function during knee rehabilitation after injury.[117] Four RCTs that compared knee rehabilitation exercise programs with and without biofeedback were identified. Sample sizes in individual studies ranged from 26 to 60 patients. Two of the four studies found a statistically significantly greater benefit in the programs that included biofeedback, and the other two did not find a significant difference between groups. The positive studies assessed intermediate outcomes e.g., contraction values of the quadriceps muscles. None of the studies were designed to assess functional outcomes.

RANDOMIZED CONTROLLED TRIALS

Tiryaki (2023) published the results of a RCT comparing the effectiveness of exercise with EMG biofeedback (n=23) to control exercise without biofeedback group (n=23) in patients rehabilitating from a massive rotator cuff tear.[118] The intervention lasted six weeks and the patients were followed for 12 months. Both groups improved similarly on most outcome scores. The biofeedback group had greater change in shoulder flexion strength and patient satisfaction score at six weeks and at 12 months follow-up ($p<0.05$).

MOTOR FUNCTION AFTER STROKE

Stanton (2017) updated a SR published in 2011 which evaluated the effect of biofeedback on lower-limb activities in patients who have had a stroke.[119] Only high-quality RCTs or quasi-RCTs with Physiotherapy Evidence Database (PEDro) scores greater than four were included. The literature search, conducted through September 2015, identified 18 trials (total N=429 patients) for inclusion. Training activities were walking (nine trials), standing (eight trials), and standing up (one trial). Trials were small, with study populations ranging from 12 to 50 patients. Biofeedback techniques included weight distribution from a force platform or sensor (11 trials), muscle activity from EMG (three trials), linear gait parameters (three trials), and joint angle from a goniometer (one trial). Visual feedback was used in seven trials, auditory in seven trials, and a combination of visual/auditory in four trials. Pooled standardized mean difference of the short-term effect of biofeedback from 17 trials (n=417) was significant (0.50; 95% confidence interval [CI], 0.3 to 0.7). Long-term effects could not be calculated because only four trials provided that information.

Stanton (2011) conducted a SR with meta-analysis of RCTs evaluating biofeedback to improve activities involving lower limb function after stroke.[120] A total of 22 trials with 591 participants met inclusion criteria. All of the trials had relatively small sample sizes; the largest trial had 54 participants and 15 trials had 30 or fewer participants. The majority of trials (n=17) compared biofeedback plus usual therapy to usual therapy alone. The specific interventions varied; the types of biofeedback included biofeedback of ground reaction force from a force platform with visual and/or auditory feedback (13 trials), muscle activity via visual and/or auditory feedback (five trials), joint position from an electrogoniometer via visual and/or auditory feedback (three trials), and limb position via auditory feedback one trial). The duration of interventions ranged from two to eight weeks, and intensity ranged between one to five days per week.

A pooled analysis of data from 17 trials on short-term effect (i.e. one month or less) found that biofeedback significantly improved lower limb activities compared to usual care or placebo (standardized mean difference [SMD]: 0.41; 95% CI: 0.21 to 0.62). Outcomes included activities such as directional control during standing, weight distribution between the lower limbs, and gait parameters such as stride length. There was heterogeneity among studies. Trials did not report functional outcomes such as ability to perform activities of daily living (ADL). A sensitivity analysis determined that the heterogeneity was best explained by study quality. When lower quality trials were excluded, biofeedback was still found to improve lower limb activity compared to control conditions (SMD: 0.49, 95% CI: 0.22 to 0.75). A sub-group analysis was also done by type of activity. There was only one high-quality trial on standing up (n=40). A pooled analysis of five high-quality trials on short-term effect found that biofeedback significantly improved standing outcomes compared to control (SMD: 0.42, 95% CI: 0.05 to 0.78). A pooled analysis of four short-term trials on walking also found better outcomes with biofeedback compared to control (SMD: 0.57, 95% CI: 0.10 to 1.03). Five high-quality trials with a total sample size of 136 contributed data to an analysis of long-term term efficacy i.e., one-five months after cessation of the intervention. In this pooled analysis, biofeedback was found to improve outcomes compared to control (SMD: 0.41, 95% CI: 0.06 to 0.75).

A Cochrane SR that assessed EMG biofeedback for the recovery of motor function after stroke was published in 2007.[121] It included 13 randomized or quasi-randomized studies with a total of 269 patients. All of the trials compared EMG biofeedback plus standard physiotherapy to standard physiotherapy; in addition to standard physiotherapy, several studies also included a sham biofeedback group. The studies tended to be small and poorly designed. The authors did not find support for EMG biofeedback to improve motor power, functional recovery, or gait quality when compared to physiotherapy alone.

A 2010 SR by Zijlstra searched for studies evaluating biofeedback-based training to improve mobility and balance in adults older than 60 years of age.[122] Although the review was not limited to studies on motor function after stroke, more than half of the studies included older adults post-stroke. For inclusion in this review, studies needed to include a control group of patients who did not receive biofeedback and to assess at least one objective outcome measure. A total of 97 potentially relevant articles were identified, and 21 (22%) studies, including 17 RCTs, met the selection criteria. Twelve of the 21 (57%) studies included individuals post-stroke; three included older adults who had lower-limb surgery and six included frail older adults without a specific medical condition. Individual studies were small with sample sizes that ranged from five to thirty patients. The added benefit of using biofeedback could be evaluated in 13 of 21 (62%) studies. Nine of the 13 studies found a significantly greater benefit with interventions that used biofeedback compared to control interventions. However, the outcomes assessed were generally not clinical outcomes but were

laboratory-based measures related to executing a task, e.g., moving from sitting to standing in a laboratory setting and platform-based measures of postural sway. The applicability of improvements in these types of measures to clinical outcomes such as the ability to perform activities of daily living or the rate of falls is unknown. Only one study cited in this review reported an improvement in fall rates, and this trial could not isolate the effect of biofeedback from other components of treatment. In addition, only three studies reported long-term outcomes, and none of these reported a significant effect of biofeedback. Conclusions about the efficacy of biofeedback for improving mobility and balance in older adults cannot be drawn from these data due to the lack of evidence on clinical outcomes. Other methodologic limitations included limited data on the durability of effects and the inability to isolate the effect of biofeedback in many studies.

RANDOMIZED CONTROLLED TRIALS

Benfield (2023) published a RC feasibility study comparing dysphagia treatment with usual care with usual care plus sEMG biofeedback as intervention in patients after an acute stroke.[123] Twenty-seven patients (13 biofeedback, 14 control) with average age of 73.3 (Standard Deviation [SD] ± 11.0) and National Institute of Health Stroke Scale (NIHSS) of 10.7 ± 5.1 were recruited 22.4 ± 9.5 days post stroke. A total of 84.6% of participants completed >80% of sessions; failed sessions were mainly due to participant availability, drowsiness or refusal. Sessions lasted for an average of 36.2 ± 7.4 min. Although 91.7% found the intervention comfortable with satisfactory administration time, frequency, and time post stroke, 41.7% found it challenging. There were no treatment-related serious adverse events. There were no differences in the Dysphagia Severity Rating Scale (DSRS) score between the two groups at 2 weeks. Long term data were not provided.

Nordio (2022) published a small RCT comparing surface electromyography (sEMG) biofeedback (N=9) to control treatment (N=7) for rehabilitation of swallowing in post-stroke dysphagia.[124] Functional oral intake scale (FOIS) improved in all patients, regardless of treatment. sEMG-biofeedback rehabilitation led to improvements of the pharyngeal clearance and swallowing safety. The rehabilitative effects appeared stable at 2-months follow-up. Treatment with sEMG biofeedback was not different than control treatment.

Kim (2017) published a RCT on the effect of EMG on upper-extremity functions in patients who have had a stroke.[125] Patients were randomized to traditional rehabilitation therapy (n=15) or traditional rehabilitation therapy plus EMG biofeedback training (n=15). Upper-limb function was measured by Fugl-Meyer Assessment (FMA) and Manual Function Test (MFT), and activities of daily living were measured using the FIM instrument. Both FMA and MFT scores improved significantly more in the patients receiving EMG biofeedback. However, there was not a significant difference in functional independence measurement (FIM) score improvement between groups.

Yang (2016) published a limited in size RCT on the effect of biofeedback weight-bearing training on the ability to sit/stand/sit and on stability among patients who have had a stroke.[126] Patients were randomized to biofeedback weight-bearing training (n=15) or functional weight-bearing training (n=15). Outcomes were time to sit/stand/sit and stability (measured by BioRescue, which detects an area of center of pressure). Comparison statistics were calculated for pre- and post training results, and between treatment groups. Both outcomes significantly improved in the biofeedback group but not in the control group.

Ghomashchi (2016) published a RCT evaluating the effect of visual biofeedback on postural balance disorders in patients who have had a stroke.[127] Patients received conventional physical therapy and balance training exercises. During balance training, 16 patients were randomized to visual biofeedback and 15 patients to no visual information. Outcomes were the center of pressure and approximate entropy. Both groups experienced improvements in postural control, with no significant differences between rehabilitation methods.

In a small RCT published after the above SR, Barcala randomized 20 adults with hemiplegia following stroke to balance training with visual biofeedback or to conventional physical therapy alone.[128] Patients received interventions twice a week for five weeks. Both groups demonstrated significant improvement, but no statistically significant differences were found between the two groups.

SECTION SUMMARY

The evidence on biofeedback for improving motor function after stroke is limited by small studies, most of which are methodologically limited. There is variability in the type, duration, and intensity of interventions. Conclusions about the efficacy of biofeedback for improving mobility and balance in older adults cannot be drawn from the current evidence base.

MOVEMENT DISORDERS

SYSTEMATIC REVIEWS

A Cochrane SR assessing EMG biofeedback for the recovery of motor function after stroke included thirteen randomized or quasi-randomized studies.[121] The authors reported that EMG biofeedback did not improve motor power, functional recovery, or gait quality when compared to physiotherapy alone, although the results were limited due to small, poorly designed trials. Use of different assessment scales made pooling data for meta-analysis impossible.

RANDOMIZED CONTROLLED TRIALS

Yaksi (2022) published a small RCT comparing static posturography-assisted biofeedback exercises and a conventional exercise program in patients (N=40) with Parkinson Disease (PD).[129] No differences were observed between the two groups in any of the outcome measurements before and after the treatment ($p > 0.05$). The authors concluded that static posturography-assisted biofeedback exercises provided no additional benefit.

SECTION SUMMARY

The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of movement disorders.

MULTIPLE SCLEROSIS

SYSTEMIC REVIEWS

No SRs were identified for biofeedback for the treatment of multiple sclerosis.

RANDOMIZED CONTROLLED TRIAL

van der Logt (2016) published a crossover study that evaluated the effect of vibrotactile biofeedback for trunk sway on balance control in patients with multiple sclerosis.[130] Ten

patients performed a series of stance and gait tasks while trunk sway was measured using a SwayStar device attached to the waist. Patients underwent the series of tasks with and without an add-on to the SwayStar device, which provided patients with direction-specific vibrotactile feedback during the tasks. When patients performed the tasks with vibrotactile biofeedback, there was a general reduction in trunk sway, though not all the reductions differed significantly with trunk sway when performing the tasks without vibrotactile biofeedback. Studies with larger sample sizes are needed.

A 2015, MacKay published results from an (RCT) that evaluated the addition of biofeedback to standard care in 40 patients with relapsing-remitting multiple sclerosis patients to help improve emotional symptoms, coping, and fatigue in patients with multiple sclerosis.[131] The standard care psychosocial intervention consisted of relaxation, mindfulness, social support, and education. All patients attended a one-hour training and assessment sessions at weekly intervals. During the first session, all patients had training in mindfulness breathing exercises and progressive muscle relaxation techniques. Patients randomized to the biofeedback arm received additional instruction on use of biofeedback equipment for self-regulation. Following the 3 weekly sessions, patients were instructed to practice the exercises at home, with or without use of biofeedback equipment. Outcomes included breathing rate and anxiety, depression, fatigue, and muscle tension measures. At the end of treatment, there were not statistically significant differences between groups in any outcomes. However, some variables were marginally significant. The difference between the intervention and control group in breathing rate was 3.06 (95% CI, -0.17 to 6.280; p=0.06) and the difference in muscle tension was -13.91 (95% CI, -30.06 to 2.25; p=0.09). This study is limited by the small sample size, and other methodological constraints that make it hard to determine the efficacy of biofeedback for anxiety, fatigue, and stress in patients with multiple sclerosis.

SECTION SUMMARY

There is not enough research to show that biofeedback improves health outcomes for the treatment of multiple sclerosis. Additional well-designed, comparative studies are needed.

ORTHOSTATIC HYPOTENSION IN PATIENTS WITH A SPINAL CORD INJURY

SYSTEMATIC REVIEW

Gillis conducted a SR to identify and describe the body of literature pertaining to nonpharmacologic management of orthostatic hypotension during the early rehabilitation of persons with a spinal cord injury.[132] Participants with any level or degree of completeness of spinal cord injury and any time elapsed since their injuries were included. Interventions must have measured at least systolic blood pressure and have induced orthostatic stress in a controlled manner and have attempted to control orthostatic hypotension during an orthostatic challenge. Four distinct nonpharmacologic interventions for orthostatic hypotension were identified: application of compression and pressure to the abdominal region and/or legs, upper body exercise, functional electrical stimulation applied to the legs, and biofeedback. Methodologic quality varied dramatically between studies. The authors concluded that "…The clinical usefulness of compression/pressure, upper body exercise and biofeedback for treating OH [orthostatic hypotension] has not been proven."

RANDOMIZED CONTROLLED TRIALS

No RCTs identified after the above SR.

SECTION SUMMARY

There is insufficient evidence from high-quality comparative studies to permit conclusions about the impact of biofeedback on orthostatic hypotension in patients with a spinal cord injury.

PRETERM BIRTH PREVENTION

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback used to prevent preterm birth.

RANDOMIZED CONTROLLED TRIALS

In 2014, Siepmann published data on 48 women who had experienced threatened preterm labor between the 24th and 32nd gestational week.[133] Twenty-four patients received six biofeedback sessions over two weeks, and the other 24 patients were in a usual care group. Preterm delivery occurred in three patients (13%) in the biofeedback group and eight patients (33%) in the control group; the difference between groups was not statistically significant ($p>0.05$). Other gestational outcome data, such as the gestational duration and birthweight, also did not differ significantly between groups.

SECTION SUMMARY

There is insufficient evidence that biofeedback is effective in preventing preterm birth in pregnant women with a history of threatened preterm labor.

RAYNAUD'S PHENOMENON

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback for Raynaud's phenomenon.

RANDOMIZED CONTROLLED TRIALS

The Raynaud's Treatment Study Investigators conducted a randomized comparison of sustained-release nifedipine and thermal biofeedback in 313 patients with primary Raynaud's phenomenon.[134] In addition to these two treatment groups, there were two control treatments: pill placebo and EMG biofeedback. EMG biofeedback was chosen as a control because it did not address the physiological mechanism of Raynaud's phenomenon. Nifedipine significantly reduced Raynaud's attacks compared with placebo pill ($p<0.001$), but thermal biofeedback did not differ from EMG biofeedback ($p=0.37$). Better outcome for nifedipine relative to thermal biofeedback was nearly significant ($p=0.08$). With a larger sample size, the rate of 56% fewer attacks with nifedipine relative to thermal biofeedback would likely have been statistically significant. Thus, it cannot be concluded that thermal biofeedback is as effective as this form of medical therapy.

A 2009 SR identified five RCTs that reported a variety of outcomes. A pooled analysis from four RCTs (total n=110) on the change in frequency of attacks favored the sham control group over the biofeedback group.[135]

SECTION SUMMARY

There is insufficient evidence from a small number of RCTs that biofeedback is effective as a treatment of Raynaud's disease. A meta-analysis of the available RCTs did not find that biofeedback was more effective than the control intervention.

STRESS REDUCTION

SYSTEMIC REVIEWS

No SRs were identified for biofeedback for stress reduction.

RANDOMIZED CONTROLLED TRIALS

A 2015 Van der Zwan published an RCT comparing the efficacy of self-help physical activity (PA), mindfulness meditation (MM), and heart rate variability biofeedback (HRV-BF) in reducing stress and its related symptoms.[136] This study, which was limited in size and objective outcomes indicated that all interventions were equally effective in reducing stress and its related symptoms. The current evidence base is insufficient to permit conclusions on the impact of biofeedback on stress reduction.

SECTION SUMMARY

There is not enough research to show that biofeedback improves health outcomes for stress reduction. Additional well-designed, comparative studies are needed.

TINNITUS

SYSTEMATIC REVIEWS

No SRs were identified for biofeedback for tinnitus.

RANDOMIZED CONTROLLED TRIALS

Weise investigated the efficacy of a biofeedback-based cognitive-behavioral treatment for tinnitus in Germany. Tinnitus patients (n=130) were randomly assigned to an intervention or a wait-list control group.[137] Treatment consisted of 12 sessions of a biofeedback-based behavioral intervention over a three-month period. The primary outcome measures were global tinnitus annoyance and a daily rating of tinnitus disturbance measured by a Tinnitus Questionnaire (TQ) and a daily diary using visual analog scale (VAS) scores. Patients in the wait-list group participated in the treatment after the intervention group had completed the treatment. Results showed improvements regarding the following: tinnitus annoyance; diary ratings of loudness; feelings of controllability; changes in coping cognitions; changes in depressive symptoms; TQ: total score (range 0–84) pre-assessment mean 54.7, post-assessment mean 32.52; TQ: emotional distress (range 0–24) pre-assessment mean 16.00, post-assessment mean 8.15; and diary: loudness VAS (range 0–10) pre-assessment mean 5.68, post-assessment mean 4.38. Improvements were maintained over a six-month follow-up period in which variable effect sizes were observed. The study did not investigate the possible additive effect of biofeedback with cognitive-behavioral therapy and did not include an active treatment control group.

SECTION SUMMARY

The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of tinnitus.

URINARY DISORDERS

POST-PROSTATECTOMY URINARY INCONTINENCE

Systematic Reviews

Hsu (2016) published a SR evaluating pelvic floor muscle training (PFMT) with biofeedback in men who had radical prostatectomy.[138] Thirteen trials met reviewers' inclusion criteria. However, on closer inspection, not all trials included a biofeedback intervention, and other trials did not compare PFMT alone to PFMT plus biofeedback. Thus, conclusions about the added efficacy of biofeedback cannot be determined from the results of this SR.

In 2015 a Cochrane SR was conducted by Anderson to determine the effectiveness of conservative management interventions for urinary incontinence in men after a prostatectomy, which updated the 2012 review by Campbell et all.[139, 140] Conservative therapies include pelvic floor muscle training with or without feedback, electrical stimulation, extra-corporeal magnetic innervation, compression devices, lifestyle changes, or a combination of methods. Fifty randomized and quasi-Rs were included in the review; however, just eight of these trials examined biofeedback compared to pelvic floor muscle training. Per the rating of moderate quality studies, the authors found no evidence that pelvic floor muscle training with or without biofeedback was better than control for men who had urinary incontinence up to 12 months after radical prostatectomy.

A SR of PMFT to improve post-prostatectomy urinary incontinence identified three studies (281 men) that focused on the incremental value of biofeedback over written/verbal PME.[141] Although PPMFT appeared to reduce the time to recover continence compared to no training, there was no evidence for an advantage of training with biofeedback over written/verbal instructions. None of the individual trials found a statistically significant difference in outcomes between groups.

A 2003 randomized trial by Wille randomized 139 men prior to radical prostatectomy to one of three groups.[142] Group one received verbal and written instructions about PFMT from a physical therapist. Group two received PFMT instruction and instruction on using an electrical stimulation device. Group three received the previous two intervention components and training on using biofeedback with the electrical stimulation device. Patients had regular contact with a health care provider for the first five weeks after surgery. In the immediate postsurgical period, 20.5% in group one, 22.9% in group two, and 20.7% in group three were continent (p=0.815). After six and 12 months, continence rates remained similar among the groups. Twelve-month continence rates were 88% in group one, 81% in group two, and 88.6% in group three (p=0.524).

Bales (2000) randomized 100 men scheduled to undergo radical prostatectomy to PFMT plus biofeedback intervention (n=50) or to a control group (n=50) that received written and brief verbal instructions performing PFMT [143] The intervention consisted of a single session with a trained nurse two to four weeks before surgery. Three men dropped out of the PFMT plus intervention group. At six months after surgery, the incidence of urinary incontinence was 94% (44/47) in the PFMT plus biofeedback group and 96% (948/40) in the control group. The difference between groups was not statistically significant.

Randomized Controlled Trials

Oh (2020) randomized 84 patients undergoing robot-assisted laparoscopic radical prostatectomy to receive biofeedback with an extracorporeal perineometer plus PFMT or PFMT alone.[144] Although the average urine loss volume was lower in the biofeedback plus PFMT group compared to PFMT alone at month 1 after catheter removal (p=0.028), there was no difference between groups at months 2 or 3 after catheter removal. At study end (month 3), the percentage of continent patients was not significantly different between the biofeedback plus PFMT group (67.5%) and PFMT alone (61.9%).

A 2013 trial by Dijkstra-Eshuis compared the impact of preoperative pelvic floor muscle training (PFMT) with biofeedback (n=65) to standard care (n=56) on postoperative SUI in men undergoing laparoscopic radical prostatectomy.[145] Patients in the intervention group received four weekly sessions of biofeedback-assisted muscle training before surgery. Patients assigned to the control group did not have a presurgical intervention. The primary outcome was the rate of continence one year after surgery. Among the 74 patients available for follow-up analysis, 66% in the intervention group and 80% in the control group were continent at one year. The investigators originally planned to enroll 248 patients. However, an interim analysis after 122 patients were enrolled showed no significant benefit for the intervention group, even if the trial was completed as planned and therefore the trial was halted prematurely.

In 2012, Tienforti compared biofeedback (a session before and after surgery) in combination with written/verbal instructions on performing pelvic floor muscle exercises to a control intervention of written/verbal instructions alone.[146] The study included 34 patients, 32 of whom (16 in each group) were available for the final 6-month analysis. By six months, 10 of 16 patients (62.5%) in the treatment group and one of sixteen patients (6.3%) in the control group had achieved continence; this difference was statistically significant (p value not reported). The mean number of incontinence episodes per week was also significantly lower in the intervention group (2.7) than the control group (13.1) at six months.

STRESS, URGE OR MIXED URINARY INCONTINENCE

Systematic Reviews

Zhu (2022) performed a meta-analysis of 17 RCTs in postpartum women with lower urinary tract symptoms.[147] Fifteen studies (n=1965) compared PMFT plus biofeedback and electrical stimulation with PMFT alone. The analysis reported a significantly greater likelihood of achieving a therapeutic effect with combined PFMT plus biofeedback and electrical stimulation versus PMFT alone (risk ratio, 1.20; 95% confidence interval [CI], 1.15 to 1.24; I^2=0%). Pelvic floor muscle strength was also significantly higher with combination therapy (p<0.0001), but there was high heterogeneity among studies for this outcome (I^2=66%). Limitations of this analysis include risk of bias, lack of blinding, and heterogeneity in the definition of therapeutic effect.

Wu (2021) conducted a meta-analysis (N=21 studies; 13 RCTs, 8 nonrandomized) of PMFT with biofeedback versus PMFT alone in women with stress incontinence or pelvic floor dysfunction.[148] Most studies were conducted in China and none were from the U.S. There was a significant benefit of PMFT with biofeedback compared to PMFT alone in patients with both urinary incontinence (odds ratio, 4.82; 95% CI, 2.21 to 10.51; I^2=85.3%; n=11 studies) and pelvic floor dysfunction (odds ratio, 2.81; 95% CI, 2.04 to 3.86; I^2=13.1%; n=6 studies). Analyses of quality of life and quality of sexual life results were limited by substantial heterogeneity (>80%). Limitations of this analysis include an unclear, moderate, or high risk of

bias in all studies and use of Kegel exercises only in some studies rather than a complete PMFT program.

An updated Agency for Healthcare Research and Quality (AHRQ) SR and comparative effectiveness report of nonsurgical treatments for urinary incontinence in women was published by Blak (2018).[149] Biofeedback was considered among nonpharmacological behavioral therapy approaches. The report evaluated 42 studies that compared 19 active nonpharmacological interventions (including combinations of nonpharmacological interventions) with each other. One study reported statistically significant improvements in the daily activities domain with PFMT and biofeedback compared with PFMT alone, and one study reported significant improvements in distress for bladder training combined with PFMT and biofeedback when compared to bladder training, however, nine studies either reported discordant or nonsignificant differences across all other domains for this comparison. No adverse events were reported for any of the studies evaluating biofeedback. The report concludes that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- and second-line interventions alone for both stress and urgency UI.

A SR by Mateus-Vasconcelos (2018) assessed various physiotherapy methods to strengthen the pelvic floor muscles for women with stress urinary incontinence.[150] Their review included six studies which were RCTs, quasi-experimental trials, and systematic reviews. One study (an uncontrolled RCT) included biofeedback as a comparator; the effectiveness of pelvic floor muscle training (PFMT) with biofeedback (group n=6) to PFMT with palpation (group n=5) was evaluated. The exercises for the biofeedback group consisted of achieving the same number of rapid and slow contractions of the same duration as that achieved during the PERFECT scheme (8 series). The palpation group strengthened the pelvic floor muscles while a physiotherapist performed palpations on the central perineal tendon and vagina (4 sessions). At the end of treatment, there was no statistical difference in improvement between the biofeedback group and the palpation group in power, endurance, or rapidity of contractions. This RCT was limited in its small sample size and lack of control group and masking of assessors.

Oliveira (2017) published a SR that evaluated the protocols and/or PFMT parameters for women with stress urinary incontinence.[151] Seven studies were included, two of which involved biofeedback. The authors concluded that strengthening exercises for pelvic floor training combined with biofeedback was the most effective training protocol, but because of the limited studies and heterogeneity of the intervention protocols they could not identify what the most effective training protocol would be.

Moroni (2016) published a SR of 37 RCTs on conservative treatment of stress urinary incontinence in women.[152] Five trials (N=250) were identified that compared PFMT plus biofeedback with biofeedback alone. A pooled analysis of four studies found significantly more urine loss as measured by a posttreatment pad test with PFMT alone than with PFMT plus biofeedback (mean difference [MD], 0.90; 95% confidence interval [CI], 0.71 to 1.10). Reviewers noted that the difference between groups was likely not clinically significant because there was only about a one-gram difference. Moreover, the finding was largely due to the effect of one study. Results on other outcomes (eg, quality of life, number of incontinence episodes) could not be pooled due to imprecision of the estimates.

A 2011 Cochrane SR evaluated feedback or biofeedback in conjunction with pelvic floor

muscle training (PFMT) for treating urinary incontinence (UI) in women.[153] The review included RCTs in women with stress, urge or mixed UI in which at least two arms of the study included exercise training and at least one arm included feedback and/or biofeedback. Feedback was defined as verbal feedback by a clinician, whereas biofeedback involved use of an instrument or device. After examining 36 full-text articles, 24 trials were found to meet the review's inclusion criteria and 17 contributed data to the analysis of at least one primary outcome measure. Sixteen of the 24 trials included a comparison of PFMT plus biofeedback to PFMT alone; nine of these included the same PFMT programs in both groups. The primary outcomes of the review were quality of life and improvement or cure. Nine trials used one of several validated quality-of-life instruments; however, only four of these reported data in a form that could be used for meta-analysis. Thus, quality-of-life results were not pooled. Data were pooled for the other primary outcome, improvement or cure, but there were a sufficient number of studies only for the comparison between PFMT with and without biofeedback. In a pooled analysis of seven studies, there was a significant reduction in the proportion of women reporting 'no improvement or cure' when biofeedback was added to muscle exercise (risk ratio [RR]: 0.75, confidence interval [CI]: 0.66 to 0.86). The authors noted that there may have been other differences between groups, such as more frequent contact with a healthcare professional or a greater number of treatment sessions, which might partially explain the difference in the improvement or cure rate in women who did or did not receive biofeedback. Moreover, when only the outcome 'no cure' was examined, there was not a significant difference between groups that did and did not receive biofeedback (5 studies: RR: 0.92, 95% CI: 0.81-1.05). Among secondary outcomes, a pooled analysis of seven trials did not find a significant difference in leakage episodes in a 24-hour period after treatment (mean difference: -0.01, 95% CI: -0.21 to 0.01). For the outcomes frequency and nocturia, data could not be combined but the review authors reported that the pattern was one of no difference between groups.

A number of significant design flaws in the 24 trials that met inclusion criteria (N=1583 women) limit the reliability of the reported outcomes. These flaws included:

- It was common for the women in the biofeedback arm to have more contact with healthcare professionals than those who did not receive biofeedback;
- Many of the trials were at moderate to high risk of bias; and
- There was significant variation in the regimens proposed for feedback and biofeedback, and the intervention's purpose and composition were often unclear.

The authors concluded that feedback or biofeedback may provide additional benefit to pelvic floor muscle exercises (PME) alone; however, further research is needed to differentiate whether the beneficial effect was due to feedback, biofeedback, or some other difference between the trial arms.

Randomized Controlled Trials

Kannan (2022) published a single blinded three-arm randomized control pilot trial evaluating safety, feasibility, effectiveness of a new biofeedback device (PelviSense; PS) with that of conventional biofeedback (CB) using an intravaginal probe for the treatment of stress urinary incontinence (SUI) in women.[154] Patients (n=51) were randomly allocated to one of three study groups: PS-assisted pelvic floor muscle training (PFMT), CB-assisted PFMT, or PFMT alone. The PFMT adherence was greater in the PS-assisted PFMT group than in the unassisted or CB-assisted PFMT groups. Between-groups analysis revealed significant effects

on improved SUI symptoms, urine loss severity, and PFM strength for the PS-assisted PFMT group compared with the CB-assisted and PFMT alone groups. This pilot study is limited in sample size, study duration, and lack of long-term follow-up.

Sahin (2022) conducted a prospective, randomized study to examine the effect of pelvic floor exercises performed with EMG biofeedback or a vaginal cone in women (N=40) with stress urinary incontinence.[155] Patients were randomly divided into two groups; pelvic floor muscle exercise (PFME) with a vaginal cone at home (N = 20) and PFME with EMG biofeedback in the hospital (N = 20). Both groups improved in the pad test, muscle strength, social anxiety index, quality of life, and treatment satisfaction measurement compared with the pre-treatment period ($p < 0.05$). No significant difference was found between the groups in terms of assessment parameters in intergroup analyses during follow-up ($p > 0.05$).

Hagen (2020) conducted a multicenter RCT in 600 women with stress or mixed urinary incontinence. Participants were randomized to 16 weeks of PMFT with electromyographic biofeedback or PMFT alone. Both groups received supervised PMFT during clinic appointments and a home PMFT regimen. The mean number of appointments attended was about four in both groups. Urinary incontinence symptoms (self-reported at month 24 via the International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form [ICIQ-UI-SF]) were similar in both groups (mean difference, -0.09; 95% CI, -0.92 to 0.75; p=.84). ICIQ-UI-SF scores were also similar between groups at earlier times (6 and 12 months). At 24 months, the proportion of patients who achieved the study's definition of cure, improvement, and symptoms that were very much better or much better was similar between groups. Pelvic floor muscle strength and endurance was assessed at 6 months, with similar findings in both groups. A limitation of this study is the short duration of the intervention compared to the length of follow-up.

A double-blind, sham-controlled RCT by Terlikowski (2013) compared transvaginal electrical stimulation (TVES) with active (n=68) or sham (n=34) EMG-biofeedback in premenopausal women with stress urinary incontinence (SUI).[156] The group receiving active biofeedback had significantly better results than the sham group for reduction in urinary leakage, pelvic floor muscle strength, and incontinence-related quality of life. No significant between group difference was found in urodynamic data. The authors concluded that TVES with active EMG biofeedback “is a trustworthy method for treating premenopausal women with stress urinary incontinence; however reliability needs to be established.”

Other RCTs comparing the efficacy of PFMT alone with PFMT with biofeedback have been published. Statistically significant differences in outcomes between interventions were not consistently found, however, sample sizes were small (<25 per group) and thus the studies may have been underpowered.

VOIDING DYSFUNCTION

Systematic Reviews

Fazeli published a SR with meta-analysis to better understand how biofeedback has been used to treat children, up to age 18, with symptoms of bladder dysfunction not responding to standard therapy alone.[157] Five eligible studies were included in the SR. Four of the studies were pooled in the meta-analysis for a total of 382 participants. The overall proportion of cases with resolved incontinence at six months was similar in biofeedback and control groups (OR1.37 [95% CI 0.64 to 2.93], RD 0.0.7 [-0.9, 0.23]). There was no significant different in

mean maximum urinary flow rate mean difference 0.50 ml, range -0.56 to 1.55) or likelihood of urinary tract infection (OR 1.30 [95% CI 0.65 to 2.58]). This SR was limited by the paucity of research, high quality studies, and small sample sizes.

Randomized Controlled Trials

In 2015, Sener published results from a retrospective RCT that compared the outcomes of four biofeedback sessions (group one; n=20) with six to ten biofeedback sessions (group two; n=20) on treating children with dysfunctional voiding. [158] Normalized voiding after the treatment was determined in 18 subjects from group one, and 19 subjects in group two. Fifteen out of the 40 total study sample were determined to have reflux. At the six month evaluation of group one, voiding dysfunction had resolved in seven, had improved in three, and persisted in one. In group two, voiding dysfunction had resolved in ten, improved in three. This study is limited by a small sample size and other methodological constraints that make it difficult to determine the efficacy of biofeedback for children with dysfunctional voiding.

In 2015, Minardi published results from a four arm RCT to evaluate the therapeutic effects of tamsulosin and biofeedback on recurrent urinary tract infections in 155 women with dysfunctional voiding.[159] The study consisted of four groups: group one received uroflowmetry biofeedback, group two received α1-adrenoceptor antagonists, group three received uroflowmetry biofeedback combined with α1-adrenoceptor antagonists, and group four received no treatment. Patients were evaluated by the American Urological Association Symptom Index. Urodynamics was carried out in patients of groups one, two and three at three, six and 12 months, whereas urodynamics was only carried out at 12 months in group four. The incidence of storage and emptying symptoms, mean post-void residual, mean flow rate, flow time, voiding volume, and urinary tract infections decreased at three, six, and twelve month for all four groups. This study was limited by the small sample size, attrition, and other methodological constraints making it hard to determine the efficacy of biofeedback for women with recurrent urinary tract infections and dysfunctional voiding.

OTHER URINARY INCONTINENCE

Systemic Reviews

No SRs were identified for biofeedback for the treatment of other urinary incontinence.

Randomized Control Trials

An RCT of 74 patients with multiple sclerosis reported that the addition of neuromuscular electrical stimulation with biofeedback training resulted in 85% incontinence reduction, compared to a 47% incontinence reduction in the control group trained only with biofeedback.[160]

Section Summary

The available evidence for the use of biofeedback in the treatment of stress and/or or urge urinary incontinence in female patients includes several RCTs and SRs. Although there is some heterogeneity across these studies, there is enough research to show that biofeedback improves outcomes in women with urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT). The current evidence base is insufficient to draw conclusions regarding the role of biofeedback for the treatment of urinary incontinence other than in this setting.

OTHER INDICATIONS

Other indications for which there are no clinical trial publications sufficient to demonstrate the effectiveness of biofeedback include, but are not limited to the following:

- Cardiovascular disorders
- Childhood Apraxia of Speech[161]
- Chronic fatigue syndrome
- Chronic obstructive pulmonary disease (COPD)
- Epilepsy[162]
- Facial palsy
- Hand hemiplegia
- Low vision
- Side-effects of cancer chemotherapy

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF SLEEP MEDICINE (AASM)

In 2008, an AASM special committee released a guideline on evaluation and management of chronic insomnia in adults.[163] The AASM considers biofeedback as one of a number of common therapies that are “effective and recommended in the treatment of chronic primary and comorbid (secondary) insomnia (Guideline)” The AASM definition for guideline is “a patient-care strategy, which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level two Evidence (RCTs with high alpha and beta error) or a consensus of Level three Evidence (non-randomized concurrently controlled studies).”

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2014, the American College of Gastroenterology (ACG) published guidelines on the management of fecal incontinence.[164] The guideline indicated that pelvic floor rehabilitation techniques (eg, biofeedback, therapeutic exercises) are effective in patients with fecal incontinence who do not respond to conservative measures (strong recommendation, moderate quality of evidence).

In 2021, the American College of Gastroenterology (ACG) published a guideline on the management of benign anorectal disorders.[165] The guideline notes: "We recommend that instrumented anorectal biofeedback therapy should be used to manage symptoms in DD [defecation disorder] (strong recommendation; minimal risk of harm; quality of evidence: moderate)." Furthermore, the guideline notes the following key concepts related to biofeedback in the setting of DD:

- "Biofeedback should involve 4–6 sessions with well-trained therapists aimed at normalizing rectoanal coordination, ensuring good rectal pressure on strain, sensory retraining, and balloon expulsion retraining.

- Baseline ARM [anorectal manometry] and balloon expulsion is useful to predict the outcome and guide biofeedback therapy
- Defecography (MR [magnetic resonance] or barium) may be indicated in patients with DD who fail conservative therapy and biofeedback."
- The guideline also provides a suggested treatment protocol for anorectal biofeedback.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)[166]

In 2015 ACOG reaffirmed their 2009 clinical practice guidelines on urinary incontinence in women. Biofeedback was not included in these recommendations.

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians published a guideline titled “Noninvasive Treatments for Acute, Subacute, and Chronic Back Pain: a Clinical Practice Guideline From the American College of Physicians”. The guideline stated low quality evidence supports biofeedback for chronic low back pain.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE (ACOEM)

In 2020, the ACOEM updated their guideline on noninvasive and minimally invasive management of low back disorders.[167] The role of biofeedback is not addressed in this updated guideline.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

The updated AGA position statement (2013) on constipation considers biofeedback a possible treatment for patients with dyssynergia-type constipation with severe symptoms and proven pelvic floor dysfunction “to train patients to relax their pelvic floor muscles during straining and to correlate relaxation and pushing to achieve defecation (Strong Recommendation, High-Quality Evidence).”[168, 169]

The following statement on biofeedback was included: “Pelvic floor retraining by biofeedback therapy rather than laxatives is recommended for defecatory disorders (Strong Recommendation, High-Quality Evidence).”

AMERICAN HEART ASSOCIATION

A 2013 the American Heart Association published a statement based on a systematic literature review on alternatives to diet and medication for lowering blood pressure (BP) in patients with hypertension.[170] The report found meta-analyses to have had mixed results, though some recent trials showed reduction in BP with certain biofeedback techniques. However, recommendations for any specific techniques could not be made due to the paucity of data. The statement recommended that biofeedback could be considered for treatment of hypertension. This recommendation was rated as Class IIB, Level of Evidence B recommendation, defined as usefulness/efficacy less well-defined based on conflicting evidence from a single RCT or nonrandomized studies; additional studies with broad objectives needed.

AMERICAN NEUROGASTROENTEROLOGY AND MOTILITY SOCIETY

In 2015, the American Neurogastroenterology and Motility Society and the European Society of Neurogastroenterology and Mobility jointly published consensus-based guidelines on biofeedback therapy for anorectal disorders.[171] The guidelines included the following recommendations:

- "Biofeedback is recommended for the short-term and long-term treatment of constipation with dyssynergic defecation."
- "Biofeedback therapy is recommended for the short-term and long-term treatment of fecal incontinence"
- "Biofeedback therapy is not recommended for the routine treatment of children with functional constipation, with or without overflow fecal incontinence."

AMERICAN SOCIETY OF COLON AND RECTAL SURGEONS (ASCRS)

In 2016, ASCRS published guidelines on the evaluation and management of constipation.[172] The guideline states that biofeedback therapy is a first-line treatment for symptomatic pelvic floor dyssynergia (strong recommendation, moderate quality of evidence).

An American Society of Colon and Rectal Surgeons practice parameter recommended biofeedback "as an initial treatment for motivated patients with incontinence with some voluntary sphincter contraction. Biofeedback may be considered a first-line option for many patients with fecal incontinence who have not responded to simple dietary modification or medication. Supportive counseling and practical advice regarding diet and skin care can improve the success of biofeedback. Biofeedback may be considered before attempting sphincter repair or for those who have persistent or recurrent symptoms after sphincter repair. It may have a role in the early postpartum period in females with symptomatic sphincter weakness. Biofeedback and a pelvic floor exercise program can produce improvement that lasts more than two years. Biofeedback home training is an alternative to ambulatory training programs, especially in the elderly." The authors assigned a level of evidence of III and grade of recommendation B, defined as well-designed, quasi-experimental nonrandomized studies with generally consistent findings.

AMERICAN UROLOGICAL ASSOCIATION AND THE SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE & UROGENITAL RECONSTRUCTION (AUA/SUFU)[173]

The 2020 AUA/SUFU evidence-based practice guidelines recommended offering behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training) as first line therapy to all patients with overactive bladder. This recommendation was rated as a Standard, defined as a directive statement that an action should or should not be taken. The strength of evidence was rated as Grade B (moderate quality; moderate certainty). Biofeedback was included among a number of other modalities as a component of behavioral therapies. The guideline reported that the limited literature did not show any single component of behavioral therapy to be essential to efficacy or to be superior in efficacy.

TENSION AND MIGRAINE HEADACHES

Clinical practice guidelines from professional associations include biofeedback in their recommendations for prevention of tension and migraine headaches.[174-177] The associations included the American Academy of Neurology, the National Institute of Neurologic Disorders and Stroke, the U.S. Headache Consortium, and the European Federation of Neurological Societies.

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

In 2017, the National Institute for Clinical Excellence (NICE) issued evidence-based guidance on constipation in children and young people, which was reaffirmed in 2014.[178] The guidance indicated that biofeedback should not be used for ongoing treatment.

SUMMARY

It appears that biofeedback may improve health outcomes for some people for prevention of tension-type and migraine headaches. Clinical guidelines based on research recommend biofeedback for people with tension and migraine headaches. Therefore, biofeedback may be considered medically necessary when policy criteria are met.

There is enough research to show that biofeedback improves health outcomes for people with dyssynergia-type constipation. Clinical guidelines based on research recommend biofeedback for pelvic floor training for dyssynergia constipation in adults. Therefore, biofeedback may be considered medically necessary when policy criteria are met.

There is enough research to show that biofeedback improves outcomes in individuals with stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT). Clinical practice guidelines recommended behavioral therapies including biofeedback as to patients with overactive bladder. Therefore, biofeedback may be considered medically necessary in individuals with stress and/or urge urinary incontinence when administered in conjunction with pelvic floor muscle training (PFMT).

There is not enough research to show that biofeedback improves health outcomes for people with the variety of investigational indications listed in the criteria. In addition, no clinical guidelines based on research recommend biofeedback for these indications. Therefore, biofeedback is considered investigational for all other indications.

REFERENCES

1. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. *Gastroenterology.* 2016. PMID: 27144627
2. Yorke J, Fleming S, Shuldham C, et al. Nonpharmacological interventions aimed at modifying health and behavioural outcomes for adults with asthma: a critical review. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology.* 2015;45(12):1750-64. PMID: 25675860
3. Meuret AE, Ritz T, Wilhelm FH, et al. Targeting pCO(2) in asthma: pilot evaluation of a capnometry-assisted breathing training. *Appl Psychophysiol Biofeedback.* 2007;32(2):99-109. PMID: 17564826
4. Lehrer PM, Vaschillo E, Vaschillo B, et al. Biofeedback treatment for asthma. *Chest.* 2004;126(2):352-61. PMID: 15302717
5. Lehrer P, Carr RE, Smetankine A, et al. Respiratory sinus arrhythmia versus neck/trapezius EMG and incentive inspirometry biofeedback for asthma: a pilot study. *Appl Psychophysiol Biofeedback.* 1997;22(2):95-109. PMID: 9341966
6. Coben R, Myers TE. The relative efficacy of connectivity guided and symptom based EEG biofeedback for autistic disorders. *Appl Psychophysiol Biofeedback.* 2010;35(1):13-23. PMID: 19649702

7. Yang HC, Lee IC. Visual feedback and target size effects on reach-to-grasp tasks in children with autism. *Journal of autism and developmental disorders.* 2014;44(12):3129-39. PMID: 24974254
8. Kouijzer ME, van Schie HT, Gerrits BJ, et al. Is EEG-biofeedback an effective treatment in autism spectrum disorders? A randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2013;38(1):17-28. PMID: 22903518
9. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev.* 2011(12):CD006283. PMID: 22161401
10. Cardoso JR, Teixeira EC, Moreira MD, et al. Effects of exercises on Bell's palsy: systematic review of randomized controlled trials. *Otol Neurotol.* 2008;29(4):557-60. PMID: 18520590
11. Manfredini D, Ahlberg J, Winocur E, et al. Management of sleep bruxism in adults: a qualitative systematic literature review. *Journal of oral rehabilitation.* 2015;42(11):862-74. PMID: 26095208
12. Wang LF, Long H, Deng M, et al. Biofeedback treatment for sleep bruxism: a systematic review. *Sleep & breathing = Schlaf & Atmung.* 2013. PMID: 23756884
13. Sato M, Iizuka T, Watanabe A, et al. Electromyogram biofeedback training for daytime clenching and its effect on sleep bruxism. *Journal of oral rehabilitation.* 2015;42(2):83-9. PMID: 25256380
14. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev.* 2012;11:CD007407. PMID: 23152245
15. Palermo TM, Eccleston C, Lewandowski AS, et al. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *Pain.* 2010;148(3):387-97. PMID: 19910118
16. Richards R, van den Noort JC, Dekker J, et al. Gait Retraining With Real-Time Biofeedback to Reduce Knee Adduction Moment: Systematic Review of Effects and Methods Used. *Arch Phys Med Rehabil.* 2017;98(1):137-50. PMID: 27485366
17. Astin JA, Beckner W, Soeken K, et al. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum.* 2002;47(3):291-302. PMID: 12115160
18. Eid MA, Aly SM, El-Shamy SM. Effect of Electromyographic Biofeedback Training on Pain, Quadriceps Muscle Strength, and Functional Ability in Juvenile Rheumatoid Arthritis. *American journal of physical medicine & rehabilitation.* 2016;95(12):921-30. PMID: 27149595
19. Theadom A, Cropley M, Smith HE, et al. Mind and body therapy for fibromyalgia. *Cochrane Database Syst Rev.* 2015;4:CD001980. PMID: 25856658
20. Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-Biofeedback in Fibromyalgia Syndrome: A Meta-Analysis and a Systematic Review of Randomized Controlled Trials. *Evidence-based complementary and alternative medicine : eCAM.* 2013;2013:962741. PMID: 24082911
21. Collins NJ, Bisset LM, Crossley KM, et al. Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials. *Sports Med.* 2012;42(1):31-49. PMID: 22149696
22. Rixe JA, Glick JE, Brady J, et al. A review of the management of patellofemoral pain syndrome. *The Physician and sportsmedicine.* 2013;41(3):19-28. PMID: 24113699
23. Sielski R, Rief W, Glombiewski JA. Efficacy of Biofeedback in Chronic back Pain: a Meta-Analysis. *Int J Behav Med.* 2017;24(1):25-41. PMID: 27307013

24. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-30. PMID: 28192789
25. Haines T, Bowles KA. Cost-effectiveness of using a motion-sensor biofeedback treatment approach for the management of sub-acute or chronic low back pain: economic evaluation alongside a randomised trial. *BMC musculoskeletal disorders.* 2017;18(1):18. PMID: 28095832
26. Daffada PJ, Walsh N, McCabe CS, et al. The impact of cortical remapping interventions on pain and disability in chronic low back pain: a systematic review. *Physiotherapy.* 2015;101(1):25-33. PMID: 25442672
27. Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev.* 2010(7):CD002014. PMID: 20614428
28. Bush C, Ditto B, Feuerstein M. A controlled evaluation of paraspinal EMG biofeedback in the treatment of chronic low back pain. *Health Psychol.* 1985;4(4):307-21. PMID: 2932330
29. Nouwen A. EMG biofeedback used to reduce standing levels of paraspinal muscle tension in chronic low back pain. *Pain.* 1983;17(4):353-60. PMID: 6229707
30. Newton-John TR, Spence SH, Schotte D. Cognitive-behavioural therapy versus EMG biofeedback in the treatment of chronic low back pain. *Behaviour research and therapy.* 1995;33:691-7. PMID: 7654161
31. Stuckey SJ, Jacobs A, Goldfarb J. EMG biofeedback training, relaxation training, and placebo for the relief of chronic back pain. *Perceptual and motor skills.* 1986;63(3):1023-36. PMID: 2949196
32. Kent P, Haines T, O'Sullivan P, et al. Cognitive functional therapy with or without movement sensor biofeedback versus usual care for chronic, disabling low back pain (RESTORE): a randomised, controlled, three-arm, parallel group, phase 3, clinical trial. *Lancet.* 2023;401(10391):1866-77. PMID: 37146623
33. Tan G, Rintala DH, Jensen MP, et al. A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain. *Eur J Pain.* 2015;19(2):271-80. PMID: 24934738
34. Kapitza KP, Passie T, Bernateck M, et al. First non-contingent respiratory biofeedback placebo versus contingent biofeedback in patients with chronic low back pain: a randomized, controlled, double-blind trial. *Appl Psychophysiol Biofeedback.* 2010;35(3):207-17. PMID: 20237953
35. Glombiewski JA, Hartwich-Tersek J, Rief W. Two psychological interventions are effective in severely disabled, chronic back pain patients: a randomised controlled trial. *Int J Behav Med.* 2010;17(2):97-107. PMID: 19967572
36. Campo M, Zadro JR, Pappas E, et al. The effectiveness of biofeedback for improving pain, disability and work ability in adults with neck pain: A systematic review and meta-analysis. *Musculoskelet Sci Pract.* 2021;52:102317. PMID: 33461043
37. Kamonseki DH, Calixtre LB, Barreto RPG, et al. Effects of electromyographic biofeedback interventions for shoulder pain and function: Systematic review and meta-analysis. *Clin Rehabil.* 2021;35(7):952-63. PMID: 33517777
38. Shearer HM, Carroll LJ, Wong JJ, et al. Are psychological interventions effective for the management of neck pain and whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *The spine journal : official journal of the North American Spine Society.* 2016;16(12):1566-81. PMID: 26279388

39. Hesselstrand M, Samuelsson K, Liedberg G. Occupational Therapy Interventions in Chronic Pain--A Systematic Review. *Occupational therapy international.* 2015;22(4):183-94. PMID: 26076994
40. de Oliveira AKA, da Costa KSA, de Lucena GL, et al. Comparing exercises with and without electromyographic biofeedback in subacromial pain syndrome: A randomized controlled trial. *Clin Biomech (Bristol, Avon).* 2022;93:105596. PMID: 35183878
41. Ma C, Szeto GP, Yan T, et al. Comparing biofeedback with active exercise and passive treatment for the management of work-related neck and shoulder pain: a randomized controlled trial. *Arch Phys Med Rehabil.* 2011;92(6):849-58. PMID: 21621660
42. Aggarwal VR, Lovell K, Peters S, et al. Psychosocial interventions for the management of chronic orofacial pain. *Cochrane Database Syst Rev.* 2011(11):CD008456. PMID: 22071849
43. Medlicott MS, Harris SR. A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. *Phys Ther.* 2006;86(7):955-73. PMID: 16813476
44. McNeely ML, Armijo Olivo S, Magee DJ. A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders. *Phys Ther.* 2006;86(5):710-25. PMID: 16649894
45. Greco CM, Rudy TE, Manzi S. Effects of a stress-reduction program on psychological function, pain, and physical function of systemic lupus erythematosus patients: a randomized controlled trial. *Arthritis Rheum.* 2004;51(4):625-34. PMID: 15334437
46. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. *J Pediatr Gastroenterol Nutr.* 2000;31(1):47-51. PMID: 10896070
47. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. *Pediatrics.* 2003;111(1):e1-11. PMID: 12509588
48. Morin M, Carroll MS, Bergeron S. Systematic Review of the Effectiveness of Physical Therapy Modalities in Women With Provoked Vestibulodynia. *Sexual medicine reviews.* 2017;5(3):295-322. PMID: 28363763
49. Bergeron S, Binik YM, Khalife S, et al. A randomized comparison of group cognitive--behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain.* 2001;91(3):297-306. PMID: 11275387
50. CADTH. Post-Traumatic Stress Disorder: Summary of Evidence of the Clinical Effectiveness of Treatments. [cited 9/25/2023]. 'Available from:' https://www.cadth.ca/post-traumatic-stress-disorder-summary-evidence-clinical-effectiveness-treatments.
51. Neurofeedback and Biofeedback for Mood and Anxiety Disorders: A Review of the Clinical Evidence and Guidelines. [cited 09/25/2023]. 'Available from:' https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0939%20Neurofeedback%20Biofeedback%20Final.pdf.
52. Goessl VC, Curtiss JE, Hofmann SG. The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychological medicine.* 2017:1-9. PMID: 28478782
53. Schoenberg PL, David AS. Biofeedback for psychiatric disorders: a systematic review. *Appl Psychophysiol Biofeedback.* 2014;39(2):109-35. PMID: 24806535
54. Maynart W, Albuquerque M, Santos RCS, et al. The use of biofeedback intervention in the improvement of depression levels: a randomised trial. *Acta Neuropsychiatr.* 2021;33(3):126-33. PMID: 33427129

55. Park SM, Jung HY. Respiratory sinus arrhythmia biofeedback alters heart rate variability and default mode network connectivity in major depressive disorder: A preliminary study. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology.* 2020;158:225-37. PMID: 33148502
56. Chen YF, Huang XY, Chien CH, et al. The Effectiveness of Diaphragmatic Breathing Relaxation Training for Reducing Anxiety. *Perspectives in psychiatric care.* 2016. PMID: 27553981
57. Woodward S, Norton C, Chiarelli P. Biofeedback for treatment of chronic idiopathic constipation in adults. *Cochrane Database Syst Rev.* 2014;3:CD008486. PMID: 24668156
58. Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. *Gastroenterology.* 2006;130:657-64. PMID: 16530506
59. Heymen S, Scarlett Y, Jones K, et al. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. *Dis Colon Rectum.* 2007;50(4):428-41. PMID: 17294322
60. Hart SL, Lee JW, Berian J, et al. A randomized controlled trial of anorectal biofeedback for constipation. *International journal of colorectal disease.* 2012;27(4):459-66. PMID: 22159695
61. Farid M, El Monem HA, Omar W, et al. Comparative study between biofeedback retraining and botulinum neurotoxin in the treatment of anismus patients. *International journal of colorectal disease.* 2009;24(1):115-20. PMID: 18719924
62. Simon MA, Bueno AM. Behavioural treatment of the dyssynergic defecation in chronically constipated elderly patients: a randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2009;34(4):273-7. PMID: 19618262
63. You YT WJ, ChangChien CR, et al. The treatment of outlet obstruction constipation. . *Formosan Journal of Surgery.* 2001;34:3-10. PMID: No PMID Entry
64. Hu WH LJ, Chan AO, et al Biofeedback is an effective treatment for functional constipation: a randomized controlled study. *Gastroenterology.* 2001;130(4Suppl 2):A287. PMID: No PMID Entry
65. Koutsomanis D, Lennard-Jones JE, Roy AJ, et al. Controlled randomised trial of visual biofeedback versus muscle training without a visual display for intractable constipation. *Gut.* 1995;37(1):95-9. PMID: 7672690
66. Heymen S, Wexner SD, Vickers D, et al. Prospective, randomized trial comparing four biofeedback techniques for patients with constipation. *Dis Colon Rectum.* 1999;42(11):1388-93. PMID: 10566525
67. Pourmomeny AA, Emami MH, Amooshahi M, et al. Comparing the efficacy of biofeedback and balloon-assisted training in the treatment of dyssynergic defecation. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie.* 2011;25(2):89-92. PMID: 21321680
68. Bleijenberg G, Kuijpers HC. Biofeedback treatment of constipation: a comparison of two methods. *The American journal of gastroenterology.* 1994;89(7):1021-6. PMID: 8017359
69. Glia A, Gylin M, Gullberg K, et al. Biofeedback retraining in patients with functional constipation and paradoxical puborectalis contraction: comparison of anal manometry and sphincter electromyography for feedback. *Dis Colon Rectum.* 1997;40(8):889-95. PMID: 9269803

70. Chang HS, Myung SJ, Yang SK, et al. Effect of electrical stimulation in constipated patients with impaired rectal sensation. *International journal of colorectal disease.* 2003;18(5):433-8. PMID: 12677456
71. Faried M, El Nakeeb A, Youssef M, et al. Comparative study between surgical and non-surgical treatment of anismus in patients with symptoms of obstructed defecation: a prospective randomized study. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2010;14(8):1235-43. PMID: 20499203
72. Lehur PA, Stuto A, Fantoli M, et al. Outcomes of stapled transanal rectal resection vs. biofeedback for the treatment of outlet obstruction associated with rectal intussusception and rectocele: a multicenter, randomized, controlled trial. *Dis Colon Rectum.* 2008;51(11):1611-8. PMID: 18642046
73. Rao SS, Seaton K, Miller M, et al. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. *Clin Gastroenterol Hepatol.* 2007;5(3):331-8. PMID: 17368232
74. Jung KW MS, Byeon JS, et al. Combined therapy with electrical stimulation and biofeeback in pelvic floor dyssynergia. *Neurogastroenterology and Motility* 2007;19(Suppl S3):74. PMID: No PMID Entry
75. Jung KW MS, Byeon JS, et al. Electrical stimulation therapy in pelvic floor dyssynergia: prospective, randomized study combined with biofeedback. *Journal of Gastroenterology and Hepatology* 2007;22(Suppl 2):A209. PMID: No PMID Entry
76. Enck P, Van der Voort IR, Klosterhalfen S. Biofeedback therapy in fecal incontinence and constipation. *Neurogastroenterol Motil.* 2009;21(11):1133-41. PMID: 19566591
77. Koh CE, Young CJ, Young JM, et al. Systematic review of randomized controlled trials of the effectiveness of biofeedback for pelvic floor dysfunction. *The British journal of surgery.* 2008;95(9):1079-87. PMID: 18655219
78. Chiarelli P. Systematic review: the management of constipation using physical therapies including biofeedback. Australian and New Zealand Continence Journal. *Australian and New Zealand Continence Journal.* 2008;14(1):6-13. PMID: No PMID Entry
79. Zhou LK CM, Ke MY. Systematic review of biofeedback for adult chronic constipation. *Journal of Gastroenterology and Hepatology* 2008;23(Suppl 5):A115. PMID: No PMID Entry
80. Vonthein R, Heimerl T, Schwandner T, et al. Electrical stimulation and biofeedback for the treatment of fecal incontinence: a systematic review. *International journal of colorectal disease.* 2013;28(11):1567-77. PMID: 23900652
81. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. *Cochrane Database Syst Rev.* 2012;7:CD002111. PMID: 22786479
82. Damon H, Siproudhis L, Faucheron JL, et al. Perineal retraining improves conservative treatment for faecal incontinence: a multicentre randomized study. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver.* 2014;46(3):237-42. PMID: 24444704
83. Brazzelli M, Griffiths PV, Cody JD, et al. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev.* 2011(12):CD002240. PMID: 22161370
84. Borowitz SM, Cox DJ, Sutphen JL, et al. Treatment of childhood encopresis: a randomized trial comparing three treatment protocols. *J Pediatr Gastroenterol Nutr.* 2002;34(4):378-84. PMID: 11930093

85. Davila E, de Rodriguez GG, Adrianza A, et al. [The usefulness of biofeedback in children with encopresis. A preliminary report]. *G E N.* 1992;46(4):297-301. PMID: 1340834
86. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. *J Pediatr.* 1990;116(2):214-22. PMID: 2299491
87. Loening-Baucke V, Desch L, Wolraich M. Biofeedback training for patients with myelomeningocele and fecal incontinence. *Dev Med Child Neurol.* 1988;30(6):781-90. PMID: 3234607
88. Nolan T, Catto-Smith T, Coffey C, et al. Randomised controlled trial of biofeedback training in persistent encopresis with anismus. *Arch Dis Child.* 1998;79(2):131-5. PMID: 9797593
89. van der Plas RN, Benninga MA, Buller HA, et al. Biofeedback training in treatment of childhood constipation: a randomised controlled study. *Lancet.* 1996;348(9030):776-80. PMID: 8813983
90. van der Plas RN, Benninga MA, Redekop WK, et al. Randomised trial of biofeedback training for encopresis. *Arch Dis Child.* 1996;75(5):367-74. PMID: 8957948
91. Wald A, Chandra R, Gabel S, et al. Evaluation of biofeedback in childhood encopresis. *J Pediatr Gastroenterol Nutr.* 1987;6(4):554-8. PMID: 3430263
92. Sunic-Omejc M, Mihanovic M, Bilic A, et al. Efficiency of biofeedback therapy for chronic constipation in children. *Collegium antropologicum.* 2002;26 Suppl:93-101. PMID: 12674840
93. Brazzelli M, Griffiths P. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev.* 2006(2):CD002240. PMID: 16625557
94. Brazzelli M, Griffiths P. Behavioral and cognitive interventions with or without other treatments for defaecation disorders in children. *Cochrane Database of Systematic Reviews.* 2003(2). PMID: No PMID Entry
95. Coulter ID, Favreau JT, Hardy ML, et al. Biofeedback interventions for gastrointestinal conditions: a systematic review. *Altern Ther Health Med.* 2002;8(3):76-83. PMID: 12017503
96. Wegh CAM, Baaleman DF, Tabbers MM, et al. Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis. *J Pediatr.* 2022;240:136-49 e5. PMID: 34536492
97. van Ginkel R, Buller HA, Boeckxstaens GE, et al. The effect of anorectal manometry on the outcome of treatment in severe childhood constipation: a randomized, controlled trial. *Pediatrics.* 2001;108(1):E9. PMID: 11433088
98. Sullivan A, Cousins S, Ridsdale L. Psychological interventions for migraine: a systematic review. *Journal of neurology.* 2016;263(12):2369-77. PMID: 27159991
99. Nestoriuc Y, Martin A. Efficacy of biofeedback for migraine: a meta-analysis. *Pain.* 2007;128(1-2):111-27. PMID: 17084028
100. Nestoriuc Y, Rief W, Martin A. Meta-analysis of biofeedback for tension-type headache: efficacy, specificity, and treatment moderators. *J Consult Clin Psychol.* 2008;76(3):379-96. PMID: 18540732
101. Trautmann E, Lackschewitz H, Kroner-Herwig B. Psychological treatment of recurrent headache in children and adolescents--a meta-analysis. *Cephalalgia.* 2006;26(12):1411-26. PMID: 17116091

102. Damen L, Bruijn J, Koes BW, et al. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. *Cephalalgia.* 2006;26(4):373-83. PMID: 16556238
103. Verhagen AP, Damen L, Berger MY, et al. Behavioral treatments of chronic tension-type headache in adults: are they beneficial? *CNS Neurosci Ther.* 2009;15(2):183-205. PMID: 19499626
104. Verhagen AP, Damen L, Berger MY, et al. Lack of benefit for prophylactic drugs of tension-type headache in adults: a systematic review. *Fam Pract.* 2010;27(2):151-65. PMID: 20028727
105. Eccleston C, Palermo TM, Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev.* 2009(2):CD003968. PMID: 19370592
106. Martin PR, Forsyth MR, Reece J. Cognitive-behavioral therapy versus temporal pulse amplitude biofeedback training for recurrent headache. *Behav Ther.* 2007;38(4):350-63. PMID: 18021950
107. Mullally WJ, Hall K, Goldstein R. Efficacy of biofeedback in the treatment of migraine and tension type headaches. *Pain Physician.* 2009;12(6):1005-11. PMID: 19935987
108. Bussone G, Grazzi L, D'Amico D, et al. Biofeedback-assisted relaxation training for young adolescents with tension-type headache: a controlled study. *Cephalalgia.* 1998;18(7):463-7. PMID: 9793698
109. Scharff L, Marcus DA, Masek BJ. A controlled study of minimal-contact thermal biofeedback treatment in children with migraine. *Journal of pediatric psychology.* 2002;27(2):109-19. PMID: 11821495
110. Sartory G, Muller B, Metsch J, et al. A comparison of psychological and pharmacological treatment of pediatric migraine. *Behaviour research and therapy.* 1998;36(12):1155-70. PMID: 9745800
111. Gerber WD, Petermann F, Gerber-von Muller G, et al. MIPAS-Family-evaluation of a new multi-modal behavioral training program for pediatric headaches: clinical effects and the impact on quality of life. *J Headache Pain.* 2010;11(3):215-25. PMID: 20376520
112. Nagele E, Jeitler K, Horvath K, et al. Clinical effectiveness of stress-reduction techniques in patients with hypertension: systematic review and meta-analysis. *J Hypertens.* 2014;32(10):1936-44; discussion 44. PMID: 25084308
113. Greenhalgh J, Dickson R, Dundar Y. Biofeedback for hypertension: a systematic review. *J Hypertens.* 2010;28(4):644-52. PMID: 20090553
114. Rainforth MV, Schneider RH, Nidich SI, et al. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr Hypertens Rep.* 2007;9(6):520-8. PMID: 18350109
115. Wang MY, Chang NC, Hsieh MH, et al. Effect of feedback signal on blood pressure self-regulation capability in individuals with prehypertension or stage I hypertension: a randomized controlled study. *The Journal of cardiovascular nursing.* 2016;31(2):166-72. PMID: 25774838
116. Landman GW, Drion I, van Hateren KJ, et al. Device-guided breathing as treatment for hypertension in type 2 diabetes mellitus: a randomized, double-blind, sham-controlled trial. *JAMA Intern Med.* 2013;173:1346-50. PMID: 23752780
117. Silkman C, McKeon J. The effectiveness of electromyographic biofeedback supplementation during knee rehabilitation after injury. *J Sport Rehabil.* 2010;19(3):343-51. PMID: 20811082
118. Tiryaki P, Çelik D, Bilsel K, et al. Effectiveness of Exercises With Electromyographic Biofeedback in Conservative Treatment of Massive Rotator Cuff Tears: A Randomized

Controlled Study. *American journal of physical medicine & rehabilitation.* 2023;102(5):419-26. PMID: 36166658
119. Stanton R, Ada L, Dean CM, et al. Biofeedback improves performance in lower limb activities more than usual therapy in people following stroke: a systematic review. *Journal of physiotherapy.* 2017;63(1):11-16. PMID: 27989731
120. Stanton R, Ada L, Dean CM, et al. Biofeedback improves activities of the lower limb after stroke: a systematic review. *Journal of physiotherapy.* 2011;57(3):145-55. PMID: 21843829
121. Woodford H, Price C. EMG biofeedback for the recovery of motor function after stroke. *Cochrane Database Syst Rev.* 2007(2):CD004585. PMID: 17443550
122. Zijlstra A, Mancini M, Chiari L, et al. Biofeedback for training balance and mobility tasks in older populations: a systematic review. *J Neuroeng Rehabil.* 2010;7:58. PMID: 21143921
123. Benfield JK, Hedstrom A, Everton LF, et al. Randomized controlled feasibility trial of swallow strength and skill training with surface electromyographic biofeedback in acute stroke patients with dysphagia. *Journal of oral rehabilitation.* 2023;50(6):440-51. PMID: 36810785
124. Nordio S, Arcara G, Berta G, et al. Biofeedback as an Adjunctive Treatment for Post-stroke Dysphagia: A Pilot-Randomized Controlled Trial. *Dysphagia.* 2022;37(5):1207-16. PMID: 34767083
125. Kim JH. The effects of training using EMG biofeedback on stroke patients upper extremity functions. *J Phys Ther Sci.* 2017;29(6):1085-88. PMID: 28626331
126. Yang DJ. Influence of biofeedback weight bearing training in sit to stand to sit and the limits of stability on stroke patients. *J Phys Ther Sci.* 2016;28(11):3011-14. PMID: 27942111
127. Ghomashchi H. Investigating the effects of visual biofeedback therapy on recovery of postural balance in stroke patients using a complexity measure. *Topics in stroke rehabilitation.* 2016;23(3):178-83. PMID: 27077976
128. Barcala L, Grecco LA, Colella F, et al. Visual Biofeedback Balance Training Using Wii Fit after Stroke: A Randomized Controlled Trial. *J Phys Ther Sci.* 2013;25:1027-32. PMID: 24259909
129. Yakşi E, Yaşar MF, Türel CA, et al. Are static posturography-assisted biofeedback exercises effective in Parkinson's disease? *Arq Neuropsiquiatr.* 2022;80(9):935-43. PMID: 36351419
130. van der Logt RP, Findling O, Rust H, et al. The effect of vibrotactile biofeedback of trunk sway on balance control in multiple sclerosis. *Mult Scler Relat Disord.* 2016;8:58-63. PMID: 27456875
131. Mackay AM, Buckingham R, Schwartz RS, et al. The Effect of Biofeedback as a Psychological Intervention in Multiple Sclerosis: A Randomized Controlled Study. *International journal of MS care.* 2015;17(3):101-8. PMID: 26052255
132. Gillis DJ, Wouda M, Hjeltnes N. Non-pharmacological management of orthostatic hypotension after spinal cord injury: a critical review of the literature. *Spinal Cord.* 2008;46(10):652-9. PMID: 18542098
133. Siepmann M, Hennig UD, Siepmann T, et al. The effects of heart rate variability biofeedback in patients with preterm labour. *Appl Psychophysiol Biofeedback.* 2014;39(1):27-35. PMID: 24271650
134. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med.* 2000;160(8):1101-8. PMID: 10789602

135. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology (Oxford).* 2009;48(7):791-5. PMID: 19433434
136. van der Zwan JE, de Vente W, Huizink AC, et al. Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2015;40:257-68. PMID: 26111942
137. Weise C, Heinecke K, Rief W. Biofeedback-based behavioral treatment for chronic tinnitus: results of a randomized controlled trial. *J Consult Clin Psychol.* 2008;76(6):1046-57. PMID: 19045972
138. Hsu LF, Liao YM, Lai FC, et al. Beneficial effects of biofeedback-assisted pelvic floor muscle training in patients with urinary incontinence after radical prostatectomy: A systematic review and metaanalysis. *International journal of nursing studies.* 2016;60:99-111. PMID: 27297372
139. Anderson CA, Omar MI, Campbell SE, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev.* 2015;1:CD001843. PMID: 25602133
140. Campbell SE, Glazener CM, Hunter KF, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev.* 2012;1:CD001843. PMID: 22258946
141. MacDonald R, Fink HA, Huckabay C, et al. Pelvic floor muscle training to improve urinary incontinence after radical prostatectomy: a systematic review of effectiveness. *BJU Int.* 2007;100(1):76-81. PMID: 17433028
142. Wille S, Sobottka A, Heidenreich A, et al. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomized trial. *J Urol.* 2003;170(2 Pt 1):490-3. PMID: 12853806
143. Bales GT, Gerber GS, Minor TX, et al. Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy. *Urology.* 2000;56(4):627-30. PMID: 11018619
144. Oh JJ, Kim JK, Lee H, et al. Effect of personalized extracorporeal biofeedback device for pelvic floor muscle training on urinary incontinence after robot-assisted radical prostatectomy: A randomized controlled trial. *Neurourol Urodyn.* 2020;39(2):674-81. PMID: 31793032
145. Dijkstra-Eshuis J, Van den Bos TW, Splinter R, et al. Effect of preoperative pelvic floor muscle therapy with biofeedback versus standard care on stress urinary incontinence and quality of life in men undergoing laparoscopic radical prostatectomy: A randomised control trial. *Neurourol Urodyn.* 2013. PMID: 24249542
146. Tienforti D, Sacco E, Marangi F, et al. Efficacy of an assisted low-intensity programme of perioperative pelvic floor muscle training in improving the recovery of continence after radical prostatectomy: a randomized controlled trial. *BJU Int.* 2012;110(7):1004-10. PMID: 22332815
147. Zhu D, Xia Z, Yang Z. Effectiveness of physiotherapy for lower urinary tract symptoms in postpartum women: systematic review and meta-analysis. *International urogynecology journal.* 2022;33(3):507-21. PMID: 34302516
148. Wu X, Zheng X, Yi X, et al. Electromyographic Biofeedback for Stress Urinary Incontinence or Pelvic Floor Dysfunction in Women: A Systematic Review and Meta-Analysis. *Adv Ther.* 2021;38(8):4163-77. PMID: 34176082
149. Balk E, Adam GP, Kimmel H, et al. Nonsurgical Treatments for Urinary Incontinence in Women: A Systematic Review Update. Rockville (MD), 2018.

150. Mateus-Vasconcelos ECL, Ribeiro AM, Antonio FI, et al. Physiotherapy methods to facilitate pelvic floor muscle contraction: A systematic review. *Physiother Theory Pract.* 2018;34(6):420-32. PMID: 29278967
151. Oliveira M, Ferreira M, Azevedo MJ, et al. Pelvic floor muscle training protocol for stress urinary incontinence in women: A systematic review. *Rev Assoc Med Bras (1992).* 2017;63(7):642-50. PMID: 28977091
152. Moroni RM, Magnani PS, Haddad JM, et al. Conservative treatment of stress urinary incontinence: a systematic review with meta-analysis of randomized controlled trials. *Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia.* 2016;38(2):97-111. PMID: 26883864
153. Herderschee R, Hay-Smith EJ, Herbison GP, et al. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev.* 2011(7):CD009252. PMID: 21735442
154. Kannan P, Cheing GLY, Fung BKY, et al. Effectiveness of pelvic floor muscle training alone or combined with either a novel biofeedback device or conventional biofeedback for improving stress urinary incontinence: A randomized controlled pilot trial. *Contemp Clin Trials.* 2022;123:106991. PMID: 36332826
155. Sahin N, Yesil H, Gorcan B. The effect of pelvic floor exercises performed with EMG biofeedback or a vaginal cone on incontinence severity, pelvic floor muscle strength, and quality of life in women with stress urinary incontinence: a randomized, 6-month follow-up study. *International urogynecology journal.* 2022;33(10):2773-79. PMID: 35028701
156. Terlikowski R, Dobrzycka B, Kinalski M, et al. Transvaginal electrical stimulation with surface-EMG biofeedback in managing stress urinary incontinence in women of premenopausal age: a double-blind, placebo-controlled, randomized clinical trial. *International urogynecology journal.* 2013;24(10):1631-8. PMID: 23443345
157. Fazeli MS, Lin Y, Nikoo N, et al. Biofeedback for nonneuropathic daytime voiding disorders in children: a systematic review and meta-analysis of randomized controlled trials. *J Urol.* 2015;193(1):274-9. PMID: 25072179
158. Sener NC, Altunkol A, Unal U, et al. Can a four-session biofeedback regimen be used effectively for treating children with dysfunctional voiding? *International urology and nephrology.* 2015;47(1):5-9. PMID: 25218618
159. Minardi D, Pellegrinelli F, Conti A, et al. alpha1-Blockers for the treatment of recurrent urinary tract infections in women with dysfunctional voiding: a prospective randomized study. *International journal of urology : official journal of the Japanese Urological Association.* 2015;22(1):115-21. PMID: 25141907
160. McClurg D, Ashe RG, Lowe-Strong AS. Neuromuscular electrical stimulation and the treatment of lower urinary tract dysfunction in multiple sclerosis--a double blind, placebo controlled, randomised clinical trial. *Neurourol Urodyn.* 2008;27(3):231-7. PMID: 17705160
161. McCabe P, Preston JL, Evans P, et al. A Pilot Randomized Control Trial of Motor-Based Treatments for Childhood Apraxia of Speech: Rapid Syllable Transition Treatment and Ultrasound Biofeedback. *Am J Speech Lang Pathol.* 2023;32(2):629-44. PMID: 36848673
162. Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. *Cochrane Database Syst Rev.* 2008(3):CD002029. PMID: 18646083
163. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine : JCSM :*

official publication of the American Academy of Sleep Medicine. 2008;4(5):487-504. PMID: 18853708
164. Wald A, Bharucha AE, Cosman BC, et al. ACG clinical guideline: management of benign anorectal disorders. *The American journal of gastroenterology.* 2014;109:1141-57; (Quiz) 058. PMID: 25022811
165. Wald A, Bharucha AE, Limketkai B, et al. ACG Clinical Guidelines: Management of Benign Anorectal Disorders. *The American journal of gastroenterology.* 2021;116(10):1987-2008. PMID: 34618700
166. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 155: Urinary Incontinence in Women. *Obstet Gynecol.* 2015;126:e66-81. PMID: 26488524
167. Hegmann KT, Travis R, Andersson GBJ, et al. Non-Invasive and Minimally Invasive Management of Low Back Disorders. *J Occup Environ Med.* 2020;62(3):e111-e38. PMID: 31977923
168. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. *Gastroenterology.* 2013;144(1):211-7. PMID: 23261064
169. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical review on constipation. *Gastroenterology.* 2013;144(1):218-38. PMID: 23261065
170. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the american heart association. *Hypertension.* 2013;61:1360-83. PMID: 23608661
171. Rao SS, Benninga MA, Bharucha AE, et al. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. *Neurogastroenterol Motil.* 2015;27(5):594-609. PMID: 25828100
172. Paquette IM, Varma M, Ternent C, et al. The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Evaluation and Management of Constipation. *Dis Colon Rectum.* 2016;59:479-92. PMID: 27145304
173. American Urological Association and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (AUA/SUFU). [cited 09/25/2023]. 'Available from:' https://www.auanet.org/guidelines-and-quality/guidelines/overactive-bladder-(oab)-guideline.
174. National Institute of Neurological Disorders and Stroke. Headache information page. [cited 9/25/203]. 'Available from:' https://www.ninds.nih.gov/health-information/disorders/headache.
175. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. *Am Fam Physician.* 2000;62(10):2359-60, 63. PMID: 11126860
176. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55(6):754-62. PMID: 10993991
177. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *Eur J Neurol.* 2010;17(11):1318-25. PMID: 20482606
178. National Institue of Health and Care Excellence (NICE): Constipation in children and young people: diagnosis and management. [cited 9/25/2023]. 'Available from:' https://www.nice.org.uk/guidance/cg99/chapter/1-Guidance#psychological-interventions.

CODES

Codes	Number	Description
CPT	90875-90876	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (e.g., insight oriented, behavior modifying, or supportive psychotherapy); code range
	90901	Biofeedback training by any modality
	90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient
	90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health care professional contact with the patient (List separately in addition to code for primary procedure)
HCPCS	E0746	Electromyography (EMG), biofeedback device
ICD-10-PCS	GZC9ZZZ	Mental health, biofeedback, other biofeedback

Date of Origin: *March 2009*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 18

Definitive Lower Limb Prostheses

Effective: April 1, 2024

Next Review: July 2024
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A prosthesis is a fabricated substitute for a missing body part. Lower limb prostheses may include a number of components, such as prosthetic feet, ankles, knees, and socket insertions and suspensions. A definitive prosthesis is provided after the surgical wound has healed and the residual limb has matured.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address microprocessor-controlled prostheses. Please refer to the *Cross References* section below for the appropriate medical policy.
- Preauthorization is only required for definitive (permanent) prostheses. Please check the preauthorization website to confirm requirements.
- This policy does not address preparatory prostheses, which may be considered medically necessary.
- This policy applies to the codes listed in the policy criteria as noted. Unlisted codes should not be used if there is a specific code that is applicable (see Coding Note below).

I. A definitive lower limb prosthesis may be considered **medically necessary** when all of the following criteria (A. – B.) are met:

A. All of the following general criteria are met:

1. The patient is motivated to ambulate using the requested prosthesis; and
2. The prosthesis is furnished incident to a physician's services or on a physician's order; and
3. The residual limb has matured; and
4. The member has been using a prosthesis, has achieved a defined functional state and is cognitively capable of using the prosthesis to ambulate effectively at the determined functional level (K0 – K4); and
5. The member had an in-person medical evaluation with the ordering physician to establish their overall functional capabilities and functional level (K level). (NOTE: The ordering physician might delegate this assessment to a licensed/certified medical professional (LCMP) defined as a physical therapist (PT) or occupational therapist (OT), or physician with training and expertise in the functional evaluation of beneficiaries with amputations.)

B. One or more of the following are met:

1. The request is for a lower limb prosthesis (L5010-L5341).
2. The request is for one of the following prosthetic feet:
   a. Request is for an external keel SACH foot (L5970) or single axis ankle/foot (L5974) for patients demonstrating a functional Level 1 or above.
   b. Request is for a flexible-keel foot (L5972) or multiaxial ankle/foot (L5978) for patients demonstrating a functional Level 2 or greater.
   c. Request is for a flex foot system (L5980), energy storing foot (L5976), multiaxial ankle/foot, dynamic response foot (L5979), or flex walk system or equal (L5981) or shank foot system with vertical loading pylon (L5987) for patients demonstrating a functional Level 3 or above.
3. Request is for one of the following prosthetic knees:
   a. Request is for a high activity knee control frame (L5930) for patients demonstrating a functional Level 4.
   b. Request is for a fluid (hydraulic) or pneumatic knee (L5610, L5613, L5614, L5722 - L5780, L5814, L5822-L5841, L5848) for patients demonstrating a functional Level 3 or above.
   c. Request is for other knee system (L5611, L5616, L5710-L5718, L5810-L5812, L5816-L5818) for patients demonstrating a functional Level 1 or above.
4. Request is for an axial rotation unit (L5982-L5986) or a multiaxial rotation unit with swing phase (L5968) for patients demonstrating a functional level 2 or above.
5. Request is for up to two test (diagnostic) sockets (L5618–L5628) for an

individual prosthetic. Additional documentation of medical necessity is required for more than two test sockets.

6. Request is for prosthesis replacement when one or more of the following criteria are met:
    a. A change in the physiological condition of the patient; or
    b. An irreparable change in the condition of the device, or in a part of the device; or
    c. The condition of the device, or the part of the device, requires repairs and the cost of such repairs would be more than 60 percent of the cost of a replacement device, or, as the case may be, of the part being replaced.
7. Request is for socket replacements (L5700–L5703) when both of the following criteria are met:
    a. The member has an existing prosthesis
    b. One of the following is met:
        i. Changes in the residual limb that cannot be accommodated through the use of socket inserts and/or liners and/or stump stockings, and/or modifications to the existing socket; or
        ii. The existing socket is irreparable due to damage or wear.

II. Definitive prostheses are considered **not medically necessary** if Criterion I. is not met.

III. Replacement is considered **not medical necessary** for the following:
    A. Criterion I. is not met.
    B. Replacement is covered under manufacturer warranty and maintenance services.

IV. Replacement requests for same/similar items which include upgraded features or components (additional or deluxe features which exceed the member's medical need) or upgrades to DME, prosthetics, or orthotics already in use are considered **not medically necessary**.

V. Definitive prostheses are considered **not medically necessary** if the patient's potential functional level is "0."

VI. More than two of the same socket inserts (L5654-L5665, L5673, L5679, L5681, L5683) per individual prosthesis at the same time are considered **not medically necessary**.

VII. Use of a mechanical reel-based socket volume adjustment system, including but not limited to the RevoFit®, is considered **not medically necessary.**

VIII. Prostheses are considered **not medically necessary** if the member is unable or unwilling to use the prosthesis.

IX. Accessories for any non-covered DMEPOS item are considered **not medically necessary** (See the health plan’s Reimbursement Policy for “Associated Claims,” Administrative 119). Note, accessories in this situation would be non-covered regardless of whether the original DMEPOS item was billed to the health plan.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

For purposes of this policy, the following definitions apply:

Preparatory Prosthesis. An unfinished, functional replacement for an amputated limb, fitted and aligned to accelerate the rehabilitation process, control edema, and prepare the residual limb for the external forces associated with wearing a prosthesis on a day to day basis.[1]

Permanent (i.e. definitive) Prosthesis. A permanent prosthesis is an artificial limb used by amputees whose residual limb has matured and the amputee has satisfactorily completed the temporary limb phase. The socket and components are manufactured to provide lasting durability and a proper cosmetic appearance.[2]

Mature Residual Limb: A mature residual limb is defined as one that has healed, reached its optimal volume, and been shaped appropriately to accommodate the chosen socket configuration

FUNCTIONAL CLASSIFICATION LEVELS

Following are the functional classification levels used to determine patient rehabilitation potential:[3]

Functional Classification Levels	
Level 0:	Does not have the ability or potential to ambulate or transfer safely with or without assistance, and a prosthesis does not enhance quality of life or mobility.
Level 1:	Has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence. Typical of the limited and unlimited household ambulator.
Level 2:	Has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs or uneven surfaces. Typical of the limited community ambulator.
Level 3:	Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion.
Level 4:	Has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes (including prior prosthetic use)
    - Medical records should document the patient's current functional capabilities and expected functional potential, including an explanation for any difference. Bilateral amputees cannot be strictly bound by functional level classifications.
- Current condition, including the status of the residual limb and the nature of other medical problems
- Functional level
- Desire to ambulate
- Physician's order (if applicable)
- Product information (manufacturer name, model number)
- For replacement items:
    - Comparative limb measurements (if applicable) or specific physiological change that necessitates replacement.
    - The date of service the prosthesis or component was provided.
    - The make/model and serial number (if applicable) for the component(s)
    - Warranty information
    - A repair vs. replacement analysis (i.e. cost to replace vs. cost to repair)

CROSS REFERENCES

1. Durable Medical Equipment, Prosthetic and Orthotic Replacements, Duplicates, Repairs, and Upgrades to Existing Equipment, Durable Medical Equipment, Policy No. 75
2. Myoelectric Prosthetic and Orthotic Components for the Upper Limb, Durable Medical Equipment, Policy No. 80
3. Powered and Microprocessor-Controlled Knee and Ankle-Foot Prosthesis and Microprocessor-Controlled Ankle-Foot Orthoses, Durable Medical Equipment, Policy No. 81
4. General Medical Necessity Guidance for Durable Medical Equipment, Prosthetic, Orthotics and Supplies (DMEPOS), Durable Medical Equipment, Policy No. 88
5. Powered Exoskeleton for Ambulation, Durable Medical Equipment, Policy No. 89
6. Associated Claims, Reimbursement Policy, Administrative, No. 119

BACKGROUND

In 2005, there were 1.6 million people living with limb loss in the U.S., and the number is predicted to be 3.6 million by 2050.[4] Common causes of lower limb amputation are dysvascular complications from diabetes, arteriosclerosis, smoke, or a combination of factors, and less commonly, traumatic injury, such as motor vehicle and industrial accidents, congenital limb development deficiency, and tumors.[5]

A standard timeline of amputation and prosthetic use includes multiple stages, including recovery and healing, maturation, and prosthetic selection and adjustments. Initially following an amputation, there is a period of limb management, where a variety of dressings may be used. Then a preparatory prosthesis is used while the limb volume stabilizes. Once the residual limb has matured and the patient's functional level has been determined, a definitive prosthesis is fitted.

PRACTICE GUIDELINE SUMMARY

Department of Veterans Affairs and the Department of Defense

A 2017 clinical practice guideline from the Department of Veterans Affairs and the Department of Defense (VA/DoD) included the following recommendation:[5]

- We suggest that in the perioperative phase following amputation, patients receive physical rehabilitation and appropriate durable medical equipment/assistive technology. (Weak strength of evidence)
- We recommend the use of valid, reliable, and responsive functional outcome measures, including, but not limited to, the Comprehensive High-level Activity Mobility Predictor, Amputee Mobility Predictor, 10-meter walk test, and 6-minute walk test. (Strong strength of evidence)
- We suggest the use of a combination of measures with acceptable psychometric properties to assess functional outcomes. (Weak strength of evidence)

SUMMARY

Definitive lower limb prosthetics improve health outcomes for select individuals missing part of a lower limb. Therefore, they may be considered medically necessary when policy criteria are met. When policy criteria are not met, the requested items are considered not appropriate in these individuals and are considered not medically necessary.

REFERENCES

1. Amputee Coalition National Limb Loss Resource Center. [cited 11/28/2023]. 'Available from:' https://www.amputee-coalition.org/limb-loss-resource-center/resources-filtered/resources-by-topic/definitions/.
2. Veterans Affairs Prosthetics Handbook. [cited 11/28/2023]. 'Available from:' https://helpdesk.vetsfirst.org/index.php?pg=kb.book&id=53.
3. Local Coverage Determination (LCD): Lower Limb Prostheses (L33787). Centers for Medicare and Medicaid Services. . [cited 11/28/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33787.
4. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, et al. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil.* 2008;89(3):422-9. PMID: 18295618
5. VA/DoD Clinical Practice Guidelines. Rehabilitation of Lower Limb Amputation (2017). [cited 11/28/2023]. 'Available from:' https://www.healthquality.va.gov/guidelines/Rehab/amp/.

CODES

NOTE: All items must be reported with the appropriate Healthcare Common Procedure Coding System (HCPCS) code. Most prosthetics and accessories have an applicable, specific HCPCS code available. Only when there is no appropriate descriptive code to use may an “unlisted code” (e.g., HCPCS codes E1399) be reported. Inappropriate use of unlisted codes or failure to use specific codes when available may result in inaccurate reviews. The health plan will defer to the Medicare Pricing, Data Analysis, and Coding (PDAC) contractor (Palmetto GBA) for proper code assignment of most items.

Codes	Number	Description
CPT	None	
HCPCS	L5010	Partial foot, molded socket, ankle height, with toe filler
	L5020	Partial foot, molded socket, tibial tubercle height, with toe filler
	L5050	Ankle, Symes, molded socket, SACH foot
	L5060	Ankle, Symes, metal frame, molded leather socket, articulated ankle/foot (SACH)
	L5100	Below knee (BK), molded socket, shin, SACH foot
	L5105	Below knee (BK), plastic socket, joints and thigh lacer, SACH foot
	L5150	Knee disarticulation (or through knee), molded socket, external knee joints, shin, SACH foot
	L5160	Knee disarticulation (or through knee), molded socket, bent knee configuration, external knee joints, shin, SACH foot
	L5200	Above knee (AK), molded socket, single axis constant friction knee, shin, SACH foot
	L5210	Above knee (AK), short prosthesis, no knee joint (stubbies), with foot blocks, no ankle joints, each
	L5220	Above knee (AK), short prosthesis, no knee joint (stubbies), with articulated ankle/foot, dynamically aligned, each
	L5230	Above knee (AK), for proximal femoral focal deficiency, constant friction knee, shin, SACH foot
	L5250	Hip disarticulation, Canadian type; molded socket, hip joint, single axis constant friction knee, shin, SACH foot
	L5270	Hip disarticulation, tilt table type; molded socket, locking hip joint, single axis constant friction knee, shin, SACH foot
	L5280	Hemipelvectomy, Canadian type; molded socket, hip joint, single axis constant friction knee, shin, SACH foot
	L5301	Below knee (BK), molded socket, shin, SACH foot, endoskeletal system
	L5312	Knee disarticulation (or through knee), molded socket, single axis knee, pylon, SACH foot, endoskeletal system
	L5321	Above knee (AK), molded socket, open end, SACH foot, endoskeletal system, single axis knee
	L5331	Hip disarticulation, Canadian type, molded socket, endoskeletal system, hip joint, single axis knee, SACH foot
	L5341	Hemipelvectomy, Canadian type, molded socket, endoskeletal system, hip joint, single axis knee, SACH foot
	L5610	Addition to lower extremity, endoskeletal system, above knee (AK), hydracadence system
	L5611	Addition to lower extremity, endoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with friction swing phase control
	L5613	Addition to lower extremity, endoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with hydraulic swing phase control
	L5614	Addition to lower extremity, exoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with pneumatic swing phase control
	L5616	Addition to lower extremity, endoskeletal system, above knee (AK), universal multiplex system, friction swing phase control
	L5700	Replacement, socket, below knee (BK), molded to patient model
	L5701	Replacement, socket, above knee (AK)/knee disarticulation, including attachment plate, molded to patient model
	L5702	Replacement, socket, hip disarticulation, including hip joint, molded to patient model
	L5703	Ankle, Symes, molded to patient model, socket without solid ankle cushion heel (SACH) foot, replacement only

Codes	Number	Description
	L5710	Addition, exoskeletal knee-shin system, single axis, manual lock
	L5711	Additions exoskeletal knee-shin system, single axis, manual lock, ultra-light material
	L5712	Addition, exoskeletal knee-shin system, single axis, friction swing and stance phase control (safety knee)
	L5714	Addition, exoskeletal knee-shin system, single axis, variable friction swing phase control
	L5716	Addition, exoskeletal knee-shin system, polycentric, mechanical stance phase lock
	L5718	Addition, exoskeletal knee-shin system, polycentric, friction swing and stance phase control
	L5722	Addition, exoskeletal knee-shin system, single axis, pneumatic swing, friction stance phase control
	L5724	Addition, exoskeletal knee-shin system, single axis, fluid swing phase control
	L5726	Addition, exoskeletal knee-shin system, single axis, external joints, fluid swing phase control
	L5728	Addition, exoskeletal knee-shin system, single axis, fluid swing and stance phase control
	L5780	Addition, exoskeletal knee-shin system, single axis, pneumatic/hydra pneumatic swing phase control
	L5783	Addition to lower extremity, user adjustable, mechanical, residual limb volume management system
	L5810	Addition, endoskeletal knee-shin system, single axis, manual lock
	L5811	Addition, endoskeletal knee-shin system, single axis, manual lock, ultra-light material
	L5812	Addition, endoskeletal knee-shin system, single axis, friction swing and stance phase control (safety knee)
	L5814	Addition, endoskeletal knee-shin system, polycentric, hydraulic swing phase control, mechanical stance phase lock
	L5816	Addition, endoskeletal knee-shin system, polycentric, mechanical stance phase lock
	L5818	Addition, endoskeletal knee-shin system, polycentric, friction swing and stance phase control
	L5822	Addition, endoskeletal knee-shin system, single axis, pneumatic swing, friction stance phase control
	L5824	Addition, endoskeletal knee-shin system, single axis, fluid swing phase control
	L5826	Addition, endoskeletal knee-shin system, single axis, hydraulic swing phase control, with miniature high activity frame
	L5828	Addition, endoskeletal knee-shin system, single axis, fluid swing and stance phase control
	L5830	Addition, endoskeletal knee-shin system, single axis, pneumatic/swing phase control
	L5840	Addition, endoskeletal knee-shin system, four-bar linkage or multiaxial, pneumatic swing phase control
	L5841	Addition, endoskeletal knee-shin system, polycentric, pneumatic swing, and stance phase control
	L5848	Addition to endoskeletal knee-shin system, fluid stance extension, dampening feature, with or without adjustability
	L5926	Addition to lower extremity prosthesis, endoskeletal, knee disarticulation, above knee, hip disarticulation, positional rotation unit, any type
	L5930	Addition, endoskeletal system, high activity knee control frame

Codes	Number	Description
	L5968	Addition to lower limb prosthesis, multiaxial ankle with swing phase active dorsiflexion feature
	L5970	All lower extremity prostheses, foot, external keel, SACH foot
	L5972	All lower extremity prostheses, foot, flexible keel
	L5974	All lower extremity prostheses, foot, single axis ankle/foot
	L5976	All lower extremity prostheses, energy storing foot (Seattle Carbon Copy II or equal)
	L5978	All lower extremity prostheses, foot, multiaxial ankle/foot
	L5979	All lower extremity prostheses, multiaxial ankle, dynamic response foot, one-piece system
	L5980	All lower extremity prostheses, flex-foot system
	L5981	All lower extremity prostheses, flex-walk system or equal
	L5982	All exoskeletal lower extremity prostheses, axial rotation unit
	L5984	All endoskeletal lower extremity prostheses, axial rotation unit, with or without adjustability
	L5985	All endoskeletal lower extremity prostheses, dynamic prosthetic pylon
	L5986	All lower extremity prostheses, multiaxial rotation unit (MCP or equal)
	L5987	All lower extremity prostheses, shank foot system with vertical loading pylon

Date of Origin: *July 2022*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 37

Power Wheelchairs: Group 3

Effective: November 1, 2023

Next Review: July 2024
Last Review: September 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Power wheelchairs are battery powered mobility devices with integrated or modular seating system, electronic steering and four or more-wheel non-highway construction.

MEDICAL POLICY CRITERIA

Note: This policy only addresses the initial provision of Group 3 power wheelchairs (HCPCS codes K0848-K0864). Replacement of a wheelchair or of wheelchair components, as well as wheelchair accessories, are addressed by a separate medical policy, Durable Medical Equipment, Prosthetic and Orthotic Replacements, Duplicates, Repairs, and Upgrades to Existing Equipment (DME75).

I. Group 3 power wheelchairs (PWC) may be considered **medically necessary** when both of the following Criteria (A. and B.) are met:

A. All of the following general Criteria (1. – 12.) are met:

1. The patient has had a specialty evaluation that was performed by a licensed/certified medical professional, such as a PT or OT, or practitioner who has specific training and experience in rehabilitation wheelchair

evaluations and that documents the medical necessity for the wheelchair and its special features; and

2. The patient has a mobility limitation that significantly impairs their ability to participate in one or more mobility-related activities of daily living (MRADLs) such as toileting, feeding, dressing, grooming, and bathing in customary locations in the home. A mobility limitation is one that:
    a. Prevents the member from accomplishing a MRADL entirely, or
    b. Places the patient at reasonably determined heightened risk of morbidity or mortality secondary to the attempts to perform a MRADL, or
    c. Prevents the member from completing MRADLs within a reasonable time frame.
3. Use of a power wheelchair in the home will significantly improve the patient's ability to participate in MRADLs, with or without caregiver assistance; and
4. The patient does not have sufficient upper extremity function to self-propel an optimally configured manual wheelchair (see Policy Guidelines) in the home to perform MRADLs during a typical day. Notes: Limitations of strength, endurance, range of motion, or coordination, presence of pain, or deformity or absence of one or both upper extremities are relevant to the assessment of upper extremity function; and
5. The underlying condition is not reversible, and the length of need is more than 3 months; and
6. The patient's mobility limitation cannot be sufficiently and safely resolved by the use of an appropriately fitted cane or walker; and
7. The patient's mobility needs cannot be met by a power operated vehicle (POV) (see Policy Guidelines); and
8. The patient has the mental (e.g., cognition, judgment) and physical (e.g., vision) capabilities to safely operate the power wheelchair that is provided in the home setting; or if the patient is unable to safely operate the power wheelchair, the patient has a caregiver who is unable to adequately propel an optimally configured manual wheelchair (see Policy Guidelines), but is available, willing, and able to safely operate the power wheelchair that is provided; and
9. The patient's weight is less than or equal to the weight capacity of the PWC that is provided and greater than or equal to 95% of the weight capacity of the next lower weight class, i.e., a Heavy Duty PWC is covered for a patient weighing 285 – 450 pounds; a Very Heavy Duty PWC is covered for a patient weighing 428 – 600 pounds; an Extra Heavy Duty PWC is covered for a patient weighing 570 pounds or more; and
10. The patient's home provides adequate access between rooms, maneuvering space, and surfaces for the operation of the power wheelchair that is provided; and
11. The patient has not expressed an unwillingness to use a power wheelchair in the home; and

12. Any coverage criteria pertaining to the specific wheelchair type (see below) are met.

B. Any of the following Group 3 power wheelchairs (PWC) may be considered **medically necessary** when all of Criteria A. above are met:

1. A Group 3 PWC with no power options (K0848-K0855) when the patient's mobility limitation is due to a neurological condition, myopathy, or congenital skeletal deformity.
2. A Group 3 PWC with single power option (K0856-K0860) or multiple power option (K0861-K0864) when **both** of the following (a. and b.) are met:
    a. The patient's mobility limitation is due to a neurological condition, myopathy, or congenital skeletal deformity; and
    b. Any one of the following are met:
        i. The patient requires a drive control interface other than a hand or chin-operated standard proportional joystick (examples include but are not limited to head control, sip and puff, switch control); or
        ii. The patient uses a ventilator which is mounted on the wheelchair; or
        iii. The patient has a power tilt or a power recline seating system and the system is being used on the wheelchair and one of the following are met:
            a.) The patient is at high risk for development of a pressure ulcer and is unable to perform a functional weight shift; or
            b.) The patient utilizes intermittent catheterization for bladder management and is unable to independently transfer from the wheelchair to bed; or
            c.) The power seating system is needed to manage increased tone or spasticity.

II. Group 3 power wheelchairs are considered **not medically necessary** when the above criteria are not met, including but not limited to the following:

A. The patient is capable of ambulation within the home but requires a wheelchair for movement outside the home; or

B. The primary benefit of the wheelchair is to allow the patient to perform leisure or recreational activities; or

C. The patient has been approved for a power operated vehicle (POV); or

D. The accessory is used for the convenience of the patient or caregiver and is not necessary for performance of mobility related activities of daily living (MRADLs); or

E. The patient's functional mobility limitation can be sufficiently resolved with a cane, walker, or manual wheelchair, as described above; or

F. The patient's home does not provide adequate access, maneuvering space, physical layout (e.g., doorway thresholds), or appropriate surfaces to support the requested device; or

G. The underlying condition is reversible, and the length of need is less than 3 months (e.g., following lower extremity surgery which limits ambulation).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

APPROPRIATE POPULATIONS

Group 3 power wheelchairs are reserved for the severely impaired patient afflicted with diseases such as: Amyotrophic Lateral Sclerosis (ALS), spinal cord injuries resulting in quadriplegia, stroke (CVA) with hemiplegia, late stage Parkinson's, late stage Multiple Sclerosis (MS), cerebral palsy, or Muscular Dystrophy.[1]

A Group 3 power wheelchair would not be appropriate for a beneficiary who has diabetes with peripheral neuropathy. Peripheral neuropathy affects the nerves. It is not a primary neurological condition but rather a symptom of another disease. The Power Mobility Device LCD specifically states that the patient must have a neurological condition; therefore, the beneficiary with peripheral neuropathy does not meet coverage criteria for a group 3 power wheelchair.

DEFINITIONS

Optimally configured wheelchair

An optimally configured wheelchair is one with an appropriate wheelbase, device weight, seating options (seat height and seat tilt/slope), and other appropriate non-powered accessories.

Power operated vehicle (POV)

A POV (scooter) is a chair-like battery powered mobility device for people with difficulty walking due to illness or disability, with integrated seating system, tiller steering, and three or four-wheel non-highway construction.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Medical records and chart notes pertinent to the PWC request, including history of the present condition(s) and past medical history relevant to mobility needs. Required information includes:
    - Date of face-to-face encounter by the treating practitioner, with signed and dated documentation;
        - Elements of the face-to-face should include:

- Mobility limitation and how it interferes with the performance of ADLs (the physical examination should focus on body systems responsible for ambulatory difficulty or impact on ambulatory ability); (
- Explanation of why a cane, walker, manual wheelchair, or POV (scooter) is unable to meet the mobility needs in the home; and,
- If the member has the physical and mental abilities to operate a power wheelchair safely in the home.

  - The underlying condition, and whether or not it is reversible.
  - Ambulation-limiting symptoms and the diagnoses responsible for them;
  - Medications or other treatment for these symptoms;
  - Progression of ambulation difficulty over time;
  - Other diagnoses that may relate to ambulatory problems;
  - How far the beneficiary can walk without stopping and the pace of ambulation;
  - What ambulatory assistance (e.g., cane, walker, wheelchair, caregiver) currently used. If the prior mobility device is not a POV, provide details regarding the physical and functional changes that now require the use of a power mobility device;
  - Ability to stand up from a seated position without assistance; and,
  - Description of the home setting and the ability to perform activities of daily living in the home.
  - Length of need
- Physical examination relevant to mobility needs;
  - Weight and height;
  - Cardiopulmonary examination;
  - Musculoskeletal examination (i.e., arm and leg strength and range of motion);
  - Neurological examination (i.e., gait, balance and coordination); and,
  - Clearly distinguish the beneficiary's abilities and needs within the home from any additional needs for use outside the home.

CROSS REFERENCES

1. Durable Medical Equipment, Prosthetic and Orthotic Replacements, Duplicates, Repairs, and Upgrades to Existing Equipment, Durable Medical Equipment, Policy No. 75
2. General Medical Necessity Guidance for Durable Medical Equipment, Prosthetic, Orthotics and Supplies (DMEPOS), Durable Medical Equipment, Policy No. 88

BACKGROUND

Wheelchairs can be described in HCPCS coding with one code for the wheelchair base and then additional codes for wheelchair options and accessories. The decision for a particular wheelchair base may be influenced by the chair's intended use, the patient's size or level of disability, or based on specific features that will be incorporated into the chair (for example, a heavy-duty base with additional electronics features may be needed to support a power tilt and/or recline option.)

The following is a list of wheelchair bases and their characteristics:

POWER WHEELCHAIRS (PWCS)

Power wheelchairs are battery powered mobility devices with integrated or modular seating system, electronic steering and four or more-wheel non-highway construction. PWCs are divided into six performance-based groups as listed in Table 1.[2] This policy only addresses Group 3 PWCS:

Table 1. Power Wheelchairs: Six Performance-based Groups

CHAIR/ HCPCS	GROUP 1 K0813-16	GROUP 2 K0820-K0843	GROUP 3 K0848-K0864	GROUP 4 K0868-K0886	GROUP 5 K0890-K0891	GROUP 6 K0898-99
Length	40 inches	48 inches	48 inches	48 inches	48 inches	NA
Width	≤24 inches	≤34 inches	≤34 inches	≤34 inches	≤34 inches	NA
Obstacle Height	20 mm	40 mm	60 mm	75 mm	60 mm	NA
Minimum Top End Speed-Flat	3 MPH	3 MPH	4.5 MPH	6 MPH	4 MPH	NA
Range	5 miles	7 miles	12 miles	16 miles	12 miles	NA
Obstacle height or obstacle climb denotes the vertical height of a solid obstruction that can be climbed.						
Minimum top end speed denotes the minimum speed on a flat hard surface that is acceptable for a given category of devices.						
Range denotes the minimum distance acceptable for a given category of devices on a single charge of the batteries.						
The above six PWC groups are subdivided based on patient weight capacity, seat type, portability and/or power seating system capability.						

There are four weight capacity groups. Those listed in Table 2. represent patient weight handling capacity and are not intended to reflect performance.

Table 2. Weight Capacity Groups

Standard Duty	Heavy Duty	Very Heavy Duty	Extra Heavy Duty
Up to and including 300 pounds	301-450 pounds	451-600 pounds	601 pounds or more

Table 3. Seat Types

Sling Seat/Back-Flexible	Solid Seat/ Back-Rigid	Captains Chair	Stadium Style Seat
Cloth, vinyl, leather or equal material designed to serve as the support for buttocks or back. They may or may not have thin padding but are not intended to provide cushioning or positioning for the user.	Metal or plastic material usually covered with cloth, vinyl, leather or equal material, with or without some padding material designed to serve as the support for the buttocks or back. They may or may not have thin padding but are not intended to provide cushioning or positioning for the user. PWCs with an automotive-style back and a solid seat pan are considered as a solid	A one or two-piece automotive-style seat with rigid frame, cushioning material in both seat and back sections, covered in cloth, vinyl, leather or equal as upholstery, and designed to serve as a complete seating, support, and cushioning system for the user. It may have armrests that can be fixed, swingaway, or detachable. It may or may not have a	A one or two piece stadium-style seat with rigid frame and cushioning material in both seat and back sections, covered in cloth, vinyl, leather or equal as upholstery, and designed to serve as a complete seating, support, and cushioning system for the user. It may have armrests that can be fixed, swingaway, or detachable. It does not have a headrest. Chairs with stadium style seats

Sling Seat/Back-Flexible	Solid Seat/ Back-Rigid	Captains Chair	Stadium Style Seat
	seat/back system, not a Captains Chair.	headrest, either integrated or separate.	are billed using the Captains Chair HCPCS codes.

Portable denotes a PWC that is built of lightweight construction or can be disassembled into lightweight components that allow easy placement into a vehicle for use in a distant location.

Power options that may be added to a PWC to include power tilt, recline, elevating legrests, seat elevators or standing systems. There are three categories of PWCs based on the capability to accept and operate these power options:

- No-power-options PWCs are incapable of accommodating any power options
- Single power option PWCs have the capability to accept and operate only one power accessory at a time on the base.
- Multiple power option PWCs have the capability to accept and operate more than one power accessory at a time on the base.

Pediatric PWCs are uniquely sized for use with very small individuals and have the capability for extensive growth through frame adjustments (not just seating) and special features to address developmental issues (e.g., seat to floor placement, standing capability).

Each power wheelchair base code is intended to include all of the following Basic Equipment Package items on initial issue:

- Lap belt or safety belt (E0978)
- Battery charger single mode (E2366)
- Complete set of tires and casters, any type
- Legrests: Fixed, swingaway, or detachable nonelevating leg rests with or without calf pad (E0995)
- Footrests: Fixed, swingaway, or detachable nonelevating foot rests/plates or foot platform without angle adjustment for any PWC or angle adjustable footplates with Group 1 or 2 PWCs (K0037, K0040, K0041, K0042, K0043, K0044, K0045, K0052)
- Fixed, swingaway, or detachable nonadjustable height armrests (E0994, K0015, K0019) with arm pad (K0019)
- Upholstery for seat and back of proper strength and type for patient weight capacity of the power wheelchair (E0981, E0982)
- Weight specific components per patient weight capacity
- Any seat width and depth or back width except for Group 3 or 4 PWCs with a sling/solid seat/back
- Controller and Input Device.

SUMMARY

Group 3 power wheelchairs may improve overall health outcomes for some people with mobility limitations. According to the U.S. Centers for Medicare & Medicaid Services, Group 3 power wheelchairs are considered reasonable and medically necessary for specific populations when certain situations exist. Therefore, Group 3 power wheelchairs may be considered medically necessary when policy criteria are met. In all other situations, Group 3

power wheelchair use does not change management and does not improve health outcomes. Therefore, Group 3 power wheelchairs are not medically necessary when policy criteria are not met.

REFERENCES

1. Noridian Healthcare Solutions. Group 3 Power Wheelchair Requirements. Last updated Jun 19, 2019. [cited 07/26/2023]. 'Available from:' https://med.noridianmedicare.com/web/jddme/dmepos/pmds/group-3-power-wheelchair-requirements.
2. U.S. Centers for Medicare & Medicaid Services. Local Coverage Article (LCA): Power Mobility Devices - Policy Article (A52498). Effective Date 01/01/2020. [cited 07/26/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=52498&ver=50&bc=CAAAAAAAAAAA.
3. U.S. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): Power Mobility Devices (L33789) For services performed on or after 01/01/2020 [cited 07/26/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33789&ver=31&Date=&DocID=L33789&bc=iAAAABAAgAAA&.

CODES

NOTE: This policy only addresses Group 3 PWC (HCPCS codes K0848-K0864).

Codes	Number	Description
CPT	None	
HCPCS	K0848	Power wheelchair, group 3 standard, sling/solid seat/back, patient weight capacity up to and including 300 pounds
	K0849	Power wheelchair, group 3 standard, captains chair, patient weight capacity up to and including 300 pounds
	K0850	Power wheelchair, group 3 heavy duty, sling/solid seat/back, patient weight capacity 301 to 450 pounds
	K0851	Power wheelchair, group 3 heavy duty, captains chair, patient weight capacity 301 to 450 pounds
	K0852	Power wheelchair, group 3 very heavy duty, sling/solid seat/back, patient weight capacity 451 to 600 pounds
	K0853	Power wheelchair, group 3 very heavy duty, captains chair, patient weight capacity 451 to 600 pounds
	K0854	Power wheelchair, group 3 extra heavy duty, sling/solid seat/back, patient weight capacity 601 pounds or more
	K0855	Power wheelchair, group 3 extra heavy duty, captains chair, patient weight capacity 601 pounds or more
	K0856	Power wheelchair, group 3 standard, single power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
	K0857	Power wheelchair, group 3 standard, single power option, captains chair, patient weight capacity up to and including 300 pounds
	K0858	Power wheelchair, group 3 heavy duty, single power option, sling/solid seat/back, patient weight 301 to 450 pounds
	K0859	Power wheelchair, group 3 heavy duty, single power option, captains chair, patient weight capacity 301 to 450 pounds
	K0860	Power wheelchair, group 3 very heavy duty, single power option, sling/solid seat/back, patient weight capacity 451 to 600 pounds

Codes	Number	Description
	K0861	Power wheelchair, group 3 standard, multiple power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
	K0862	Power wheelchair, group 3 heavy duty, multiple power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
	K0863	Power wheelchair, group 3 very heavy duty, multiple power option, sling/solid seat/back, patient weight capacity 451 to 600 pounds
	K0864	Power wheelchair, group 3 extra heavy duty, multiple power option, sling/solid seat/back, patient weight capacity 601 pounds or more

Date of Origin: *July 2019*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 42

Negative Pressure Wound Therapy in the Outpatient Setting

Effective: December 1, 2023

Next Review: December 2024
Last Review: October 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Negative pressure wound therapy (NPWT) involves the use of negative pressure or suction device to aspirate and remove fluids, debris, and infectious materials from the wound bed to promote the formation of granulation tissue and wound healing. This policy addresses NPWT in the outpatient setting.

MEDICAL POLICY CRITERIA

I. A *1-month therapeutic trial* of a powered negative pressure wound therapy (NPWT) system (pump and supplies), may be considered **medically necessary** when both of the following criteria (A. - B.) are met:

   A. Documentation regarding conventional wound care is provided meeting either of the following:

      1. The wound care program meets all of the following (a. – e.):

         a. Documentation in the medical record of evaluation, care, and wound measurements by a licensed medical professional; and

         b. Application of dressings to maintain a moist wound environment; and

         c. Debridement of necrotic tissue if present; and

d. Evaluation of and provision for adequate nutritional status; and

e. Documentation the open wound has not responded to conventional treatment after 30 days OR documentation of the decision-making process supporting less than 30 days of conventional treatment.

2. Documentation is provided indicating that a comprehensive wound care program may not be indicated prior to NPWT for one or more of the following:

a. Open sternal wounds or repeat median sternotomy in high-risk obese patients; or

b. Skin grafts placed on an irregular surface/bed or compromised blood flow, with size >100 cm^2 requiring initial placement of NPWT for graft fixation; or

c. Diabetic foot ulcer with wound classification of Wagner grade II or greater.

B. Any of the following wound-specific criteria are met:

1. For Stage 3 or 4 pressure ulcers all of the following (a. - c.) are met:

a. Appropriate turning and positioning; and

b. Use of group 2 or 3 support surface for pressure ulcers on the posterior trunk or pelvis; and

c. Moisture and incontinence have been appropriately managed; or

2. For neuropathic (for example, diabetic) ulcers all of the following (a. - b.) must be met:

a. A comprehensive diabetic management program; and

b. Reduction in pressure on a foot ulcer with appropriate modalities; or

3. For venous insufficiency ulcers all of the following (a. - b.) must be met:

a. Compression bandages and/or garments applied consistently; and

b. Leg elevation and ambulation have been encouraged; or

4. Chronic (at least 30 days) ulcer of mixed etiology; or

5. Open wounds (including but not limited to post-operative dehiscence, non-healing amputation site in diabetics, high-risk open fracture); or

6. Repeat median sternotomy in high-risk obese patients; or

7. Skin grafts placed on an irregular surface/bed or compromised blood flow, with size >100 cm^2 requiring initial placement of NPWT for graft fixation.

II. Therapeutic trials of powered NPWT systems for the treatment of acute or chronic wounds are considered **not medically necessary** for any of the following:

A. Criterion I. is not met;

B. One or more of the following contraindications are present:

1. The presence in the wound of necrotic tissue with eschar, if debridement is not attempted; or

2. Osteomyelitis within the vicinity of the wound that is not concurrently being treated with intent to cure; or
3. Cancer present in the wound; or
4. The presence of an open fistula to an organ or body cavity within the vicinity of the wound.

III. Associated clinical care and supplies for the effective use of a NPWT system (e.g., wound care services; including for initiation and continuation of care) may be considered **medically necessary** if the primary NPWT system itself was determined to be medically necessary.

IV. Associated clinical care and supplies for the effective use of a NPWT system (e.g., wound care services; including for initiation and continuation of care) are considered **not medically necessary** if the primary NPWT system itself was determined to be not medically necessary or has not been reviewed for medical necessity.

V. *Continuation after a one-month therapeutic trial* of the powered NPWT system, as part of a comprehensive wound care program, may be considered **medically necessary** for up to 3 more months when both of the following criteria are met (A. – B.):
   A. There is documentation that a licensed medical professional has directly assessed the wound(s) being treated with the NPWT system; and
   B. There is continuous documentation of improvement (volume reduction, changes in dimensions and characteristics) which supports objective improvement in the wound.

VI. *Continuation after a one-month therapeutic trial* of the powered NPWT system is considered **not medically necessary** when any of the following occurs:
   A. Criterion III. is not met; or
   B. There is evidence of wound complications contraindicating continued use of NPWT.

VII. *Continuation after four total months* is considered **not medically necessary**.

VIII. Single-use/disposable NPWT systems (powered or nonpowered) and/or associated clinical care, supplies, and accessories are considered **investigational** for the treatment of acute or chronic wounds.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Wagner Grade Classification of Diabetic Foot Ulcers:[1]

Grade	Description
Grade 0	Skin intact but bony deformities lead to “foot at risk”
Grade 1	Superficial ulcer

Grade 2	Deeper; full thickness extension
Grade 3	Deep abscess formation or osteomyelitis
Grade 4	Partial Gangrene of forefoot
Grade 5	Extensive Gangrene

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

For *initial* one-month therapeutic trial:

1. History and physical/chart notes documenting policy criteria; and
2. Documentation, by provider, of indication for NPWT; and
3. Documentation of wound therapy program, including documentation of evaluation, care and wound measurements.

For *continuation* after a one-month therapeutic trial:

1. Documentation that a licensed medical professional has directly assessed the wound(s) being treated with the NPWT system; and
2. There is continuous documentation of improvement (volume reduction, changes in dimensions and characteristics) which supports objective improvement in the wound.

CROSS REFERENCES

1. Electrical Stimulation for the Treatment of Wounds, Durable Medical Equipment, Policy No. 83.09
2. Non-Contact Ultrasound Treatments for Wounds, Medicine, Policy No. 131

BACKGROUND

CHRONIC WOUNDS

Management

The management and treatment of chronic wounds, including decubitus ulcers, is challenging. Most chronic wounds will heal only if the underlying cause (ie, venous stasis, pressure, infection) is addressed. Also, cleaning the wound to remove nonviable tissue, microorganisms, and foreign bodies is essential to create optimal conditions for either re-epithelialization (ie, healing by secondary intention) or preparation for wound closure with skin grafts or flaps (ie, healing by primary intention). Therefore, debridement, irrigation, whirlpool treatments, and wet-to-dry dressings are common components of chronic wound care.

Negative pressure wound therapy (NPWT) involves the use of a negative pressure therapy or suction device to aspirate and remove fluids, debris, and infectious materials from the wound bed to promote the formation of granulation tissue. The devices may also be used as an adjunct to surgical therapy or as an alternative to surgery in a debilitated patient. Although the exact mechanism has not been elucidated, it is hypothesized that negative pressure

contributes to wound healing by removing excess interstitial fluid, increasing the vascularity of the wound, reducing edema, and/or creating beneficial mechanical forces that lead to cell growth and expansion.

A nonpowered (mechanical) NPWT system has also been developed; the Smart Negative Pressure Wound Care System is portable and lightweight (3 oz) and can be worn underneath clothing. This system consists of a cartridge, dressing, and strap; the cartridge acts as the negative pressure source. The system is reported to generate negative pressure levels similar to other NPWT systems. This system is fully disposable.

The focus of this evidence review is the use of NPWT in the outpatient setting. It is recognized that patients may begin using the device in the inpatient setting as they transition to the outpatient setting.

Regulatory Status

Negative pressure therapy or suction devices cleared by the U.S. Food and Drug Administration (FDA) for treating chronic wounds include, but are not limited to: Vacuum-Assisted Closure® Therapy (V.A.C., also known as negative pressure wound therapy; KCI); Versatile 1™ (V1) Wound Vacuum System (Blue Sky Medical), RENASYS™ EZ PLUS (Smith & Nephew), Foryou NPWT NP32 Device (Foryou Medical Electronics), SVED® (Cardinal Health), and PICO Single Use Negative Pressure Wound Therapy System (Smith & Nephew).

Portable systems include the RENASYS™ GO (Smith & Nephew), XLR8 PLUS (Genadyne Biotechnologies), extriCARE® 2400 NPWT System (Devon Medical), the V.A.C. Via™ (KCI), NPWT PRO to GO (Cardinal Health), and the PICO Single Use Negative Pressure Wound Therapy System (Smith & Nephew). The Prevena™ Incision Management System (KCI) is designed specifically for closed surgical incisions.

A nonpowered NPWT device, the SNaP® Wound Care System (Spiracur, acquired by Acelity in 2015), is a class II device requiring notification to market but not having the FDA premarket approval. In 2009, it was cleared for marketing by the FDA through the 510(k) pathway (K081406) and is designed to remove small amounts of exudate from chronic, traumatic, dehisced, acute, or subacute wounds and diabetic and pressure ulcers.

NPWT devices with instillation include the V.A.C. VERAFLO™ Therapy device (KCI/Acelity). It was cleared for marketing in 2011 by the FDA through the 510(k) pathway (K103156) and is designed to allow for controlled delivery and drainage of topical antiseptic and antimicrobial wound treatment solutions and suspensions. It is to be used with the V.A.C. Ulta unit, which is commercially marketed for use in the hospital setting. Instillation is also available with Simultaneous Irrigation™ Technology tubing sets (Cardinal Health) for use with Cardinal Health SVED® and PRO NPWT devices, however, its use is not indicated for use in a home care setting (K161418).

No NPWT device has been cleared for use in infants and children.

In November 2009, the FDA issued an alert concerning complications and deaths associated with NPWT systems. An updated alert was issued in February 2011.[2]

FDA product code: OMP.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review was informed by a 2000 TEC Assessment that evaluated negative pressure therapy of pressure ulcers, venous ulcers, and diabetic ulcers.[3] Literature updates for this review have focused on comparative trials with the features described in the 2000 TEC Assessment (e.g., enrollment of patients with wounds refractory to standard treatment, randomization, optimal standard wound care treatment in the control arm, and clinically important endpoints). Also, literature has been sought on the potential benefits of negative pressure wound therapy (NPWT) for the healing of acute wounds.

NPWT devices are classified as either powered (i.e., requiring an electrical power source or batteries) or nonpowered (mechanical). Most evidence found in the literature is for electrically powered devices with large canisters (e.g., the Vacuum-Assisted Closure Therapy device [V.A.C. system]), and so the main discussion of evidence refers to this type of device. A number of portable devices have entered the market and are particularly relevant for use in the outpatient setting. Some portable devices are designed specifically for surgical incisions. Evidence on the newer portable devices is discussed following the review of evidence on the larger electrically powered devices.

The primary endpoints of interest for trials of wound healing are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:[4]

- Incidence of complete wound closure
- Time to complete wound closure (reflecting accelerated wound closure)
- Incidence of complete wound closure following surgical wound closure
- Pain control

SYSTEMATIC REVIEWS

The authors of a systematic review for the Agency for Healthcare Research and Quality and the Centers for Medicare & Medicaid Services (2014) reported that due to insufficient evidence, they were unable to draw conclusions about the efficacy or safety of NPWT in the home setting.[5] There were three retrospective cohort studies on diabetic foot ulcers and arterial ulcers, an RCT and two retrospective cohort studies on pressure ulcers, and a retrospective cohort on venous ulcers. Six studies used the V.A.C., and the other used the Smart Negative Pressure (SNaP) Wound Care System device. Reviewers found that interpretation of available data was limited by variability in the types of comparator groups, methodologic limitations, and poor reporting of outcomes.[6]

Another Agency for Healthcare Research and Quality assessment was performed to inform the HCPCS coding decisions for NPWT devices. This 2009 assessment found no studies showing a therapeutic distinction between different NPWT devices.[7]

A 2020 Cochrane review update by Norman evaluated NPWT compared with standard dressings for surgical wound healing by primary closure.[8] Forty-four RCTs were included for analysis (n=7,447). NPWT was associated with a reduced risk of surgical site infection (SSI) (31 studies [n=6,204]; RR 0.66; 95% CI, 0.55 to 0.80; I^2=23%). However, subgroup analysis by surgery type did not maintain a significant benefit for orthopedic, abdominal, or mixed/general surgeries. Treatment benefit for SSI was significant in clean and clean-contaminated procedures only. No significant difference was found for the rates of mortality and wound dehiscence. No significant benefit was seen for rates of reoperations or hospital readmissions. Certainty of evidence was deemed low to moderate per GRADE criteria. Studies were generally limited by imprecision and unclear or high-risk of bias in allocation concealment and blinding of outcome assessors. The analysis was also limited by inclusion of studies with mixed or unclear intervention types and no subgroup analysis for traditional or portable, single-use systems. An update to this above-mentioned systematic review was published by Norman in 2022 to assess the effects of NPWT for preventing SSI in wounds healing through primary closure.[9] In this update to their existing systematic review series, the authors added 18 new randomized controlled trials (RCTs) and one new economic study, resulting in a total of 62 RCTs (13,340 included participants) and six economic studies. Studies evaluated NPWT in a wide range of surgeries, including orthopaedic, obstetric, vascular and general procedures. All studies compared NPWT with standard dressings. This review also confirmed that the use of NPWT could reduce the risk of SSI in wound healing compared to the standard dressing group. But there is probably little or no difference in wound dehiscence between people treated with NPWT and those treated with standard dressing.

A systematic review and meta-analysis by Li (2019) was conducted comparing the effectiveness and safety of NPWT with standard surgical dressing or conventional therapy for prevention of SSI.[10] A total of 45 RCTs assessing 6,624 adult patients were included for analysis. Studies utilized a variety of NPWT devices, including V.A.C., PICO, and Prevena systems. Inclusion criteria did not impose restrictions on SSI grading systems or on surgery types. Surgeries for infected or chronic non-healing wounds including diabetic, venous, and arterial ulcers were excluded. Overall, NPWT was associated with a 40% reduction in SSI risk compared to control, with moderate heterogeneity (RR 0.58; 95% CI, 0.49 to 0.69; I^2=19%; p<0.00001). This significant reduction in risk was particularly maintained in high-risk surgical patients (32 RCTs; RR 0.60; 95% CI, 0.50 to 0.73; I^2=23%; p<0.00001). There was no significant effect of NPWT on wound dehiscence, hematoma occurrence, hospital admission, or length of hospital stay. The certainty of the evidence, based on GRADE criteria was graded

as low to very low due to serious risk of bias stemming from lack of blinding and methodological flaws in SSI assessment and standardization. The authors suggest that further studies are warranted to elucidate the optimal protocol for NPWT utilization.

DIABETIC LOWER-EXTREMITY ULCERS AND AMPUTATION WOUNDS

Clinical Context and Therapy Purpose

The purpose of outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with diabetic lower-extremity ulcers or amputation wounds.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

Systematic Reviews

A systematic review and meta-analysis by Chen (2021) evaluating NPWT for diabetic foot ulcers compared to standard care reported a significant improvement in the wound healing rate with NPWT (odds ratio [OR], 3.60; 95% CI, 2.38 to 5.45; p<.001) based on 6 RCTs representing 536 patients.[11] No significant difference in the incidence of adverse events was reported between groups (OR, 0.49; 95% CI, 0.10 to 2.42; p=.38). The reviewers noted several limitations in the body of evidence, including lack of blinding, unclear follow-up durations, and heterogeneous pressure settings.

A systematic review by Wynn and Freeman (2019) evaluating NPWT for diabetic foot ulcers reported similar benefits in wound healing and the reduction of amputation incidence.[12] However, reviewers emphasized limitations in the present body of evidence, including methodological flaws such as the absence of validated tools for the measurement of wound depth and area, lack of statistical power calculations, and heterogeneity in pressure settings employed during therapy.

A 2013 Cochrane review of NPWT for treating foot wounds in patients with diabetes[13] was updated in 2018 to include 11 RCTs (n=972) with sample sizes ranging from 15 to 341 participants.[14] Two studies addressed post-amputation wounds and all other studies described treatment of diabetic foot ulcers. Only 1 study comparing NPWT and moist dressings for post-amputation wounds reported a follow-up time (n=162), and a statistically

significant improvement in the proportion of wounds healed (RR 1.44, 95% CI, 1.03 to 2.01) was demonstrated after a follow-up duration of 16 weeks. The median time to healing was 21 days shorter for the NPWT group (hazard ratio 1.91, 95% CI, 1.21 to 2.99) compared with moist dressings. Data from 3 studies suggest that people with diabetic foot ulcers allocated to NPWT may be at reduced risk of amputation compared to moist dressings (RR 0.33, 95% CI, 0.15 to 0.70, I2=0%). Reviewers concluded that there was some evidence to suggest that NPWT was more effective than standard care, but the findings were uncertain due to the risk of bias in the unblinded studies. Reviewers recommended further study to reduce uncertainty around decision-making.

Randomized Controlled Trials

Seidel (2020) reported the results of a multicenter, industry-sponsored, blinded RCT that evaluated the superiority of NPWT (n=171) compared to standard moist wound care (n=174) in patients with diabetic foot ulcers.[15] The NPWT devices used included V.I.A. and Renasys systems. Based on intention-to-treat analysis, the primary outcomes of complete, sustained, and confirmed wound closure or time to wound closure, as defined by 100% epithelialization, no drainage, no suture material, and no need for wound dressing or adjuvants within 16 weeks, was not significantly different between NPWT and control groups (p=.53 and p=.100, respectively). The incidence of adverse events was significantly higher in the NPWT arm (56.1%) compared to the control arm (41.4%; p=.007); however, only 16 adverse events were considered related to NPWT. Amputation rates were not significantly different between groups (difference, 0.2%; 95% CI, -19.0% to 18.6%; p=1.00). Limitations include a high number of patients (n=191) with missing data or protocol deviations.

Associated to the study mentioned above, Seidel (2022) published another RCT to compare resource utilization of negative pressure wound therapy (NPWT) and standard moist wound care (SMWC) for diabetic foot wounds after amputation, surgical debridement or wound cleansing.[16] Treatment duration was 16 days shorter with NPWT (mean (SD) 82.8 (31.6), SMWC 98.8 (24.6); U test, p = 0.001) with 14.9 days shorter outpatient treatment (mean (SD) NPWT 68.3 (31.1), SMWC 83.2 (29.7)). The number of dressing changes per study participant was lower with NPWT (mean (SD) 35.1 (18.6), SMWC (42.9 (21.4); U test, p = 0.067). Time per dressing change was significantly lower with SMWC (mean (SD) 19.7 (12.8), NPWT (16.5 (8.2) minutes; U test, p < < 0.0001). Time for surgical debridements per study participant was 23.3 minutes shorter with NPWT (mean (SD) 20.5 (20.5), SMWC (43.8 (46.7); U test, p = 0.395).

The largest study of NPWT for diabetic foot ulcers was a multicenter industry-sponsored RCT by Blume (2008) that compared NPWT with advanced moist wound therapy.[17] Included were 342 patients with Wagner grade 2 or grade 3 foot ulcers of at least 2 cm2; the chronicity of the ulcers was not described. Based on intention-to-treat analysis, a greater proportion of NPWT-treated foot ulcers achieved the primary endpoint of complete ulcer closure (43.2% vs. 28.9%, p=0.007) within the 112-day active treatment phase. For the 240 (72%) patients who completed the active treatment phase, 60.8% of NPWT-treated ulcers closed compared with 40.0% of ulcers treated with advanced moist wound therapy. NPWT patients also experienced significantly fewer secondary amputations (4.1% vs. 10.2%, p=0.035).

Nonrandomized Studies

Borys (2018) conducted a prospective observational study to assess the short-term efficacy, safety, and long-term outcomes of NPWT in treating diabetic foot ulcers. Researchers

assigned 75 patients to NPWT (n=53) or standard care (n=22) based on wound size. Analysis after one-year follow-up showed similar results for both groups, leading researchers to conclude NPWT is a safe alternative to but not necessarily more efficacious than the current standard of care. Limitations include small sample size, the observational design, and nonconsideration of risk factors other than wound size.[18]

Section Summary: Diabetic Lower-Extremity Ulcers and Amputation Wounds

The evidence on NPWT for diabetic lower-extremity ulcers and amputation wounds includes RCTs and systematic reviews of RCTs. Although there is some uncertainty due to the risk of bias in the unblinded studies, there were higher rates of wound healing and fewer amputations with NPWT, supporting its use for diabetic lower-extremity ulcers and amputation wounds.

PORTABLE, SINGLE-USE THERAPY FOR DIABETIC LOWER-EXTREMITY ULCERS AND AMPUTATION WOUNDS

Clinical Context and Therapy Purpose

The purpose of portable, single-use outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with diabetic lower-extremity ulcers or amputation wounds.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

<u>PICO Dressing</u>

PICO is a portable single-use NPWT system that comes with 2 sterile dressings and has a lifespan of 7 to 14 days.

Kirsner (2019) published an RCT that allocated 164 patients with venous leg ulcers (VLU; n=104) or diabetic foot ulcers (DFU; n=60) to treatment with PICO single-use NPWT (s-NPWT; N=80) or traditional, reusable NPWT systems (t-NPWT; N=84).[19] Prior to randomization, patients were excluded if a reduction in target ulcer area ≥30% was achieved with compression or offloading during a two week run-in period as a way to exclude 'quick healers'. Three patients in the t-NPWT arm were excluded from the intention-to-treat (ITT) analysis. For the per protocol (PP) analysis, 16 (20%) and 30 (37%) patients were excluded from the s-

NPWT and t-NPWT arms, respectively. Randomization was stratified by wound type and wound size. The PICO dressing was set to provide -80 mmHg of negative pressure. Choice of traditional, NPWT device manufacturer and pressure setting was at the discretion of the treating physician, with an average pressure of -118.3 mmHg (median, -125 mmHg; SD, 23.4 mmHg) applied.

The study intended to test for noninferiority in the percentage change of target ulcer area with s-NPWT vs t-NPWT over the course of a 12-week treatment period, with a noninferiority margin of 12.5%. The analysis was performed with the PP population to account for dropouts and then repeated on the full analysis set (ITT). Secondary outcomes included wound closure rate, time to wound closure, and quality of life. Participants and investigators were not blinded, and it is unclear if the study utilized blinded assessors. Patients were seen weekly in outpatient wound centers. After adjustment for baseline wound area, pooled study site, wound type, and wound duration at baseline, the mean percentage difference in wound area over 12 weeks was 27% (96.9% vs 69.9%; p=0.003) in the PP analysis and 39.1% (90.24% vs 51%; P<0.001) in the ITT analysis. This treatment effect was also significant in the DFU subgroup (P=0.031). However, confidence intervals were not reported for the primary outcome.

Confirmed wound closure (ITT) was achieved in 54 (33.5%) patients (s-NPWT, 36 [45%]; t-NPWT, 18 [22%]), with an adjusted odds ratio of 0.294 (95% CI, 0.135 to 0.638; p=0.002) for all wound types and 0.161 (95% CI, 0.035 to 0.744; p=0.020) for DFU. However, the subgroup analysis for DFU patients in the PP population was not significant.

The median estimate of the time to achieve confirmed closure was 77 days for s-NPWT (95% CI, 49 to undefined limit) and could not be calculated for t-NPWT due to the low number of patients achieving this endpoint. No significant differences were noted in health-related quality of life between baseline and exit visits. Fifty-seven treatment-related adverse events were reported, 16 related to s-NPWT in 12 patients and 41 related to t-NPWT in 29 patients. Wound-related adverse events included increase in target ulcer size, inability to tolerate NPWT, and periwound skin maceration, resulting in study discontinuation by three treated with s-NPWT and nine treated with t-NPWT. While the PICO dressing met noninferiority, change in wound area is not a primary health outcome of interest due to its inherent heterogeneity. Additionally, the chosen treatment duration may have of insufficient duration to accurately assess effects on wound closure. Required use of fillers, a higher level of negative pressure, and utilization of devices from various t-NPWT manufacturers may have impacted findings. Only 20% of patients in the s-NPWT arm were treated with fillers, mainly in those with DFU.

A subanalysis of this RCT highlighting outcomes in patients with lower-extremity (foot and venous leg) diabetic ulcers was published by Kirsner.[20] The intention-to-treat population included 46 patients in the s-NPWT arm and 49 patients in the t-NPWT arm. The treatment OR for achieving confirmed wound closure at 12 weeks was 0.129 (95% CI, 0.041 to 0.404; p<0.001). In the per protocol population, which included 36 patients in the s-NPWT arm and 25 patients in the t-NPWT arm, the treatment OR for confirmed wound closure at 12 weeks was 0.179 (95% CI, 0.044 to 0.735; p=0.017). Baseline patient characteristics, including distribution of foot and venous leg ulcers in each treatment arm, were not reported. This analysis is also limited by its retrospective, post-hoc nature and insufficient follow-up duration.

SNaP Wound Care System

The portable, nonpowered (mechanical) gauze-based SNaP Wound Care System became available in 2009. The device is designed to remove small amounts of exudate from chronic, traumatic, dehisced, acute, or subacute wounds and diabetic and pressure ulcers.

Armstrong (2011) reported on results of a planned interim analysis of an RCT comparing the SNaP Wound Care System with the V.A.C. Therapy for the treatment of chronic lower-extremity wounds.[21] Final results of this industry-sponsored multicenter noninferiority trial were reported in 2012.[22] The trial enrolled 132 patients with lower-extremity venous or diabetic ulcers with a surface area between 1 cm2 and 100 cm2 and diameter less than 10 cm present for more than 30 days despite appropriate care. Approximately 30% of patients in this study had diabetic ulcers, and no subgroup analyses were conducted. Dressings were changed per the manufacturer's direction: 2 times per week in the SNaP group and 3 times per week in the V.A.C. group. Patients were assessed for up to 16 weeks or until complete wound closure; 83 (63%) patients completed the study. Intention-to-treat analysis with the last observation carried forward showed noninferiority in the primary outcome of wound size reduction at 4, 8, 12, and 16 weeks. When adjusted for differences in wound size at baseline, SNaP-treated subjects showed noninferiority to V.A.C.-treated subjects at 4, 12, and 16 weeks. Kaplan-Meier analysis showed no significant difference in complete wound closure between the 2 groups. At the final follow-up, 65.6% of the V.A.C. group and 63.6% of the SNaP group had wound closure. Survey data indicated that dressing changes required less time with the SNaP device and use of the SNaP device interfered less with mobility and activity than the V.A.C. device.

A 2010 retrospective study with historical controls compared NPWT using the SNaP device (n=28) with wound care protocols using Apligraf, Regranex, and skin grafting (n=42) for the treatment of lower-extremity ulcers.[23] Seven (25%) patients in the SNaP-treated group could not tolerate the treatment and were discontinued from the study because of complications; they were considered treatment failures. Between-group estimates of time-to-wound healing by Kaplan-Meier analysis favored the SNaP treatment group. This study is limited by the use of historical controls, multiple modalities to treat controls, and a large number of dropouts. Subgroup analyses for patients with diabetic (50%) and venous (50%) ulcers were not available. The authors noted that patients in the SNaP-treated group might have benefited from being in an experimental environment, particularly because wounds in this group were seen twice per week compared with variable follow-up in historical controls.

Section Summary: Portable, Single-Use Therapy for Diabetic Lower-Extremity Ulcers and Amputation Wounds

The evidence on portable, single-use NPWT for diabetic ulcers and amputation wounds includes an RCT of the PICO device and an RCT of the nonpowered SNaP System. A 2019 RCT compared the PICO device with standard NPWT in outpatients with diabetic and venous ulcers. In this study, the PICO device demonstrated noninferiority for wound area reduction. A statistically significant benefit in complete wound closure was noted for patients with diabetic ulcers, but was not duplicated in the per protocol population due to a high number of exclusions. Interpretation of this study is limited by variable device settings and short follow-up duration. One study of the SNaP System showed noninferiority to a V.A.C. device for wound size reduction. No significant difference in complete wound closure was reported. Interpretation of this study is limited by a high loss to follow-up. Well-designed comparative studies with larger numbers of patients powered to detect differences in complete wound closure are needed.

CHRONIC PRESSURE ULCERS

Clinical Context and Therapy Purpose

The purpose of outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic pressure ulcers.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

Systematic Reviews

Shi (2023) published an update to the 2015 Cochrane review on treating pressure ulcers in any care setting.[24] The review included eight RCTs with 327 participants total. Six of the eight included studies were deemed to be at a high risk of bias in one or more risk of bias domains, and evidence for all outcomes of interest was deemed to be of very low certainty. Most studies had small sample sizes (range: 12 to 96, median: 37 participants). Five studies compared NPWT to dressings, but only one study reported outcomes that met the review criteria (complete wound healing and adverse events). This study had only 12 participants and there were very few events; only one participant was healed in the study (risk ratio [RR] 3.00, 95% confidence interval [CI] 0.15 to 61.74, very low-certainly evidence). No difference in adverse events was reported, but the evidence for this outcome was also assessed as very low certainty (RR 1.25, 95% CI 0.64 to 2.44). The authors concluded that the efficacy, safety, and acceptability of NPWT in treating pressure ulcers compared to usual care are uncertain due to the lack of key data on complete wound healing, adverse events, time to complete healing, and cost-effectiveness.

A 2015 Cochrane review included 4 RCTs of NPWT (total n=149 patients) for treating pressure ulcers in any care setting, although most of the patients were treated in a hospital setting.[13] Three trials were considered to be at high-risk of bias, and all evidence was considered to be of very low-quality. Only one trial reported on complete wound healing, which occurred in only 1 of the 12 study participants. Reviewers concluded there is high uncertainty about the potential benefits and/or harms for this indication.

Randomized Controlled Trials

One representative trial, from 2003 (noted in the 2015 Cochrane review as “awaiting further information from the authors”), randomized 24 patients with pressure ulcers of the pelvic region to NPWT or standard wound care.[25] All patients with pelvic pressure ulcers were eligible for enrollment and were not required to be refractory to standard treatment. There was no significant group difference for the main outcome measure, time to 50% reduction of wound volume (mean, 27 days in the NPWT group vs. 28 days in the control group). Findings were limited by the small number of patients in the study, the possibility that the control group might not have received optimal wound management, and lack of information on the time to complete wound healing.

Section Summary: Chronic Pressure Ulcers

The evidence on outpatient NPWT for chronic pressure ulcers includes RCTs and systematic reviews. However, all trials were of low-quality and at high-risk of bias. Also, most patients were treated in an inpatient setting.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Clinical Context and Therapy Purpose

The purpose of outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with lower-extremity ulcers due to venous insufficiency.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

Randomized Controlled Trials

A 2015 Cochrane review of NPWT for venous insufficiency identified a single RCT with 60 patients.[26] This trial, published by Vuerstaek (2006), was performed in an inpatient setting in conjunction with skin grafts and compared the efficacy of NPWT using the V.A.C. system (n=30) with conventional moist wound care (n=30) in patients hospitalized with chronic venous and/or arterial leg ulcers of greater than six months in duration.[27] Full-thickness punch skin grafts from the thigh were applied, followed by four days of NPWT or conventional care to assure complete graft adherence. Each group then received standard care with nonadhesive dressings and compression therapy until complete healing (primary outcome) occurred. The

median time to complete healing was 29 days in the NPWT group and 45 days in the control group (p=0.001). Ninety percent of ulcers treated with NPWT healed within 43 days, compared with 48% in the control group. These results would suggest that NPWT significantly hastened wound healing, although the use of skin autografts makes it difficult to discern the contribution of NPWT to the primary outcome. The 2015 Cochrane review did not identify any RCT evidence on the effectiveness of NPWT as a primary treatment for leg ulcers, nor was there any evidence on the use of NPWT in the home setting.

Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency

A single RCT has been identified on use of NPWT for the treatment of lower-extremity ulcers due to venous insufficiency in the hospital setting. No evidence was identified on treatment in the home setting.

PORTABLE, SINGLE-USE THERAPY FOR LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Clinical Context and Therapy Purpose

The purpose of portable, single-use outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with lower-extremity ulcers due to venous insufficiency.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

PICO Dressing

Kirsner (2019) published an RCT that allocated 164 patients with venous leg ulcers (VLU; n=104) or diabetic foot ulcers (DFU; n=60) to treatment with PICO single-use NPWT (s-NPWT; N=80) or traditional, reusable NPWT systems (t-NPWT; N=84).[19] Additional study details and limitations are summarized previously in indication 2.

The primary outcome measure, mean percentage difference in wound area over 12 weeks, was 27% (96.9% vs 69.9%; P=0.003) in the per protocol (PP) analysis and 39.1% (90.24% vs 51%; P<0.001) in the intention-to-treat (ITT) analysis. This treatment effect was also significant in the VLU subgroup (P=0.007). However, confidence intervals were not reported. Confirmed

wound closure (ITT) was achieved in 54 (33.5%) patients (s-NPWT, 36 [45%]; t-NPWT, 18 [22%]), with an adjusted odds ratio of 0.294 (95% CI, 0.135 to 0.638; P=0.002) for all wound types and 0.398 (95% CI, 0.152 to 1.044; P=0.061) for VLU. The subgroup analysis for VLU patients in the PP population was also not significant.

SNaP Wound Care System

Armstrong (2011) reported on results of a planned interim analysis of an RCT comparing the SNaP Wound Care System with the V.A.C. Therapy for the treatment of chronic lower-extremity wounds.[21] Final results of this industry-sponsored multicenter noninferiority trial were reported in 2012.[22] Approximately 70% of the study population had venous leg ulcers. Additional study details and limitations are summarized previously in indication 2.

A subgroup analysis (2015) of 40 patients with venous leg ulcers who completed the study showed a significant improvement in the percentage of those with complete wound closure treated with SNaP (57.9%) compared with the V.A.C. system (38.2%; p=0.008).[28] However, this study had a high loss to follow-up and lacked a comparison with standard treatment protocols.

Section Summary: Portable, Single-Use Therapy for Lower-Extremity Venous Ulcers

The evidence on portable, single-use NPWT for lower-extremity venous ulcers includes an RCT of the PICO device and an RCT of the nonpowered SNaP System. A 2019 RCT compared the PICO device with standard NPWT in outpatients with diabetic and venous ulcers. In this study, the PICO device demonstrated noninferiority for wound area reduction. No significant benefit in complete wound closure was found in patients with venous ulcers. One study of the SNaP System showed noninferiority to a V.A.C. device for wound size reduction. A subgroup analysis of this study found a significant difference in complete wound closure for patients with venous ulcers. However, interpretation of this study is limited by a high loss to follow-up and a lack of a control group treated with standard dressings. Well-designed comparative studies with larger numbers of patients powered to detect differences in complete wound closure are needed.

BURN WOUNDS

Clinical Context and Therapy Purpose

The purpose of outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with burn wounds.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

Randomized Controlled Trials

A 2014 Cochrane review of NPWT for burn wounds identified an interim report (abstract) of an RCT on NPWT in patients with partial-thickness burns.[29] The abstract did not provide enough evidence to draw any conclusions on the efficacy of NPWT on partial-thickness burn wounds.

Not included in the Cochrane review was a trial by Bloemen (2012) on the effect of NPWT on graft take in full-thickness burn wounds.[30] This multicenter, four-armed RCT enrolled 86 patients and compared a split-skin graft with or without a dermal substitute (MatriDerm), with or without NPWT. Outcome measures included graft take at four to seven days after surgery, the rate of wound epithelialization, and scar parameters at 3 and 12 months postoperatively. Graft take, and wound epithelialization did not differ significantly between groups. Most measures of scar quality also did not differ significantly between groups.

An expert panel convened to develop evidence-based recommendations for the use of NPWT reported that the evidence base in 2011 was strongest for the use of NPWT on skin grafts and weakest as a primary treatment for burns.[31]

Case Series

A retrospective case series by Ehrl (2017) examined outcomes for 51 patients treated for burned hands with topical NPWT at a single-center; of the initial 51 patients, only 30 patients (47 hands) completed follow-up, which was conducted an average of 35 months after injury and included physical examination.[32] Before TNPW therapy, patients received escharotomy or superficial debridement if needed, or split-thickness skin grafts for third-degree burns and the NPWT gloves used allowed caregivers to assess patients' fingertips for perfusion. Ergotherapy was initiated following evidence of epithelialization. Primary endpoints were a dorsal extension of the fingers and capability of complete active fist closure, with the majority of patients achieving one or both outcomes: the first endpoint was reached in 85.1% (n=40) of the cases; the second endpoint was reached in 78.7% of hands (n=37). When evaluated using the Disabilities of the Arm, Shoulder, and Hand questionnaire (scoring range, 0-100; with 0=no disability), patients with injuries resulting in hypertrophic scarring had significantly worse scores (28.8) than patients without similar scarring (11.7; $p<0.05$). Despite a number of limitations, including heterogeneity of burned areas (2.5% to 70% throughout the series), the authors acknowledged NPWT as standard treatment at the institution from which these data were drawn.

Section Summary: Burn Wounds

The evidence on NPWT as a primary treatment of partial-thickness burns is limited. A retrospective case series reported functional outcomes in most patients treated for hand burns with NPWT. One RCT on NPWT for skin grafts showed no benefit for graft take, wound epithelialization, or scar quality.

TRAUMATIC AND SURGICAL WOUNDS

Clinical Context and Therapy Purpose

The purpose of outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with traumatic or surgical wounds.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Identified studies have described various wound types treated over periods ranging from several days to several months. Studies also differed by whether NPWT was used for nonhealing wounds or as a prophylactic treatment for surgical wounds in patients at high-risk for nonhealing.

Review of Evidence

Systematic Reviews

Selected systematic reviews and meta-analyses evaluating the use of NPWT in surgical and/or traumatic wounds are summarized in Table 1.

Table 1. Summary of SR-MAs of NPWT versus Standard Therapy in Surgical Wounds

Review	RCT	Other Studies	Participants[1]	N (Range)	Major Outcomes	Study Quality	Relevance
Cochrane (2014)[33]	9	0	Individuals with wounds expected to heal by primary intention (eg, surgical closure, skin grafts)	785	SSI (NSD) Wound dehiscence (NSD) Reoperation (NSD) Seroma/hematoma (NSD) Skin graft failure (NSD)	Unclear or high risk of bias noted	Unclear; inclusion of "home-made" devices and focus on inpatient therapy
De Vries (2016)[34]	6	15	Individuals treated with prophylactic NPWT in clean and contaminated surgery	RCT: 277 (13-141) Other: 1099 (23-237)	Surgical site infection (RCT: p=0.04; Other: p<0.00001; NSD for	Low quality of evidence due to lack of blinding in outcome assessment	Unclear; focus on inpatient therapy

Review	RCT	Other Studies	Participants[1]	N (Range)	Major Outcomes	Study Quality	Relevance
					trauma/orthopedic surgery)		
Cochrane (2018)[14]	7	0	Individuals with open traumatic wounds (open fractures and other types)	1377 (40-586)	Wound infection (NSD)	Unclear or high risk of bias noted	Limited; focus on inpatient therapy
Ren (2022)[35]	5	1 (retrospect-tive cohort trial)	Individuals who have undergone hepatopan-creatobiliary surgery	657 (345F, 311M)	superficial surgical infection, deep surgical infection, seroma incidence, hematoma incidence, and hospital re-admission		

NPWT: negative pressure wound therapy; NSD: no significant difference; RCT: randomized controlled trial; SR-MA: systematic review and meta-analysis; SSI: surgical site infection.
1 Key eligibility criteria,
2 Assessment according to Cochrane risk of bias criteria.

A 2014 Cochrane review evaluated the evidence on NPWT for skin grafts and surgical wounds expected to heal by primary intention.[33] Healing by primary intention occurs when the wound edges are brought together with sutures, staples, tape, or glue, and contrasts with healing by secondary intention, where the wound is left open to heal from the bottom up (eg, for chronic or infected wounds). Nine randomized trials (total n=785 patients) were included in the review. Three trials involved skin graft patients, four included orthopedic patients, and two included general surgery and trauma surgery patients. All trials had an unclear or high-risk of bias. There were no differences between standard dressing and NPWT for SSIs, wound dehiscence, reoperation (in incisional wounds), seroma/hematoma, or failed skin grafts. Pain intensity was reported to be lower with “home-made” NPWT compared with commercial devices. Most or all studies appeared to have used short-term application of NPWT in an inpatient setting.

A systematic review and meta-analysis by De Vries (2016) included 6 RCTs and 15 observational studies of SSIs after prophylactic NPWT.[34] One study selected used a portable device (PICO, described below), while the others used a V.A.C. Unlike the 2014 Cochrane review, studies on skin grafts were not included. Meta-analysis of the RCTs showed that use of NPWT reduced the rate of SSIs (odds ratio [OR], 0.56; 95% CI, 0.32 to 0.96; p=0.04), and reduced the SSI rate from 140 to 83 per 1000 patients. However, the quality of evidence was rated as low due to high-risk of bias in the nonblinded assessments and imprecision in the estimates. Subgroup meta-analysis of 4 RCTs in orthopedic/trauma surgery did not demonstrate significant benefit in regards to reducing risk of SSI (OR 0.58; 95% CI 0.32 to 1.07).

A 2018 Cochrane review evaluated the effects of NPWT for open traumatic wounds (eg, open fractures or soft tissue wounds) managed in any care setting.[14] Seven RCTs were identified

for the review with sample sizes ranging from 40 to 586 participants. Four studies (n=596) compared NPWT at 125 mmHg with standard care for open fracture wounds. Pooled data revealed no significant difference between groups in the number of participants with healed wounds (RR 0.48, 95% CI 0.81 to 1.27; I2=56%). Pooled data from 2 studies (n=509) utilizing NPWT at 125 mmHg on other open traumatic wounds demonstrated no significant difference in risk of wound infection compared to standard care (RR 0.61, 95% CI 0.31 to 1.18). One study (n=463) assessing NPWT at 75 mmHg against standard care in other open traumatic wounds did not demonstrate a significant difference for wound infection risk (RR 0.44, 95% CI 0.17 to 1.10). One study comparing NPWT at 125 mmHg against 75 mmHg in other open traumatic wounds also failed to demonstrate a significant difference in wound infection risk (RR 1.04, 95% CI 0.31 to 3.51). Evidence was deemed low to very low in certainty and quality due to imprecision and risk of bias.

In contrast, a systematic review and meta-analysis by Liu (2018) highlighted a significantly lower infection rate, shorter wound coverage time, shorter wound healing time, and shorter hospitalization duration for NPWT versus conventional wound dressings in the treatment of open fractures (all p<0.00001).[36] Three of six included RCTs overlapped with the Cochrane review and 1 significantly weighted RCT (n=460) (see Costa [2018][37] in Table 2 below) failing to demonstrate a benefit in infection risk for NPWT was missing in the Liu (2018) analysis, the only RCT identified by Cochrane to conduct blinded outcome assessment of wound healing and infection. However, the risk of bias in the Liu (2018) review was similarly reported as high or unclear. The baseline characteristics of cohort studies included in the analysis suffered from high heterogeneity, with most studies failing to achieve comparable initial injury severity scores based on the Gustilo-Anderson open fracture classification system. Finally, due to the severity of open fracture injuries, the outpatient clinical utility of NPWT for this form of trauma is unclear with most studies focusing on inpatient applications.

Sahebally (2018) performed a systematic review with meta-analysis to evaluate the effects of NPWT on SSIs in closed laparotomy incisions.[38] Researchers searched 4 databases through December 31, 2017, and screened bibliographies of retrieved studies to find further studies; 9 unique studies (three RCTs, two prospective studies, and four retrospective studies) representing 1,266 unique patients were included in the review. The analysis determined that NPWT was associated with a significantly lower rate of SSI compared with standard wound dressing (pooled OR: 0.25; 95% CI 0.12 to 0.52; p<0.001). The review was limited by including mostly non-randomized studies and use of different NPWT devices.

Flynn (2020) published an RCT to determine if PICO dressings reduce surgical site infections or other surgical site complications in primarily closed laparotomy incisions after clean-contaminated surgery in moderate-risk patients.[39] Patients undergoing laparotomy and bowel resection were randomly assigned to PICO or conventional dressings. There were no significant differences in the surgical site infection or development of surgical site complications between the two techniques. The authors conclude that this study does not support the routine use of PICO dressings on uncomplicated laparotomy incisions in moderate-risk patients.

Ren (2022) performed a systematic review to evaluate the comparative influence of NPWT and standard surgical dressing administration on incidence risk for surgical site infections, complications, and hospital re-admission after hepatopancreatobiliary surgery.[35] Six studies were included in this analysis; five RCTs and one retrospective cohort trial. From this study the authors report that NPWT usage slightly reduces the risk of hospital readmission as compared

to standard surgical dressing. Only two studies (featuring small sample sizes) investigated the understanding of the comparative impact of NPWT and standard surgical dressing on hematoma complications.

Randomized Controlled Trials

Selected RCTs of NPWT for surgical or traumatic wounds are summarized in Table 2.

Table 2. Summary of Key RCTs of NPWT versus Standard Therapy in Surgical Wounds

Study; Trial	Surgery Received	No. of Participants	Notes on NPWT effectiveness	P-value
Stannard (2012)[40]	Various, after fractures and other trauma	249	Fewer infections, less discharge than standard closure	0.049
Masden (2012)[41]	Various	81	NSD in infection or healing	NR
Chio and Agrawal (2010)[42]	Radial forearm donor site	43	NSD in wound complications or graft failure	NR
Javed (2018)[43]	Open pacreaticoduodenectomy	123	9.7% of NPWT group developed infections, compared with 31.1% of standard closure group	0.003
Tanaydin (2018)[44]	Bilateral breast reduction mammoplasty	32	Patients used as own control; NPWT associated with significantly lower risk of complication and improved pain and scarring compared with fixation strips	<0.004
Costa (2018); WOLLF[37]	Severe open fracture of the lower limb	460	NSD in self-rated disability, number of deep SSI, or QOL scores	Disability: 0.13 SSI: 0.64 QOL: NR
Seidel (2020); SAWHI[45]	Subcutaneous abdominal wound healing impairment	539 (randomized) 507 (modified ITT) 310 (PP)	Shorter time to wound closure and higher wound closure rate	<0.001

ITT: intention-to-treat; NPWT: negative pressure wound therapy; NR: not reported; NSD: no significant difference; QOL: quality of life; PP: per protocol; RCT: randomized controlled trial; SSI: surgical site infection.

One of the largest studies on prophylactic NPWT for surgical wounds is a report from an investigator-initiated, industry-sponsored multicenter RCT of inpatient NPWT for closed surgical incisions by Stannard (2012).[40] (A preliminary report was published in 2006.)[46] Participants included 249 blunt trauma patients with 263 high-risk fractures (tibial plateau, pilon, calcaneus) requiring surgical stabilization. Patients were randomized to NPWT applied to the closed surgical incision or to standard postoperative dressings. All trial participants were maintained as inpatients until wound drainage was minimal, at which time NPWT was discontinued (mean, 59 hours; range, 21 to 213 hours). Patients in the NPWT group were ready for discharge in 2.5 days compared with 3.0 days for the control group (the difference was not statistically significant). The NPWT group had significantly fewer infections (10% of fractures) than the control group (19% of fractures; p=0.049). Wound dehiscence after discharge was observed less frequently in the NPWT group (8.6%) than in the control group (16.5%). These results would support the efficacy of the short-term use of NPWT when used under highly controlled conditions of inpatient care, but not the effectiveness of NPWT in the outpatient setting. A small 2015 RCT (n=20) of NPWT in an outpatient setting reported that

patients treated with NPWT required significantly fewer dressing changes, reported significantly less pain, and experienced QOL improvements compared with standard wound care.[47]

Other randomized studies have reported no benefit for NPWT for surgical wounds, as reflected in the conclusions of various Cochrane reviews (described above).[14, 33] For example, the RCT by Masden (2012) examined the use of NPWT for surgical closures at high-risk for nonhealing in 81 patients with comorbidities that included diabetes and peripheral vascular disease.[41] At a mean of 113 days follow-up, there were no significant differences in the proportions of patients with wound infection, time to develop infection or dehiscence between NPWT and dry dressing groups. Chio and Agrawal (2010) published results of a randomized trial of 54 patients comparing NPWT with a static pressure dressing for the healing of the radial forearm free flap donor site.[42] There were no statistically significant differences in wound complications or graft failure (percentage of area for graft failure, 7.2% for negative pressure vs 4.5% for standard dressing). Biter (2014) found no significant advantage of two weeks of NPWT in 49 patients who underwent surgical excision for pilonidal sinus disease.[48] Complete wound healing was achieved at a median of 84 days in the NPWT group and 93 days in controls.

Javed (2018) conducted a single-site RCT to evaluate the efficacy of NPWT for SSI after an open pacreaticoduodenectomy. Researchers randomized 123 patients treated from January 2017 through February 2018 to either NPWT (n=62) or standard closure (n=61). In the study, 9.7% of patients who received NPWT developed a postoperative infection at the site, compared with 31.1% of patients who received standard closure, an RR of 0.31 (95% CI 0.13 to 0.73; p=0.003). Limitations of the study included being conducted at a high-volume treatment center and a lack of blinding.[43]

Tanaydin (2018) conducted an RCT to compare NPWT to standard wound care after a bilateral breast reduction mammoplasty.[44] In the study, 32 patients were given NPWT on one breast and fixation strips on the other, simultaneously serving as study group and control group. Sites treated with NPWT showed a significantly lower rate of complications ($p<0.004$) compared to fixation strips, as well as improved pain and scarring. Limitations included the small sample size and lack of blinding.

The Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb (WOLLF) trial by Costa (2018) randomized 460 patients with severe open fracture of the lower limb to NPWT (n=226) or standard wound management (n=234).[37] The primary outcome was the Disability Rating Index score (range, 0 [no disability] to 100 [completely disabled]) at 12 months, with a minimal clinically important difference of 8 points. Secondary outcomes included deep infection and quality of life measures based on the EuroQol 5-dimensions questionnaire. Eighty-eight percent of participants completed the trial. There were no statistically significant differences in disability scores (45.5 vs. 42.4; p=0.13), in the number of deep infections (16 [7.1%] vs. 19 [8.1%]; p=0.64), or in quality of life measures in the NPWT and standard wound management groups, respectively. A 5-year follow-up report found similar patient-reported disability, health-related quality of life, or need for surgery in patients treated with NPWT or standard management.[49] NPWT was used for a limited time frame in the inpatient setting which limits conclusions for the outpatient setting.

The Subcutaneous Abdominal Wound Healing Impairment (SAWHI) multicenter clinical trial by Seidel (2020) randomized adult patients with SAWHI to treatment with NPWT (V.A.C. Therapy) or conventional wound therapy (CWT).[45] The modified ITT population included 256 and 251 patients assigned to NPWT and CWT, respectively. The primary outcome, mean time to wound closure within 42 days, was significantly shorter in the NPWT group (difference, 3.0 d; 95% CI, 1.6 to 4.4; P<0.001) and confirmed via independent, blinded assessors. Additionally, only 35.9% of patients in the NPWT group and 21.5% of patients in the CWT group achieved complete wound closure within 42 days (difference, 14.4%; 95% CI 6.6% to 22.2%; p<0.001). While this met the prespecified non-inferiority margin of 12.5%, the study's statistical model had assumed a complete wound closure rate of 50% in the CWT arm which had not been met within the 42-day treatment period. The benefit of NPWT for these outcomes was sustained in the PP analysis, however, 39% and 31% of patients were excluded from the NPWT and CWT arms, respectively. Primary reasons for exclusion included unauthorized treatment crossovers, insufficient dressing changes, and treatment termination prior to 42 days. More wounds were sutured in the NPWT arm compared to the CWT arm, where more wounds healed by secondary intention. No significant differences were noted for quality of life or pain measures at any time point. The relative risk for adverse events (RR, 1.20; 95% CI, 0.97 to 1.47) and wound-related adverse events (RR, 1.51; 95% CI 0.99 to 2.35) was higher in the NPWT arm. The most frequently documented wound-related adverse events in the NPWT arm included periwound macerations and local infections with signs of inflammation. Overall, it is unclear if a 3-day difference in time to wound closure represents a clinically meaningful benefit. Time to hospital discharge, readmission rates, and duration of outpatient care were not reported.

As an add-on to a multicenter randomized clinical trial, Seidel (2022) published another RCT.[50] The authors compared aspects of hospital discharge, outpatient treatment continuation, and subsequent wound closure outcomes between the treatment arms in patients with subcutaneous abdominal wound healing impairment after surgery without fascia dehiscence in the per protocol population. Time to wound closure was shorter for outpatients in the NPWT arm (outpatient transfer with: NPWT Mean ± standard error 28.8 ± 8.0 days; CWT 28.9 ± 9.5 days) than in the conventional treatment arm (30.4 ± 8.0 days). The authors also report that study site specific avoidance of outpatient NPWT emerges as an additional reason for the prolonged hospitalization time.

Seidel (2022) also published the comparison of resource utilization of NPWT and CWT for SAWHI after surgery.[51] The resource use analysis was primarily based on the per protocol population (NPWT 157; CWT 174). Although treatment length within 42 days was significantly shorter in the NPWT arm (Mean [Standard deviation (SD)] NPWT 22.8 (13.4); CWT 30.6 (13.3); P < 0.001 U-test), hospitalization time was shorter with CWT [Mean (SD) NPWT 13.9 (11.1); CWT 11.8 (10.8); P = 0.047 U-test]. Significantly more study participants were outpatient with CWT [N=167 (96.0%)] than with NPWT [N = 140 (89.2%) (P = 0.017)]. Time for dressing changes per study participant [Mean (SD) (min) NPWT N = 133, 196 (221.1); CWT N = 152, 278 (208.2); P < .001 U-test] and for wound-related procedures [Mean (SD) (min) NPWT 167 (195); CWT 266 (313); P < 0.001 U-test] was significantly lower with NPWT.

Section Summary: Traumatic and Surgical Wounds

The evidence on the use of NPWT for individuals who have traumatic or surgical wounds includes RCTs and systematic reviews. One RCT found no benefit of NPWT on graft take and wound epithelialization in patients with full-thickness burns. Another RCT found a significant decrease in time to wound closure in patients with wound healing impairment following

abdominal surgery; however, it is unclear if this difference is clinically meaningful. An RCT reported significantly shorter treatment length in the NPWT compared to the conventional wound healing. In addition, it also reported shorter hospitalization time, significantly more number of outpatients, and significantly lesser time for dressing. Another RCT also reported shorter time to wound closure and it was noted that study site specific avoidance of outpatient NPWT emerges as an additional reason for the prolonged hospitalization time. A small RCT suggested that prophylactic NPWT might reduce the number of dressing changes and pain when used in an outpatient setting. A small retrospective study reported improved epithelialization in patients free of comorbidities treated with NPWT. In other studies, NPWT showed no benefit for the treatment of patients with surgical wounds or skin grafts healing by primary intention, and a systematic review of NPWT for traumatic and surgical wounds found no differences between standard dressing and NPWT for any wound outcome measure. Another systematic review reported that NPWT was associated with lower rate of surgical site infections. Yet another systematic review reported that NPWT usage slightly reduces the risk of hospital readmission as compared to standard surgical dressing. Additional study in a larger, outpatient sample may be needed to evaluate this outcome measure.

PORTABLE, SINGLE-USE THERAPY FOR TRAUMATIC AND SURGICAL WOUNDS

Clinical Context and Therapy Purpose

The purpose of portable, single-use outpatient NPWT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with traumatic and surgical wounds.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies conducted exclusively in the inpatient setting were excluded.

Review of Evidence

PICO Dressing

PICO is a portable single-use NPWT system that comes with 2 sterile dressings and has a lifespan of 7 to 14 days. Karlakki (2016) reported on an RCT with 220 patients that evaluated the use of the PICO device in a surgical center immediately after hip and knee arthroplasties.[52] The device was left on for 7 days, including the time after the hospital stay. Strengths of the trial included powered intention-to-treat analysis, but evaluators were not blinded. There were trends toward reductions in hospital length of stay (0.9 days; 95% CI -0.2

to 2.5 days; p=0.07) and postoperative surgical wound complications (8.4% control vs. 2.0% PICO, p=0.06). However, most of the difference in length of stay was due to wound complications in 2 outliers in the control group (up to 61 days). The level of wound exudate was significantly reduced by the PICO device (p=0.007), with 4% of the study group and 16% of the control group having grade 4 (scale grade, 0 to 4) exudate. Blisters were observed in 11% of patients treated with the PICO system, although the blister occurrence was reported to be reduced when the dressing was stretched less.

Peterson (2021) reported on a single-site RCT evaluating the PICO system for incisional NPWT following cesarean delivery in women with class III obesity (body mass index ≥40; n=55) compared to standard dressings (n=55).[53] An unplanned interim analysis was performed due to slow enrollment and publication of larger trials reporting no benefit for NPWT. The interim analysis demonstrated no significant difference in the primary composite outcome of wound complications between groups (risk difference, 9.1%; 95% CI, -8.3% to 25.8%; p=0.38) and the trial was terminated early. In the systematic review by Norman (2022) an RCT by Hyldig (2020) evaluated the cosmetic result of using incisional negative-pressure wound therapy (iNPWT) compared with standard postsurgical dressings in obese women undergoing cesarean delivery.[9] The authors report that this study was not able to detect a difference in the long-term cosmetic result after CD when compared with standard dressings. On the other hand, a few other RCTs in this systematic reviews demonstrated a reduction of surgical site infections by prophylactic incisional negative pressure wound therapy compared with standard postoperative dressings in obese women giving birth by cesarean section. The effect remained statistically significant when adjusted for BMI and other potential risk factors. Another systematic review and meta-analysis by Gillespie (2022) also looked at effect of NPWT (mostly PICO or Prevena) on wound complications in obese women after cesarean birth.[54] Ten RCTs with 5583 patients were included in this study. Meta-analysis results suggested a significant difference favoring the NPWT group [relative risk(RR) 0.79, 95% CI 0.65-0.95, p<0.01], indicating an absolute risk reduction of 1.8% among those receiving NPWT compared to usual care. This study also reports a significant higher risk of blistering in the NPWT group.

Darwisch (2020) published an RCT to evaluate NPWT as a prevention and therapy of superficial infection.[55] In this single-center prospective randomized controlled trial, patients after cardiac surgery performed via median sternotomy (n = 528) were after stratification according to the marker body mass index (BMI ≥35 yes/no) randomized to receive either a disposable PICO dressing (PD) (n = 56/193) or a standard dry dressing (SDD) (n = 66/213) over the incision immediately at the conclusion of surgery. The authors report that use of PICO dressing NPWT compared with SDD did not improve the rate of SSIs in 30 days, but PD treatment reduced the rate of deep type of SSIs; so, there is a shift toward more superficial SSIs.

Prevena System

Pauser (2016) reported on a small RCT (n=21) evaluating Prevena in patients who had hemiarthroplasty for femoral neck fractures.[56] Use of the Prevena System significantly reduced seroma size, days of wound secretion, wound care time, and need for dressing changes.

In 2013, Grauhan published a controlled clinical trial to evaluate negative pressure wound dressing treatment for the prevention of infection.[57] For this study, 150 consecutive obese

patients (body mass index ≥ 30) with cardiac surgery performed via median sternotomy were analyzed. The authors concluded that Negative pressure wound dressing treatment over clean, closed incisions for the first 6 to 7 postoperative days significantly reduces the incidence of wound infection after median sternotomy in a high-risk group of obese patients.

Murphy (2019) published findings from the Negative Pressure Wound Therapy Use to Decrease Surgical Nosocomial Events in Colorectal Resections (NEPTUNE) trial, a single-center, superiority designed prospective randomized open blinded endpoint controlled trial evaluating the use of the Prevena System on closed incisions compared to standard gauze dressings in patients undergoing colorectal resection via laparotomy (n=300).[58] The was no significant difference in the incidence of SSI at 30 days post-surgery between the Prevena and control groups (32% vs. 34%; p=0.68). No significant difference in length of hospital stay was reported.

Hussamy (2019) reported on an open-label RCT evaluating the Prevena System for incisional NPWT following cesarean delivery in women with class III obesity (Body Mass Index ≥ 40; n=222) compared to standard dressings (n=219).[59] The overall composite wound morbidity rate was not significantly different between the Prevena and control cohorts (17% vs. 19%; RR 0.9; 95% CI 0.5 to 1.4).

Tuuli (2020) reported on a large, multicenter RCT evaluating the Prevena System for incisional NPWT following cesarean delivery in women with obesity (body mass index >30; n=806) compared to standard dressings (n=802).[60] The risk of superficial or deep SSI was not significantly different between groups (difference, 0.36%; 95% CI, -1.46% to 2.19%; p=0.70). The trial was terminated following a planned interim analysis which indicated an increased rate of adverse events in the Prevena group (difference, 6.95%; 95% CI, 1.86% to 12.03%; p<0.001) and futility for the primary outcome.

Bertges (2021) conducted a multicenter RCT evaluating the Prevena System for groin incisions in patients undergoing infrainguinal revascularization (n=118) compared to standard dressing (n=124).[61] The primary composite outcome of groin wound complications, SSI, major noninfectious wound complications, or graft infections within 30 days of surgery was not significantly different between Prevena and control groups (31% vs. 28%; p=0.55).

Kim (2020) published a meta-analysis to determine the effective indications of closed-incisional negative-pressure wound therapy (ciNPWT) following total hip or knee arthroplasty.[62] The systematic search was performed on MEDLINE, Embase, and Cochrane Library, and 11 studies were included. The studies comparing between ciNPWT and conventional dressings were categorized into following subgroups based on patient risk and revision procedures: routine vs high-risk patient; primary vs revision arthroplasty. These studies either used the Prevena or PICO system for the ciNPWT. Overall the analysis found that the the wound complication (odds ratio [OR] = 0.38; 95% confidence interval [CI] 0.15-0.93; p = 0.030) and surgical site infection (SSI) (OR = 0.24; 95% CI = 0.09-0.64; p = 0.005) in high-risk patients were significantly lower than the routine patients after ciNPWT. Further, in cases involving revision arthroplasties, the overall rates of wound complication (OR = 0.33; 95% CI = 0.18-0.62; P < .001) and SSI (OR = 0.26; 95% CI = 0.11-0.66; p = o.004) were significantly lower in the ciNPWT.

Cooper (2022) published an RCT to assess whether ciNPWT could decrease SSCs in high-risk patients undergoing direct anterior (DA) approach to total hip arthroplasty (THA).[63] This prospective randomized controlled trial (RCT) enrolled high-risk DA THA patients at 3 centers.

Patients were offered enrollment if they had previously identified risk factors for surgical site complications (SSC): Body mass index (BMI) >30 kg/m2, diabetes, active smoking, or prior hip surgery. Patients were randomized after closure to either an occlusive (control) dressing or ciNPWT (Prevena) dressing for 7 days. One hundred and twenty two patients enrolled; 120 completed data collection. SSCs occurred in 18.3% (11/60) of control patients compared to 8.3% (5/60) of ciNPT patients ($\chi 2 = 2.60$, p = o.107). SSCs included dehiscence to the subcutaneous level and prolonged drainage. Nine control (15.0%) and 2 ciNPWT (3.3%) patients met CDC criteria for superficial surgical site infection (SSI) ($\chi 2 = 4.90$, p = 0.027). Overall, there was a significant reduction in superficial SSIs and a trend toward lower SSCs after ciNPWT.

Section Summary: Portable, Single-Use Therapy for Traumatic and Surgical Wounds

The evidence on portable single-use NPWT includes RCTs of the PICO device and the Prevena Incision Management System. The PICO device was studied in an adequately powered but unblinded RCT of combined in- and outpatient use after total joint arthroplasty. The evidence base for the Prevena System is not sufficiently robust for conclusions on efficacy to be drawn. Well-designed comparative studies with larger numbers of patients treated in an outpatient setting are needed.

SUMMARY OF EVIDENCE

For individuals who have diabetic lower-extremity ulcers or amputation wounds who receive outpatient NPWT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity. There was a higher rate of wound healing and fewer amputations with NPWT, although the studies were at risk of bias due to lack of blinding. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers or amputation wounds who receive portable, single-use outpatient NPWT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. A 2019 RCT compared the PICO device with standard NPWT. In this study, the PICO device demonstrated noninferiority for wound area reduction. A statistically significant benefit in complete wound closure was noted for patients with DFUs, but was not duplicated in the per protocol population due to a high number of exclusions. One study of the Smart Negative Pressure nonpowered Wound Care System (SNaP) showed noninferiority to a V.A.C. device for wound size reduction. No significant difference in complete wound closure was reported. Interpretation of this study is limited by a high loss to follow-up. Well-designed comparative studies with larger numbers of patients powered to detect differences in complete wound closure are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic pressure ulcers who receive outpatient NPWT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. All trials are of low-quality and at high-risk of bias. Also, most study populations were treated in inpatient settings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive outpatient NPWT, the evidence includes an RCT and a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. A single RCT in patients with nonhealing leg ulcers who were treated with skin grafts found a faster rate of healing with NPWT when used in the inpatient setting. No studies were identified on the effectiveness of NPWT as a primary treatment for leg ulcers or for the use of NPWT in the outpatient setting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive portable, single-use outpatient NPWT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. A 2019 RCT compared the PICO device with standard NPWT. In this study, the PICO device demonstrated noninferiority for wound area reduction. No significant benefit in complete wound closure was found in patients with venous ulcers. One study of the SNaP System showed noninferiority to a V.A.C. device for wound size reduction. A subgroup analysis of this study found a significant difference in complete wound closure for patients with venous ulcers. However, interpretation of this study is limited by a high loss to follow-up and a lack of a control group treated with standard dressings. Well-designed comparative studies with larger numbers of patients powered to detect differences in complete wound closure are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have burn wounds who receive outpatient NPWT, the evidence includes RCTs, systematic reviews, and case series. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. An interim report of an RCT evaluating NPWT in partial-thickness burns, summarized in a Cochrane review, did not permit conclusions on the efficacy of NPWT for this indication. A separate RCT comparing NPWT with split-skin grafts in patients with full-thickness burns did not show differences in graft take and wound epithelialization. A retrospective case series reported functional outcomes for most patients who were treated with NPWT at a single-center. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have traumatic or surgical wounds who receive outpatient NPWT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. There are limited data on NPWT as a primary treatment of partial-thickness burns. One RCT found no benefit of NPWT on graft take and wound epithelialization in patients with full-thickness burns. Another RCT found a significant decrease in time to wound closure in patients with wound healing impairment following abdominal surgery; however, it is unclear if this difference is clinically meaningful. In other studies, NPWT showed no benefit in the treatment of patients with surgical wounds or skin grafts healing by primary intention, and a systematic review of NPWT for traumatic and surgical wounds found no differences between standard dressing and NPWT for any wound outcome measure. However, a small RCT has suggested that prophylactic NPWT may reduce the number of dressing changes and pain when used in an outpatient setting. A small retrospective study reported improved epithelialization with NPWT in patients free of comorbidities. Additional study in larger, outpatient samples is needed to evaluate this outcome measure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have traumatic or surgical wounds who receive portable, single-use outpatient NPWT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. The PICO device was studied in an adequately powered but unblinded RCT of combined in- and outpatient use after total joint arthroplasty. The evidence base for the Prevena System is not sufficiently robust for conclusions on efficacy to be drawn. Well-designed comparative studies with larger numbers of patients treated in an outpatient setting are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For obese women undergoing cesarean delivery, there is evidence for NPWT that indicate a significant reduction in surgical site infection. But the contradictory nature of other results of this procedure in obese women undergoing cesarean deliveries suggest that more studies are needed to reach a consensus about use of NPWT in this situation.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL EXPERT PANEL ON NEGATIVE PRESSURE WOUND THERAPY

In 2011, an international expert panel on NPWT provided evidence-based recommendations for the use of NPWT in chronic wounds.[64] The panel made the following recommendations for the use of NPWT (see Table 3).

Table 3. Recommendations on Use of NPWT in Chronic Wounds

Condition	Recommendation	Grade[a]
Pressure ulcers, grade 3-4	"NPWT may be used until surgical closure is possible/desirable."	C
	"NPWT should be considered to achieve closure by secondary intention…. to reduce wound dimensions…. [and] to improve the quality of the wound bed."	B
Diabetic foot ulcers	"NPWT must be considered as an advanced wound care therapy…. [and] must be considered to achieve healing by secondary intention."	A
	"NPWT should be considered in an attempt to prevent amputation or reamputation."	B
Ischemic lower-limb wounds	"… NPWT … may be considered in specialist hands and never as an alternative for revascularization."	C
	"… NPWT is NOT indicated in acute limb ischemia."	D
Venous leg ulcers	"If first-line therapy (compression) is not efficacious, NPWT should be considered to prepare the wound for surgical closure…."	B

NPWT: negative pressure wound therapy.
[a] Grade A: based on high-quality meta-analyses, systematic reviews of RCTs, or RCTs with very low risk of bias; grade B: based on high-quality systematic reviews of case-control or cohort studies; Grade C: based on well-conducted case-control or cohort studies; Grade D: based on case series or expert opinion.

INTERNATIONAL MULTIDISCIPLINARY CONSENSUS RECOMMENDATIONS

Willy (2017) presented evidence-based consensus guidelines on the use of closed incision negative pressure therapy (ciNPT) following surgery.[65] Among the studies found were 100 randomized controlled studies on ciNPT, most of which found an association between the use of ciNPT and improved outcomes. Based on the evidence, the consensus panel recommended that surgeons evaluate risk in patients before surgery to determine whether patient comorbidities (ie, obesity or diabetes) or the nature of the surgery presents an increased danger of infection. In such cases, the panel recommended the use of ciNPT.

INFECTIOUS DISEASES SOCIETY OF AMERICA AND SURGICAL INFECTION SOCIETY

In 2011, guidelines for the prevention of infections associated with combat-related injuries were endorsed by the Infectious Diseases Society of America and the Surgical Infection Society.[66] The guidelines provided an IB recommendation (strong recommendation, moderate-quality evidence) that NPWT should be used to manage open wounds (excluding central nervous system injuries).

The 2012 guidelines from the Society for the diagnosis and treatment of diabetic foot infections stated that no adjunctive therapy has been proved to improve the resolution of infection, but for select diabetic foot wounds that are slow to heal, clinicians might consider using NPWT (weak recommendation, low-quality evidence).[67]

AMERICAN COLLEGE OF PHYSICIANS

In 2015, the American College of Physicians published guidelines on the treatment of pressure ulcers.[68] The guidelines stated there was low-quality evidence that the overall treatment effect of NPWT did not differ from the standard of care.

ASSOCIATION FOR THE ADVANCEMENT OF WOUND CARE

In 2010, the Association for the Advancement of Wound Care (AAWC) published guidelines on the care of pressure ulcers. NPWT was included as a potential second-line intervention if first-line treatments did not result in wound healing (level B evidence). The guidelines indicated that patients must be selected carefully for this procedure. The guidelines were updated in 2014 with additional validation.[69]

In 2010, the AAWC published guidelines on the care of venous ulcers.[70] The guidelines listed NPWT as a potential adjunctive therapy if conservative therapy does not work in 30 days. The guidelines noted there is limited evidence for NPWT (level B) compared with other adjunctive therapies.

INTERNATIONAL WORKIN GROUP ON THE DIABETIC FOOT

In 2020, the International Working Group on the Diabetic Foot (IWGDF) published updated guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes.[71] The updated guidelines make the following recommendations:

- “Consider the use of negative pressure wound therapy to reduce wound size, in addition to best standard of care, in patients with diabetes and a post-operative (surgical) wound on the foot. (GRADE strength of recommendation: Weak; Quality of evidence: Low)”
- “We suggest not using negative pressure wound therapy in preference to best standard of care in nonsurgical diabetic foot ulcers. (GRADE strength of recommendation: Weak; Quality of evidence: Low)”

THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

In 2023, the American Academy of Orthopaedic Surgeons (AAOS) released a clinical practice guideline on the prevention of surgical site infection after major extremity trauma.[72] The guideline is based on a systematic review conducted by the AAOS and the Department of Defense. Each recommendation is rated based on the strength of supporting evidence. The recommendations for the use of NPWT for open and closed fractures was rated as strong (high quality supporting evidence):

- “After closed fracture fixation, negative pressure wound therapy may mitigate the risk of revision surgery or surgery site infections; however, after open fracture fixation, negative pressure wound therapy does not appear to offer an advantage when compared with sealed dressings as it does not decrease wound complications or amputations.”

SUMMARY

One-Month Therapeutic Trial

Overall, the evidence from comparative clinical trials has demonstrated there is a subset of problematic wounds for which the use of powered negative pressure wound therapy (NPWT) may provide a significant clinical benefit. In addition, clinical practice guidelines recommend outpatient NPWT in some situations. Therefore, a one-month therapeutic trial of a NPWT system (pump and supplies) may be considered medically necessary when criteria are met.

The evidence does not show that negative pressure wound therapy (NPWT) improves health outcomes when criteria are not met. Therefore, a one-month therapeutic trial of a NPWT system (pump and supplies) is considered not medically necessary when criteria are not met.

Continuation After One-Month Therapeutic Trial

Overall, the evidence from comparative clinical trials has demonstrated there is a subset of problematic wounds for which the *continuation* of powered negative pressure wound therapy (NPWT) following a one-month trial may provide a significant clinical benefit when there is appropriate supervision and documentation. Therefore, *continuation* of the powered NPWT system may be considered medically necessary when criteria are met.

When there is not documentation of a licensed medical professional assessing the wound and/or the wound is not improving, the *continuation* of powered negative pressure wound therapy at any period of time following a one-month therapeutic trial is therefore considered not medically necessary.

The evidence does not show that negative pressure wound therapy (NPWT) improves health outcomes beyond four months. Therefore, continuation of NPWT after four total months is considered not medically necessary.

Single-Use NPWT Systems

There is not enough evidence to establish the safety and efficacy of single-use NPWT systems. Well-designed comparative studies with larger numbers of patients treated in an outpatient setting are needed. Therefore, single-use NPWT systems (powered or nonpowered) is considered investigational for the treatment of acute or chronic wounds.

REFERENCES

1. Shah P, Inturi R, Anne D, et al. Wagner's Classification as a Tool for Treating Diabetic Foot Ulcers: Our Observations at a Suburban Teaching Hospital. *Cureus.* 2022;14(1):e21501. PMID: 35223277
2. U.S. Food and Drug Administration. UPDATE on Serious Complications Associated with Negative Pressure Wound Therapy Systems: FDA Safety Communication. 2011 Feb. [cited 04/03/2023]. 'Available from:' http://wayback.archive-it.org/7993/20170722215801/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm244211.htm.
3. TEC Assessments 2000. "Vacuum-assisted closure in the treatment of chronic wounds." Blue Cross and Blue Shield Association Technology Evaluation Center (TEC), Volume 15 Tab 23.
4. Food and Drug Administration (FDA). Guidance for Industry. Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment. June 2006. [cited 04/03/2023]. 'Available from:' https://www.fda.gov/media/71278/download.
5. Rhee SM, Valle MF, Wilson LM, et al. Negative Pressure Wound Therapy Technologies For Chronic Wound Care in the Home Setting. Evidence Report/Technology Assessment (Contract No. 290-201-200007-I) Rockville, MD: Agency for Healthcare Research and Quality; 2014.
6. Rhee SM, Valle MF, Wilson LM, et al. Negative pressure wound therapy technologies for chronic wound care in the home setting: A systematic review. *Wound Repair Regen.* 2015;23(4):506-17. PMID: 25845268
7. Sullivan N, Snyder DL, Tipton K, et al. Technology assessment: Negative pressure wound therapy devices (Contract No. 290-2007-10063). Rockville, MD: Agency for Healthcare Research and Quality; 2009.
8. Norman G, Goh EL, Dumville JC, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev.* 2020;6:CD009261. PMID: 32542647
9. Norman G, Shi C, Goh EL, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev.* 2022;4(4):CD009261. PMID: 35471497
10. Li HZ, Xu XH, Wang DW, et al. Negative pressure wound therapy for surgical site infections: a systematic review and meta-analysis of randomized controlled trials. *Clin Microbiol Infect.* 2019;25(11):1328-38. PMID: 31220604
11. Chen L, Zhang S, Da J, et al. A systematic review and meta-analysis of efficacy and safety of negative pressure wound therapy in the treatment of diabetic foot ulcer. *Ann Palliat Med.* 2021;10(10):10830-39. PMID: 34763444
12. Wynn M, Freeman S. The efficacy of negative pressure wound therapy for diabetic foot ulcers: A systematised review. *J Tissue Viability.* 2019;28(3):152-60. PMID: 31056407
13. Dumville JC, Hinchliffe RJ, Cullum N, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev.* 2013(10):CD010318. PMID: 24132761
14. Iheozor-Ejiofor Z, Newton K, Dumville JC, et al. Negative pressure wound therapy for open traumatic wounds. *Cochrane Database Syst Rev.* 2018;7:CD012522. PMID: 29969521
15. Seidel D, Storck M, Lawall H, et al. Negative pressure wound therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice: results of the German DiaFu-RCT. *BMJ Open.* 2020;10(3):e026345. PMID: 32209619

16. Seidel D, Lefering R, DiaFu study g. NPWT resource use compared with standard moist wound care in diabetic foot wounds: DiaFu randomized clinical trial results. *J Foot Ankle Res.* 2022;15(1):72. PMID: 36180953
17. Blume PA, Walters J, Payne W, et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care.* 2008;31:631-6. PMID: 18162494
18. Borys S, Hohendorff J, Koblik T, et al. Negative-pressure wound therapy for management of chronic neuropathic noninfected diabetic foot ulcerations - short-term efficacy and long-term outcomes. *Endocrine.* 2018;62:611-16. PMID: 30099674
19. Kirsner R, Dove C, Reyzelman A, et al. A prospective, randomized, controlled clinical trial on the efficacy of a single-use negative pressure wound therapy system, compared to traditional negative pressure wound therapy in the treatment of chronic ulcers of the lower extremities. *Wound Repair Regen.* 2019;27(5):519-29. PMID: 31087729
20. Kirsner RS, Zimnitsky D, Robinson M. A prospective, randomized, controlled clinical study on the effectiveness of a single-use negative pressure wound therapy system, compared to traditional negative pressure wound therapy in the treatment of diabetic ulcers of the lower extremities. *Wound Repair Regen.* 2021;29(6):908-11. PMID: 34525239
21. Armstrong DG, Marston WA, Reyzelman AM, et al. Comparison of negative pressure wound therapy with an ultraportable mechanically powered device vs. traditional electrically powered device for the treatment of chronic lower extremity ulcers: a multicenter randomized-controlled trial. *Wound Repair Regen.* 2011;19(2):173-80. PMID: 21362084
22. Armstrong DG, Marston WA, Reyzelman AM, et al. Comparative effectiveness of mechanically and electrically powered negative pressure wound therapy devices: a multicenter randomized controlled trial. *Wound Repair Regen.* 2012;20(3):332-41. PMID: 22564228
23. Lerman B, Oldenbrook L, Eichstadt SL, et al. Evaluation of chronic wound treatment with the SNaP wound care system versus modern dressing protocols. *Plast Reconstr Surg.* 2010;126:1253-61. PMID: 20885246
24. Shi J, Gao Y, Tian J, et al. Negative pressure wound therapy for treating pressure ulcers. *Cochrane Database Syst Rev.* 2023;5(5):Cd011334. PMID: 37232410
25. Wanner MB, Schwarzl F, Strub B, et al. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. *Scand J Plast Reconstr Surg Hand Surg.* 2003;37(1):28-33. PMID: 12625392
26. Dumville JC, Land L, Evans D, et al. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev.* 2015(7):CD011354. PMID: 26171910
27. Vuerstaek JD, Vainas T, Wuite J, et al. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg.* 2006;44:1029-37; discussion 38. PMID: 17000077
28. Marston WA, Armstrong DG, Reyzelman AM, et al. A Multicenter Randomized Controlled Trial Comparing Treatment of Venous Leg Ulcers Using Mechanically Versus Electrically Powered Negative Pressure Wound Therapy. *Adv Wound Care (New Rochelle).* 2015;4:75-82. PMID: 25713749
29. Dumville JC, Munson C, Christie J. Negative pressure wound therapy for partial-thickness burns. *Cochrane Database Syst Rev.* 2014(12):CD006215. PMID: 25500895

30. Bloemen MC, van der Wal MB, Verhaegen PD, et al. Clinical effectiveness of dermal substitution in burns by topical negative pressure: a multicenter randomized controlled trial. *Wound Repair Regen.* 2012;20(6):797-805. PMID: 23110478
31. Krug E, Berg L, Lee C, et al. Evidence-based recommendations for the use of Negative Pressure Wound Therapy in traumatic wounds and reconstructive surgery: steps towards an international consensus. *Injury.* 2011;42 Suppl 1:S1-12. PMID: 21316515
32. Ehrl D, Heidekrueger PI, Broer PN, et al. Topical Negative Pressure Wound Therapy of Burned Hands: Functional Outcomes. *J Burn Care Res.* 2018;39:121-28. PMID: 28368916
33. Webster J, Scuffham P, Stankiewicz M, et al. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev.* 2014(10):CD009261. PMID: 25287701
34. De Vries FEE, Wallert ED, Solomkin JS, et al. A systematic review and meta-analysis including GRADE qualification of the risk of surgical site infections after prophylactic negative pressure wound therapy compared with conventional dressings in clean and contaminated surgery. *Medicine (Baltimore).* 2016;95:e4673. PMID: 27603360
35. Ren B, Jiang X, Chen J, et al. The efficacy of negative pressure wound therapy after hepatopancreatobiliary surgery: A systematic review and meta-analysis. *Pak J Med Sci.* 2022;38(8):2356-64. PMID: 36415224
36. Liu X, Zhang H, Cen S, et al. Negative pressure wound therapy versus conventional wound dressings in treatment of open fractures: A systematic review and meta-analysis. *Int J Surg.* 2018;53:72-79. PMID: 29555530
37. Costa ML, Achten J, Bruce J, et al. Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb: The WOLLF Randomized Clinical Trial. *JAMA.* 2018;319:2280-88. PMID: 29896626
38. Sahebally SM, McKevitt K, Stephens I, et al. Negative Pressure Wound Therapy for Closed Laparotomy Incisions in General and Colorectal Surgery: A Systematic Review and Meta-analysis. *JAMA Surg.* 2018;153:e183467. PMID: 30267040
39. Flynn J, Choy A, Leavy K, et al. Negative Pressure Dressings (PICO(TM)) on Laparotomy Wounds Do Not Reduce Risk of Surgical Site Infection. *Surg Infect (Larchmt).* 2020;21(3):231-38. PMID: 31618115
40. Stannard JP, Volgas DA, McGwin G, 3rd, et al. Incisional negative pressure wound therapy after high-risk lower extremity fractures. *J Orthop Trauma.* 2012;26(1):37-42. PMID: 21804414
41. Masden D, Goldstein J, Endara M, et al. Negative pressure wound therapy for at-risk surgical closures in patients with multiple comorbidities: a prospective randomized controlled study. *Ann Surg.* 2012;255(6):1043-7. PMID: 22549748
42. Chio EG, Agrawal A. A randomized, prospective, controlled study of forearm donor site healing when using a vacuum dressing. *Otolaryngol Head Neck Surg.* 2010;142:174-8. PMID: 20115970
43. Javed AA, Teinor J, Wright M, et al. Negative Pressure Wound Therapy for Surgical-site Infections: A Randomized Trial. *Ann Surg.* 2019;269(6):1034-40. PMID: 31082899
44. Tanaydin V, Beugels J, Andriessen A, et al. Randomized Controlled Study Comparing Disposable Negative-Pressure Wound Therapy with Standard Care in Bilateral Breast Reduction Mammoplasty Evaluating Surgical Site Complications and Scar Quality. *Aesthetic Plast Surg.* 2018;42:927-35. PMID: 29442143
45. Seidel D, Diedrich S, Herrle F, et al. Negative Pressure Wound Therapy vs Conventional Wound Treatment in Subcutaneous Abdominal Wound Healing

Impairment: The SAWHI Randomized Clinical Trial. *JAMA Surg.* 2020;155:469-78. PMID: 32293657
46. Stannard JP, Robinson JT, Anderson ER, et al. Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. *J Trauma.* 2006;60:1301-6. PMID: 16766975
47. Monsen C, Acosta S, Mani K, et al. A randomised study of NPWT closure versus alginate dressings in peri-vascular groin infections: quality of life, pain and cost. *J Wound Care.* 2015;24(6):252, 54-6, 58-0. PMID: 26075373
48. Biter LU, Beck GM, Mannaerts GH, et al. The use of negative-pressure wound therapy in pilonidal sinus disease: a randomized controlled trial comparing negative-pressure wound therapy versus standard open wound care after surgical excision. *Dis Colon Rectum.* 2014;57:1406-11. PMID: 25380007
49. Costa ML, Achten J, Parsons NR. Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial. *Bone Joint J.* 2022;104-b(5):633-39. PMID: 35491582
50. Seidel D, group Ss. Ambulatory negative pressure wound therapy of subcutaneous abdominal wounds after surgery: results of the SAWHI randomized clinical trial. *BMC Surg.* 2022;22(1):425. PMID: 36503505
51. Seidel D, Lefering R. NPWT Resource Use Compared With Conventional Wound Treatment in Subcutaneous Abdominal Wounds With Healing Impairment After Surgery: SAWHI Randomized Clinical Trial Results. *Ann Surg.* 2022;275(2):e290-e98. PMID: 34117147
52. Karlakki SL, Hamad AK, Whittall C, et al. Incisional negative pressure wound therapy dressings (iNPWTd) in routine primary hip and knee arthroplasties: A randomised controlled trial. *Bone Joint Res.* 2016;5:328-37. PMID: 27496913
53. Peterson AT, Bakaysa SL, Driscoll JM, et al. Randomized controlled trial of single-use negative-pressure wound therapy dressings in morbidly obese patients undergoing cesarean delivery. *Am J Obstet Gynecol MFM.* 2021;3(5):100410. PMID: 34058423
54. Gillespie BM, Thalib L, Ellwood D, et al. Effect of negative-pressure wound therapy on wound complications in obese women after caesarean birth: a systematic review and meta-analysis. *BJOG.* 2022;129(2):196-207. PMID: 34622545
55. A. Darwisch ZF. Negative Pressure Therapy after Median Sternotomy on Closed Incision: A Randomized Controlled Study. *Thorac Cardiovasc Surg* 2020;68(S 01):S1-S72. PMID:
56. Pauser J, Nordmeyer M, Biber R, et al. Incisional negative pressure wound therapy after hemiarthroplasty for femoral neck fractures - reduction of wound complications. *Int Wound J.* 2016;13(5):663-7. PMID: 25125244
57. Grauhan O, Navasardyan A, Hofmann M, et al. Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy. *J Thorac Cardiovasc Surg.* 2013;145(5):1387-92. PMID: 23111014
58. Murphy PB, Knowles S, Chadi SA, et al. Negative Pressure Wound Therapy Use to Decrease Surgical Nosocomial Events in Colorectal Resections (NEPTUNE): A Randomized Controlled Trial. *Ann Surg.* 2019;270(1):38-42. PMID: 30499799
59. Hussamy DJ, Wortman AC, McIntire DD, et al. Closed Incision Negative Pressure Therapy in Morbidly Obese Women Undergoing Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2019;134:781-89. PMID: 31503147
60. Tuuli MG, Liu J, Tita ATN, et al. Effect of Prophylactic Negative Pressure Wound Therapy vs Standard Wound Dressing on Surgical-Site Infection in Obese Women After

Cesarean Delivery: A Randomized Clinical Trial. *JAMA.* 2020;324(12):1180-89. PMID: 32960242
61. Bertges DJ, Smith L, Scully RE, et al. A multicenter, prospective randomized trial of negative pressure wound therapy for infrainguinal revascularization with a groin incision. *J Vasc Surg.* 2021;74(1):257-67 e1. PMID: 33548422
62. Kim JH, Lee DH. Are high-risk patient and revision arthroplasty effective indications for closed-incisional negative-pressure wound therapy after total hip or knee arthroplasty? A systematic review and meta-analysis. *Int Wound J.* 2020;17(5):1310-22. PMID: 32406175
63. Cooper HJ, Santos WM, Neuwirth AL, et al. Randomized Controlled Trial of Incisional Negative Pressure Following High-Risk Direct Anterior Total Hip Arthroplasty. *J Arthroplasty.* 2022;37(8S):S931-S36. PMID: 35304299
64. Vig S, Dowsett C, Berg L, et al. Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds: steps towards an international consensus. *J Tissue Viability.* 2011;20 Suppl 1:S1-18. PMID: 22119531
65. Willy C, Agarwal A, Andersen CA, et al. Closed incision negative pressure therapy: international multidisciplinary consensus recommendations. *Int Wound J.* 2017;14(2):385-98. PMID: 27170231
66. Hospenthal DR, Murray CK, Andersen RC, et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma.* 2011;71:S210-34. PMID: 21814089
67. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 infectious diseases society of america clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *J Am Podiatr Med Assoc.* 2013;103:2-7. PMID: 23328846
68. Qaseem A, Humphrey LL, Forciea MA, et al. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2015;162:370-9. PMID: 25732279
69. Association for the Advancement of Wound Care (AAWC). Guideline of Pressure Ulcer Guidelines. 2010. [cited 04/03/2023]. 'Available from:' https://s3.amazonaws.com/aawc-new/memberclicks/AAWCPressureUlcerGuidelineofGuidelinesAug11.pdf.
70. Association for the Advancement of Wound Care (AAWC). International Consolidated Venous Ulcer Guideline (ICVUG). Update of AAWC Venous Ulcer Guideline, 2005 and 2010. 2015. [cited 04/03/2023]. 'Available from:' https://aawconline.memberclicks.net/assets/appendix%20c%20guideline%20icvug-textformatrecommendations-final%20v42%20changessaved18aug17.pdf.
71. Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev.* 2020;36 Suppl 1:e3283. PMID: 32176450
72. Goldman AH, Tetsworth K. AAOS Clinical Practice Guideline Summary: Prevention of Surgical Site Infection After Major Extremity Trauma. *J Am Acad Orthop Surg.* 2023;31(1):e1-e8. PMID: 36548150

CODES

Codes	Number	Description
CPT	97605	Negative pressure wound therapy (e.g., vacuum-assisted drainage collection), utilizing durable medical equipment (DME), including topical application(s),

Codes	Number	Description
		wound assessment, and instruction(s) for ongoing care, per session; total wound(s) surface area less than or equal to 50 square centimeters
	97606	;total wound(s) surface area greater than 50 square centimeters
	97607	Negative pressure wound therapy (eg, vacuum assisted drainage collection), utilizing disposable, non-durable medical equipment including provision of exudate management collection system, topical application(s), wound assessment, and instructions for ongoing care, per session; total wound(s) surface area less than or equal to 50 square centimeters
	97608	;total wound(s) surface area greater than 50 square centimeters
HCPCS	A6550	Wound care set, for negative pressure wound therapy electrical pump, includes all supplies and accessories
	A7000-A7001	Canister for use with suction pump, code range
	A9272	Wound suction, disposable, includes dressing and all accessories and components, any type, each
	E2402	Negative pressure wound therapy electrical pump, stationary or portable
	K0743	Suction pump, home model, portable, for use on wounds
	K0744-K0746	Code range for absorptive wound dressings to be used with home suction pump coded with K0743

Date of Origin: *December 2021*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 77

Insulin Infusion Pumps, Automated Insulin Delivery and Artificial Pancreas Device Systems

Effective: January 1, 2024

Next Review: October 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

An external insulin infusion pump is typically used to deliver insulin into patients with diabetes mellitus. Automated insulin delivery systems (including but not limited to artificial pancreas devices) monitor glucose levels and automatically adjust the delivery of insulin to help achieve tight glucose control.

MEDICAL POLICY CRITERIA

Note: This policy is does not address stand-alone continuous glucose monitors (CGM) which may be considered medically necessary.

I. An *automated insulin delivery system* (including artificial pancreas devices) may be considered **medically necessary** for diabetes mellitus when either of the following Criteria are met:

A. The patient has type 1 diabetes mellitus and all of the following Criteria (1. – 3.) are met:

1. The device is approved by the Food and Drug Administration (FDA) and the patient meets the FDA approved age requirements for the device (see Policy

Guidelines); and

2. Glycated hemoglobin level (Hemoglobin A1c or HbA1c) between 5.8% and 10.0%; and
3. Used insulin pump therapy for more than 3 months.

B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).

II. An *external insulin infusion pump* may be considered **medically necessary** when either of the following Criteria are met:

A. The patient has diabetes mellitus; or

B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).

III. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) may be considered **medically necessary** when both of the following Criteria (A. and B.) are met:

A. The pump is no longer able to perform its basic function due to one or more of the following:

1. Device is out of the warranty period; or
2. Damage or wear; or
3. The device can no longer meet the patient's medical needs due to a significant change in the patient's medical condition (e.g., larger insulin reservoir needed).

B. The current device cannot be repaired or adapted adequately to meet the patient's medical needs.

IV. The use of an *external insulin infusion pump* is considered **not medically necessary** when Criterion II. is not met.

V. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) that does not meet Criterion III. is considered **not medically necessary**.

VI. The use of an *automated insulin delivery system* (including artificial pancreas device systems) is considered **investigational** when Criterion I. is not met including but not limited to a device that is not approved by the FDA.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device Systems)

Device	Age Indication	Manufacturer
MiniMed™ 530G System[a] (open-loop, LGS)	≥16 years	Medtronic
MiniMed™ 630G System with SmartGuard™[b] (open-loop, LGS):		Medtronic
o MiniMed™ 630G with Guardian™ Sensor 3	≥14 years	
o MiniMed™ 630G with Enlite™ Sensor	≥16 years	
MiniMed™ 670G System[c] (hybrid closed-loop, LGS or PLGM)	≥7 years	Medtronic
MiniMed™ 770G System[d] (hybrid closed-loop, LGS or PLGM)	≥2 years[e]	Medtronic
MiniMed 780G System (hybrid closed-loop)[f]	≥7 years	Medtronic
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS) t:slim X2 Insulin Pump with Control-IQ Technology (HCL)	≥6 years	Tandem
Omnipod 5 (hybrid closed-loop)	≥2 years	Insulet
iLet Bionic Pancreas (closed loop)	≥6 years	Beta Bionics

[a] MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).
[b] MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System, CareLink® USB, Bayer's CONTOUR ® NEXT LINK 2.4 Wireless Meter, and Bayer's CONTOUR® NEXT Test Strips (at time of approval).
[c] MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).
[d] MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription.
[e] The 770G System may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.
[f] MiniMed 780G System consists of the following devices: MiniMed 780G Insulin Pump, the Guardian 4 Transmitter, the Guardian 4 Sensor (3), One-Press Serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Automated insulin delivery system (artificial pancreas device system)
  - History and physical
  - Age of patient
  - Name and type of device requested
  - Documented use of insulin pump for more than 3 months
  - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)
- External insulin infusion pumps
  - Clinical documentation of diabetes mellitus
  - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)

- Replacement and upgrades
    - History and physical
    - Name and type of device requested
    - Documentation of specifically why pump is no longer able to perform its basic function
    - Documentation that the current device cannot be repaired or adapted adequately to meet the patient's needs

CROSS REFERENCES

1. Digital Health Products, Medicine, Policy No. 175
2. Medication Policy Manual, Note: Do a find (Ctrl+F) and enter name in the find bar to locate the appropriate policy.

BACKGROUND

Maintenance of a target blood glucose and target glycated hemoglobin (HgA1c < 7%), a marker which is used as a proxy for average blood glucose, is now considered standard of care for patients with diabetes. Also known as tight diabetes control, this strategy is intended to prevent severe hypoglycemic events and lower the risk of cardiovascular disease mortality associated with uncontrolled glycemia.[1] In order to achieve tight glucose control, several devices may be used individually or in combination which includes but is not limited to continuous glucose monitors, insulin pumps, and more recently artificial pancreas device systems. The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a continuous glucose monitor (CGM) linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose. The APDS components are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a specified range or target and to minimize the incidence and severity of hypoglycemic and hyperglycemic events. An APDS control algorithm is embedded in software in an external processor or controller that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different APDS types are currently available for clinical use. Sensor augmented pump therapy (SAPT) with low glucose suspend (LGS) (suspend on low) may reduce the likelihood or severity of a hypoglycemic event by suspending insulin delivery temporarily when the sensor value reaches (reactive) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension (LGS) automatically suspends basal insulin delivery for up to two hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (PLGM) (suspend before low) suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL above the patient-set low limit and is predicted to be 20 mg/dL above this low limit in 30 minutes. In the absence of a patient response, the insulin infusion resumes after a maximum suspend period of two hours. In certain circumstances, auto-resumption parameters may be used.

When a sensor value is above or predicted to remain above the threshold, the infusion pump will not take any action based on CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump,

and give premeal bolus insulin to control their glucose levels.

A control-to-range system reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person's glucose levels reach or approach predetermined higher and lower thresholds. When a patient's glucose concentration is within the specified range, the infusion pump will not take any action based upon CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-target system sets target glucose levels and always tries to maintain these levels. This system is fully automated and requires no interaction from the user (except for calibration of the CGM). There are two subtypes of control-to-target systems: insulin-only and bihormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

An APDS may also be referred to as a “closed-loop” system. A closed-loop system has automated insulin delivery and continuous glucose sensing and insulin delivery without patient intervention. The systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous insulin delivery based on real-time sensor glucose levels. There are no completely closed-loop insulin delivery systems marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtime, the patient enters the number of carbohydrates they are eating for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

REGULATORY STATUS

There are several APDS devices approved by the Food and Drug Administration (FDA). These systems are regulated by the FDA as class III device systems.

The MiniMed® 530G System includes a threshold suspend or LGS feature.[2] The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is at or below a preset threshold within the 60- to 90-mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond, the pump automatically suspends action for two hours, and then insulin therapy resumes.

The MiniMed® 630G System with SmartGuard™, which is similar to the 530G, includes updates to the system components including waterproofing.[3] The threshold suspend feature can be programmed to temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value. The MiniMed 630G System with SmartGuard™ is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the values provided by the MiniMed 630G system. The device is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the SmartGuard™ Suspend on Low alarm to take measures to prevent or treat hypoglycemia themselves.

The MiniMed® 670G System is a hybrid closed-loop insulin delivery system consisting of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and the SmartGuard Hybrid Closed Loop.[4] The system includes an LGS feature that suspends insulin delivery; this feature either suspends delivery on low-glucose levels or suspends delivery before low-glucose levels, and has an optional alarm (manual mode). Additionally, the system allows semiautomatic basal insulin-level adjustment (decrease or increase) to preset targets (automatic mode). As a hybrid system; basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The CGM component of the MiniMed 670G System is not intended to be used directly for making manual insulin therapy adjustments; rather it is to provide an indication of when a glucose measurement should be taken. The MiniMed 670G System was originally approved for marketing in the United States on September 28, 2016 (P160017) and received approval for marketing with a pediatric indication (ages 7-13 years) on June 21, 2018 (P160017/S031).

On August 31, 2020, the MiniMed® 770G System received Premarket Approval from the FDA. The 770G System was approved as a supplement to the previously approved MiniMed 670G System.[5] Approval of the MiniMed 770G System expanded the indications for use to users down to two years old and updated the pump communication protocol to Bluetooth. The 770G System is a hybrid closed loop system that measures glucose levels and automatically adjusts insulin delivery by either administering or withholding insulin. The 770G System consists of the MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription. The 770G System was approved for the following indications:

> The MiniMed 770G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of type 1 diabetes mellitus in persons two years of age and older requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 770G System includes SmartGuard technology, which can be programmed to automatically adjust delivery of basal insulin based on continuous glucose monitoring (CGM) sensor glucose values and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values.
>
> The Medtronic MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips. The system requires a prescription.
>
> The Guardian Sensor (3) has not been evaluated and is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. All therapy adjustments should be based on measurements obtained using a blood glucose meter and not on values provided by the Guardian Sensor (3).

Per the FDA approval, a prominent boxed warning is included in the labeling regarding use of the 770G System in users with a total daily insulin dose of less than 8 units, “Medtronic performed an evaluation of the 770G closed loop system and determined that it may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.”

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are six years of age and older.[6] The System consists of the t:slim X2 Insulin Pump paired with the Dexcom G5 Mobile CGM (Continuous Glucose Monitor), as well as the Basal-IQ Technology. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the System as the receiver for a therapeutic CGM. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on CGM sensor readings. Introduction into clinical care is planned for summer 2019.

In December 2019, the FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process.[7] The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue.

In 2022, the FDA approved the Omnipod 5 ACE Pump for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. In January, approval for the SmartAdjust™ technology was granted for ages six and up, and in September approval was expanded to allow for use in people ages two and older.[8, 9] The Omnipod 5 ACE Pump is able to reliably and securely communicate with compatible, digitally connected devices, including automated insulin dosing software, to receive, execute, and confirm commands from these devices.

In May 2023, the FDA approved the first closed-loop system (iLet Bionic Pancreas) through the 510(k) premarket clearance pathway.[10] The iLet pump is an alternate controller enabled (ACE) pump intended to deliver insulin under the skin based on input from an integrated continuous glucose monitor (iCGM) and an interoperable automated glycemic controller (iAGC), in people 6 years of age or older with diabetes mellitus. The iLet ACE Pump is intended for single-person use; it is not to be shared.[11]

There are many insulin pumps on the market that are approved by the FDA. FDA 510(k) Product Code: LZG.

EVIDENCE SUMMARY

EXTERNAL INSULIN INFUSION PUMP

Randomized controlled trials (RCTs) have evaluated insulin pumps with various functionalities including a low glucose suspend (LGS) feature.[12-17] Results of these studies have demonstrated that insulin infusion pumps may, in carefully selected patient populations, control blood glucose to near-normal levels.

ARTIFICIAL PANCREAS DEVICE SYSTEMS

The key clinical outcomes regarding the clinical utility of artificial pancreas device systems (APDSs) relate to their ability to improve morbidity and mortality associated with clinically significant, severe, and acute hypoglycemia or hyperglycemic events.

Low Glucose Suspend Devices

Systematic Review and Technology Assessments

Alotaibi (2020) published the results of a systematic review (SR) with meta-analysis on the efficacy and safety of insulin pump therapy with predictive low glucose suspend (PLGS) features in children and adolescents with type 1 diabetes (T1D).[18] RCTs evaluating sensor augmented pump (SAP) with a PLGS feature compared to SAP or insulin pump therapy without SAP in decreasing hypoglycemia in children and adolescents with type 1 diabetes were considered. Although all RCTs with patients aged 2 to 18 years with at least two weeks follow-up were evaluated, only five RCTs with total sample size of 493 children aged 6 to 18 years met inclusion criteria. The risk of bias within studies was low for allocation concealment and random sequence generation was low for most studies. Blinding was not always feasible given the nature of the intervention; three of the studies were open-label, whereas in two of the studies, participants were blinded to the intervention, and in one study the outcome assessors also were blinded to the intervention. Risk of publication bias could not be assessed due to the small number of studies evaluated. Intention-to-treat analysis was used in all studies to account for loss of follow-up. Results indicate there is high quality evidence that PLGS is superior to SAP in decreasing percent of time spent in hypoglycemia (sensor glucose [SG] <3.9 mmol/L [<70 mg/dL]/24 h) and nocturnal hypoglycemia (SG <3.9 mmol [<70 mg/dL]/L/night) with an absolute mean difference of 17.4 min/d (95% CI -19.2, -15.5) and 26.3 min/night (95% CI: -35.5, -16.7), respectively. Percent time spent in hyperglycemia or episodes of diabetic ketoacidosis were not found to be different between groups. The only study with a duration long enough to assess health related quality of life showed no significant difference from baseline to study completion. The authors concluded that among children and adolescents with type 1 diabetes treated with insulin pump therapy, the utilization of PLGS is superior to SAP in decreasing mild to moderate daytime and nocturnal hypoglycemia without increasing the risk of hyperglycemia, but note that future studies evaluating long-term safety and cost-effectiveness are warranted.

Randomized Controlled Trials

Collyns (2021) published the results of a randomized crossover study conducted at two sites comparing the MiniMed Advanced Hybrid Closed-Loop (AHCL) 670G system to sensor-augmented pump therapy with predictive low glucose management (SAP + PLGM) in patients with T1D.[19] Of the 60 patients enrolled, 59 completed the study. Patients were naive to automated insulin delivery ranged in age from seven to 80 years (mean age 23.3 ± 14.4 years), The treatment intervention sequence was randomly assigned 1:1 stratified by participants' age. Each study phase was four weeks, preceded by a two- to four-week run-in and separated by a 2-week washout. Time in target range (TIR, 3.9-10 mmol/L) was higher in the AHCL compared to the SAP + PLGM group (70.4 ± 8.1% vs. 57.9 ± 11.7%, $p < 0.001$). Mean sensor glucose (SG) at run-in was 9.3 ± 0.9 mmol/L and improved with AHCL (8.5 ± 0.7 mmol/L, $p < 0.001$) and deteriorated during PLGM (9.5 ± 1.1 mmol/L, $p < 0.001$). There was one episode of mild diabetic ketoacidosis, which occurred during the SAP + PLGM arm, attributed to an infusion set failure in combination with an intercurrent illness.

Beardsall (2020) published the results of a randomized, open-label, parallel controlled trial in 20 pre-term infants receiving CGM alone supported by a paper algorithm compared to CGM with an additional intervention period of closed-loop CGM. The closed-loop system was comprised of (i) an Enlite CGM sensor, (ii) a laptop computer running a model predictive control algorithm and (iii) two Alaris syringe pumps. All 20 babies remained in the study throughout the intervention period from 48 to 72 hours and the mean (SD) length of glucose

data collected in each study arm was 137 (16.4) hours and 136 (8.7) hours for CGM and CGM plus closed loop, respectively. During the intervention period, the median (IQR) time spent in the target range (sensor glucose [SG] 4.0–8.0 mmol/L) was significantly higher in babies in the closed-loop group 91% (78, 99) compared with controls 26% (6-64); p<0.001. In addition, the time spent in the wider target range of 2.6–10.0 mmol/L was higher in the closed-loop group: median 100% compared with control group, median 84%. Lower SG was observed in the closed-loop group median (IQR) 6.2 (6.1-7.1) mmol/L compared with the control group 8.6 (7.4-11.1) mmol/L (p=0.002). Time spent with SG levels <2.6 mmol/L and glucose variability as measured by the SD of SG were similar between groups. In the postintervention period (post-72 hours), there was qualitatively increased time in both glucose target ranges (4.0–8.0 and 2.6–10.0 mmol/L) in the closed-loop group compared with the control group, but these differences did not reach statistical significance. In the closed-loop study group, two babies had documented episodes of hypoglycemia with blood glucose (BG) <2.6 mmol/L, both associated with a change of maintenance fluids. In the control study group, no babies had a documented BG value <2.6 mmol/L. One baby in the control group had an episode lasting 205 min when the SG fell to <2.6 mmol/L (BG was not checked at this time). Limitations to this study include small sample size, lack of blinding, and short study duration. While Medtronic provided the continuous glucose monitoring systems and sensors, the company had no role in study design, data acquisition, preparation of the manuscript, or decision to publish the study.

Breton (2020) published the results of a multi-site RCT comparing a closed-loop system of insulin delivery (closed-loop group, n=78) and a sensor-augmented insulin pump (control group, n=23) in children 6 to 13 years of age who had type 1 diabetes.[20] The primary outcome was the percentage of time that glucose levels were in the target range of 70 to 180 mg per deciliter, as measured by CGM. The mean (±SD) percentage of time that the glucose level was in the target range over the 16 weeks of treatment increased from 53±17% at baseline to 67±10% in the closed-loop group and from 51±16% to 55±13% in the control group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; p<0.001). The median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95) for patients in the closed-loop group. No episodes of diabetic ketoacidosis or severe hypoglycemia were noted in either study group. Improvements were sustained through 28 weeks in an uncontrolled extension study of 100 children who were enrolled in the RCT (Kanapka 2021).[21] Health-related quality of life and patient satisfaction measures from the RCT and the extension phase were reported by Cobry (2021).[22] Neither children nor their parents in the closed-loop system group reported statistically significant changes in these outcomes compared with the sensor-augmented insulin pump group. The authors concluded that children receiving the closed-loop system did not experience increased burden compared with those using sensor-augmented insulin pump.

Outcomes of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial were reported by Bergenstal (2013).[16] This industry-sponsored trial used the Paradigm Veo insulin pump. A total of 247 patients were randomized to an experimental group, in which a continuous glucose monitor with the LGS feature was used (n=121), or a control group, which used the continuous glucose monitor but not the LGS feature (n=126). Key eligibility criteria were 16-to-70 years old, T1D, and HbA1c levels between 5.8% and 10.0%. In addition, patients had to have more than six months of experience with insulin pump therapy and at least two nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a two-week run-in phase. The randomized intervention phase lasted three months. Patients in the LGS group were required to use the feature at least between 10 PM and 8 AM. The threshold value was initially set at 70 mg/dL and could be adjusted to between 70 mg/dL and

90 mg/dL. Seven patients withdrew early from the trial; all 247 were included in the intention-to-treat analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA1c levels.

The primary end point, mean (standard deviation [SD]) AUC for nocturnal hypoglycemic events, was 980 (1200) mg/dL/min in the LGS group and 1568 (1995) mg/dL/min in the control group. The difference between groups was statistically significant ($p<0.001$), favoring the intervention group.

Similarly, the mean AUC for combined daytime and nighttime hypoglycemic events (a secondary outcome) significantly favored the intervention group ($p<0.001$). Mean (SD) AUC values were 798 (965) mg/dL/min in the intervention group and 1164 (1590) mg/dL/min in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes (mean, 3.3 per patient-week; SD=2.0) than the control group (mean, 4.7 per patient-week; SD=2.7; $p<0.001$). For patients in the LGS group, the mean number of times the feature was triggered per patient was 2.08 per 24-hour period and 0.77 each night (10 PM-8 AM). The median duration of nighttime threshold suspend events was 11.9 minutes; 43% of events lasted for less than five minutes, and 19.6% lasted more than two hours. In both groups, the mean sensor glucose value at the beginning of nocturnal events was 62.6 mg/dL. After four hours, the mean value was 162.3 mg/dL in the LGS group and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA1c level was minimal, and there was no statistically significant difference between groups. Mean HbA1c levels decreased from 7.26 to 7.24 mg/dL in the LGS group and from 7.21 to 7.14 mg/dL in the control group. During the study period, there were no severe hypoglycemic events in the LGS group and four events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

Before reporting on in-home findings, the ASPIRE researchers (Garg [2012]) published data from the in-clinic arm of the study.[23] This randomized crossover trial included 50 patients with type 1 diabetes who had at least three months of experience with an insulin pump system. After a two-week run-in period to verify and optimize basal rates, patients underwent two in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for two hours when levels reached 70 mg/dL or less. The goal of the study was to evaluate whether the severity and duration of hypoglycemia were reduced when the LGS feature was used. The study protocol called for patients to start exercise with glucose levels between 100 mg/dL and 140 mg/dL and to use a treadmill or stationary bicycle until their plasma glucose levels were 85 mg/dL or less. The study outcome (duration of hypoglycemia) was defined as the period of time glucose values were lower than 70 mg/dL and above 50 mg/dL, and hypoglycemia severity was defined as the lowest observed glucose value. A successful session was defined as an observation period of 3 to 4 hours and with glucose levels above 50 mg/dL. Patients who did not attain success could repeat the experiment up to three times.

The 50 patients attempted 134 exercise sessions; 98 of them were successful. Duration of hypoglycemia was significantly shorter during the LGS-on sessions (mean, 138.5 minutes;

SD=68) than the LGS-off sessions (mean, 170.7 minutes; SD=91; p=0.006). Hypoglycemia severity was significantly reduced in the LGS-on group. The mean (SD) lowest glucose level was 59.5 (72) mg/dL in the LGS-on group and 57.6 (5.7) mg/dL in the LGS-off group (p=0.015). Potential limitations of the Garg study included evaluation of the LGS feature in a research setting and short assessment period.

A second RCT evaluated the in-home use of the Paradigm Veo System.[12] The trial by Ly (2013) in Australia was excluded from the 2013 TEC Assessment due to the inclusion of children and adults and lack of analyses stratified by age group (the artificial pancreas system approved in the United States at the time of the review was only intended for individuals ≥16 years). The Ly trial included 95 patients with T1D between 4 and 50 years of age (mean age, 18.6 years; >30% of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA1c level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least four on the modified Clarke questionnaire). Patients were randomized to six months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the LGS feature. The primary study outcome was the combined incidence of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person). As noted, findings were not reported separately for children and adults.

The baseline rate of severe and moderate hypoglycemia was significantly higher in the LGS group (129.6 events per 100 patient-months) than in the pump-only group (20.7 events per 100 patient-months). After six months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the LGS group. The incidence rate ratio was 3.6 (95% CI, 1.7 to 7.5), which was statistically significant favoring the LGS group. Although results were not reported separately for children and adults, the trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be explained in part by two outliers (children ages nine and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the two children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA1c levels (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in HbA1c levels during the treatment period was - 0.06% (95% CI, -0.2% to 0.09%) in the pump-only group and -0.1% (95% CI, -0.3% to 0.03%) in the LGS group; the difference between groups was not statistically significant.

Prospective Studies

Gómez (2017) published the results of a cohort (n = 111) individuals with T1D with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy.[24] Participants used a combination system with the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed CGM device. At a mean follow-up of 47 months (SD=22.7), total daily insulin dose was reduced (mean difference, -0.22 U/kg; 95% CI, -0.18 to -0.26 U/kg; p<0.001). HbA1c levels were reduced from a baseline value of 8.8% (SD=1.9%) to 7.5% (SD=1.0%) at five months (mean difference, -1.3%; 95% CI, -1.09% to -1.50%; p<0.001) and 7.1% (SD=0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; p<0.001). At baseline, 80% of subjects had had at least one episode of

hypoglycemic awareness compared with 10.8% at last follow-up (p<0.001). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% (p<0.001).

Retrospective Studies

Agrawal (2015) retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.[25] This noncontrolled descriptive analysis provided information on the safety of the device when used in a practice setting. The threshold suspend feature was enabled for 100% of the time by 14,673 (70%) patients, 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean (SD) setting used to trigger suspension of insulin was a sensor glucose level of 62.8 (5.8) mg/dL. On days when the threshold suspend feature was enabled, there was a mean of 0.82 suspend events per patient day. Of these, 56% lasted for 0 to 5 minutes, and 10% lasted the full two hours. (Data on the length of the other 34% of events were not reported.) On days when the threshold suspend feature was on, sensor glucose values were 50 mg/dL or less 0.64% of the time compared with 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. Reduction in hypoglycemia was greatest at night. Sensor glucose percentages equivalent to 17 minutes per night occurred when the threshold suspend feature was off vs glucose percentages equivalent to five minutes per night when the threshold suspend feature was on. Data on the use of the device has suggested fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes were not fully discussed in this article.

Section Summary

For individuals who have T1D who receive an artificial pancreas device system with a low glucose suspend feature, the evidence includes three RCTs conducted in patients six years and older. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. All of these RCTs reported primary outcomes were favorable for the group using an artificial pancreas system; however, findings from one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (AUC for nocturnal hypoglycemic events). AUC is not used for assessment in clinical practice, but the current technology does allow user and provider review of similar trend data with a CGM.

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential DKA in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion. Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users.

In addition, one small study reported favorable outcomes for closed-loop systems in pre-term infants, however, this study is limited by very small sample size, lack of blinding, and short study duration.

The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the population with T1D is likely to be clinically significant. Limitations of the published evidence

preclude determining the effects of the technology on overall glycemic control as assessed by HbA1c and other parameters and thus, net health outcomes.

Hybrid Closed-loop Insulin Delivery Systems

Systematic Review

Michou (2023) published a SR and meta-analysis to evaluate the efficacy of automatic insulin delivery (AID) systems in children and adolescents with T1D.[26] A total of 26 RCTs (n = 915) were included in the meta-analysis. AID systems revealed statistically significant differences in the main outcomes, such as the proportion of time in the target glucose range (3.9-10 mmol/L) ($p < 0.00001$), in hypoglycemia (<3.9 mmol/L) ($p = 0.003$) and mean proportion of HbA1C ($p = 0.0007$) compared to control group. The authors conclude that AID systems are superior to insulin pump therapy, sensor-augmented pumps and multiple daily insulin injections. Most of the included studies have a high risk of bias because of allocation, blinding of patients and blinding of assessment. Sensitivity analyses showed that patients < 21 years of age with T1D can use AID systems, after proper education, following their daily activities.

Peacock (2023) published a systematic review of reported trials and real-world studies for commercial hybrid closed-loop (HCL) automated insulin delivery (AID) systems.[27] Fifty-nine studies were included in the SR (19 for 670G; eight for 780G; 11 for Control-IQ; 14 for CamAPS FX; four for Diabeloop; and three for Omnipod-5). Twenty were real-world studies, and 39 were trials or sub-analyses. These studies highlighted that HCL systems improve time in range (TIR) and arouse minimal concerns around severe hypoglycemia. A meta-analysis was not conducted, and statistical tests were not used due to broad inclusion criteria and heterogeneity of the included papers. Many of the participants in the studies included had optimal baseline TIR and HbA1c and may have been of high socioeconomic status. Furthermore, most of the studies were conducted in the USA. Due to the differences in study designs and trial populations between the various AID systems, it was not possible to conclusively determine differences between them. The authors conclude that HCL systems are an effective and safe option for improving diabetes care. Real-world comparisons between systems and their effects on psychological outcomes require further study.

Karageorgiou (2019) published a systematic review and network meta-analysis evaluating the efficacy of closed-loop systems in glycemic control for non-adults with type 1 diabetes mellitus.[28] The meta-analysis included 25 studies (n = 504). The closed-loop system group spent a significantly higher percentage of time in a target glycemic range and the mean glucose was also decreased in the closed-loop system group (MD: 3.01%, 95% CI 1.68 to 4.34%). Overall, the closed-loop system showed better outcomes compared to standard insulin pumps for non-adults.

Prospective Studies

Edd (2023) published a prospective, multicentre, open-label, RCT in people (n = 75) with T1D, with an HbA1c of at least 8.0% (64 mmol/mol), on MDI+isCGM therapy.[29] To reassess the 6-month efficacy and to assess the 12-month sustained efficacy of the MiniMed™ 780G advanced hybrid closed-loop automated insulin delivery (AID) system compared to multiple daily injections plus intermittently scanned glucose monitoring (MDI+isCGM) in people with type 1 diabetes not meeting glucose targets. After a 6-month study phase, participants randomized at baseline to MDI+isCGM switched to AID (SWITCH) while the others continued AID therapy (SUSTAIN) for an additional 6 months. The primary endpoint of this continuation

phase was the within-group change in mean HbA1c between six and 12 months, with superiority in the SWITCH group and noninferiority in the SUSTAIN group (ClinicalTrials.gov: NCT04235504). A total of 39 SWITCH and 36 SUSTAIN participants entered the continuation phase. In the SWITCH group, HbA1c was significantly decreased by -1.4% (95% confidence interval [CI] -1.7% to -1.1%; p < 0.001) from a mean ± SD of 8.9% ± 0.8% (73.9 ± 8.6 mmol/mol) at six months to 7.5% ± 0.6% (58.5 ± 6.9 mmol/mol) at 12 months. Mean HbA1c increased by 0.1% (95% CI -0.05% to +0.25%), from 7.3% ± 0.6% (56.5 ± 6.7 mmol/mol) to 7.4% ± 0.8% (57.7 ± 9.1 mmol/mol) in the SUSTAIN group, meeting noninferiority criteria. Three severe hypoglycemia events occurred in two SWITCH participants during the continuation phase. The authors concluded that ADAPT study phase glycemic improvements were reproduced and sustained in the continuation phase, supporting the early adoption of AID therapy in people with T1D not meeting glucose targets on MDI therapy.

Brown (2021) reported results of the noncomparative pivotal trial of the Omnipod 5 Automated Insulin Delivery System.[30] The study included 241 participants (112 children ages 6 to 13.9 years and 128 adults ages 14 to 70 years). The mean reduction from baseline in HbA1c was 0.71% for children and 0.38% for adults (both p<0.0001 from baseline). Change in time in range compared to baseline (hours/day) was 3.7 for children and 2.2 for adults (both p<0.0001). Reduction from baseline in time in hypoglycemia <70 mg/dL was 2.0% to 1.09% for adults while no change was reported for children. The adverse events reported were three severe hypoglycemia events not attributed to device malfunction and one diabetic ketoacidosis event from an infusion site failure.

Sherr (2022) reported outcomes in children ages 2 to 5.9 using the Omnipod 5 Automated Insulin Delivery System at 10 U.S. sites.[31] Eighty children were evaluated following use of the device for 13 weeks following 14 days of baseline data collection on their usual therapy. From baseline, HbA1c decreased by 0.55% (6.0 mmol/mol) (p< 0.0001), time with sensor glucose levels in target range (70 to 180 mg/dL) increased by 10.9%, or 2.6 h/day (p< 0.0001), and time with levels <70 mg/dL declined by median 0.27% (p=0.0204).

Bergenstal (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.[32] It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least two years, had HbA1c levels less than 10.0%, and who had used an insulin pump for at least six months. There was an initial run-in period at baseline for patients to learn how to use the device followed by a three-month period of device use. The study period included a 6-day hotel stay with a one-day period of frequent sampling of venous blood glucose levels to verify device accuracy. The primary safety end points were the incidence of severe hypoglycemia and diabetic ketoacidosis and the incidence of device-related and serious adverse events.

There were no episodes of severe hypoglycemia or ketoacidosis during the study. A total of 28 device related adverse events occurred, all of which could be resolved at home. There were four serious adverse events, one case each of appendicitis, bacterial arthritis, worsening rheumatoid arthritis, and *Clostridium difficile* diarrhea. There were also a number of predefined descriptive end points (but no statistically powered efficacy end points). The device was in the closed-loop mode for a median of 97% of the study period. Mean (SD) HbA1c levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study.

A multicenter pivotal trial published by Garg (2017) evaluated the safety of Medtronic's hybrid closed-loop system, using methods similar to those of Bergenstal (NCT02463097) and employing the same device (MiniMed 670G).[33] Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14-21 years) and 94 were adults (age range, 22-75 years), all of whom had type 1 diabetes for at least two years before the study, and used insulin pump therapy for six months or more. A three-month study period was preceded by a run-in period for subjects to be more familiar with the equipment, and the sensor glucose values were confirmed by an extended hotel stay (6-day/5-night with daily exercise). In both the adolescent and adult cohorts, the trial found improvements during the study phase over the run-in phase, with an increased percentage of glucose values in the favorable range (for adults, a mean improvement of 68.8% to 73.8%; for adolescents, a mean improvement of 60.4% to 67.2%; p<0.001 for both cohorts). Similarly, the authors reported a decrease in the percentage of values outside of the target range (<70 mg/dL or >180 mg/dL): for adults, time spent below the target range decreased from 6.4% to 3.4% (p<0.001); time above the range decreased from 24.9% to 22.8% (p=0.01). For both cohorts, HbA1c levels showed a significant reduction between baseline and the end of study: for adults, the mean decreased from 7.3% to 6.8% (p<0.001), while for adolescents, the mean decreased from 7.7% to 7.1% (p<0.001). Secondary outcomes, which included a reduction of nocturnal hyperglycemia and hypoglycemia, increase in mean overall body weight, and a reduction of basal insulin, were favorable for the study phase, compared with the run-in phase; measurements from the hotel stay verified the in-home glucose values. However, there were several limitations in the trial, including its nonrandomized design, the exclusion of individuals who had recently experienced diabetic ketoacidosis or severe hypoglycemia, and the interaction between subjects and site personnel. Additionally, most of the adult cohort were already using CGM, and baseline HbA1c levels were lower than average for both cohorts; both baseline characteristics potentially limit the generalizability of the results.

One type of hybrid insulin delivery system employs a predictive algorithm to keep the patient's glucose levels within a specific range or zone, only increasing or decreasing insulin levels if the device detects that glucose levels are going to fall outside the defined zone. Forlenza (2017) published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy; the trial included 20 subjects (19 completed), all with type 1 diabetes and having at least three months treatment with a subcutaneous insulin infusion pump.[34] The six week, in-home study was divided into 2-week blocks, with two randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary end points, which included percentage of time in the target glucose range (70-180 mg/dL) and reduction in hypoglycemia (<70 mg/dL), the algorithm-controlled artificial pancreas system was found to be superior to the sensor-augmented pump therapy (71.6 vs 65.2%, p=0.008; 1.3 vs 2%, p= 0.001, respectively); however, while the mean glucose value was lower in the artificial pancreas system than in the control group, the difference between them was not significant (p=0.059). Measurements of nocturnal hypoglycemia were consistent with day-to-day findings. For the secondary end point (safety of both systems after extended wear), the study found that the mean glucose did not change between the first and seventh day of wear. A limitation of the trial was its use of remote monitoring of subjects; also, the trialists noted that, given the marked difference in outcomes between responders and nonresponders, an error might have occurred in setting basal rates.

Pinsker (2022) published the results of a randomized crossover trial comparing sensor-augmented pump therapy to an adaptive zone model predictive control device in 35 adults with T1D.[35] The adaptive device ran on a Google Pixel 3 smartphone and wirelessly paired with a Dexcom G6 sensor and a Tandem t:AP insulin pump. The primary outcome was sensor glucose time-in-range 70 to 180 mg/dL at 13 weeks. The automated adaptation settings did not significantly improve time-in-range (66% with sensor augmented pump vs 69% with automated insulin delivery; mean adjusted difference 2%; 95% CI -1% to +6%], p =.22). The investigators concluded that additional study and further refinement of the adaptation system are needed.

The RCT by Tauschman (2018) evaluated individuals with uncontrolled type 1 diabetes as reflected in mean Hb1c <8 %.[36] Approximately, 50% of the subjects were between 6-21 years of age and 25% are 6-12 years old. Both groups achieved a reduction in HbA1c but were statistically greater in the HCL group compared to the control group. The investigators reported that the HbA1c improvements were not different among children, adolescents, and adults (data not shown in tables). No severe hypoglycemic events were reported consistent with decrease in time spent with glucose <70mg/dl.

Abraham (2018) reported the results of a six month, multicenter, RCT in children and adolescents with T1D comparing use of an insulin pump with suspend before low or predictive low-glucose management (PLGM) with sensor-augmented insulin pump therapy (SAPT) alone.[37] At six months, significant reductions were seen in day and night hypoglycemia and number of hypoglycemic events <63mg/dl lasting longer than 20 minutes. There were no differences in HbA1c at six months in either group. A follow-up analysis in 140 participants evaluated the effect of percentage time of sensor use on glycemic control in individuals on SAPT with and without PLGM.[38] The mean ± SD age of the cohort was 13.4 ± 2.8 years, duration of diabetes was 7.1 ± 3.7 years and HbA1c was 7.5 ± 0.8%. The sensor use was calculated as a percentage; the number of sensor glucose recordings was compared to the number of expected total recordings, which was then categorized into four groups <40%, 40 to <60%, 60 to <80% and ≥80%. The frequency of sensor use was 7.86% (n = 11) in <40%, 24.29% (n = 34) in 40 to <60%, 36.43% (n = 51) in 60 to <80% and 31.43% (n = 44) in ≥80%. With every 10% increase in sensor use in participants in the SAPT group, mean reduction of HbA1c was −0.14% [−0.25 to −0.04] (p = 0.007) while in the PLGM group, the mean reduction was −0.04% [−0.15 to 0.06] (p = 0.361). These results indicate that improvement in glycemic control is dependent on frequency of sensor use, with higher sensor uptake corresponding to improved glycemic outcomes.

Forlenza (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7 to 13 years of age.[39] The nonrandomized, single arm multicenter study reported the day and night use of the automated insulin delivery and PLGM for three months in the home setting. There were no serious adverse events and use of the system was associated with reduction in HbA1c and increased time in target glucose range.

Wood (2018) reported an in-clinic evaluation of a 7 to 13 year-old cohort of the 670G pivotal trial that was designed to evaluate the performance characteristics of the device when activity induced hypoglycemic patterns were used to set individual device parameters for ongoing use by the study participant.[40] The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of ≤ 55mg/dl.

Messer (2018) reported on a subanalysis of the adolescent and young adult participants in the 670G pivotal trial to better characterize the carbohydrate input and insulin bolus determination features of the device over a three-month period.[41] Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70 to 180 mg/dl).

Section Summary

For individuals who have T1D who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes a multicenter pivotal trial using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device studied and approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the three crossover RCTs two found significantly better outcomes (ie, time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care. The third study had mixed findings (significant difference in time spent in nocturnal hypoglycemia and no significant difference in time spent in preferred glycemic range). Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70 to 180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence suggests that the magnitude of reduction for hypoglycemic events in the population with T1D population is likely to be clinically significant. The variation in the definition of primary and secondary outcomes in the study design and conduct of the published evidence limit the ability to determine the effects of the technology on net health outcomes. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents and adults and are related to the future risk for end organ complications.

Closed-Loop Insulin Delivery System

Systematic Reviews

Oktavian (2023) published a SR evaluating the use of use of a bionic pancreas in patients with type 1 diabetes (T1D). Nine studies were included in this review. The data from these studies suggested that the use of a bionic pancreas could reduce the HbA1c (mean difference [MD] = −0.40% [95% confidence interval [CI] = −0.59 to −0.21], I2 = 0%, $p < 0.0001$) and mean glucose levels (MD = −21.06 [95% CI = −24.66 to −17.46], I2 = 45%, $p < 0.00001$) and improve the time in range (TIR) (MD = 14.41% [95% CI = 10.99 to 17.83], I2 = 60%, $p < 0.00001$). The most common adverse events reported were nausea and vomiting. Limitations included small sample sizes, lack of long-term follow-up, and heterogeneity of study methods. The authors conclude that the use of a bionic pancreas shows potential in preventing complications of T1D by improving the TIR and decreasing the HbA1c and mean glucose levels. Furthermore, serious adverse events with the use of a bionic pancreas and standard of care show insignificant results, suggesting a good safety profile.

Randomized Controlled Trials

Castellanos (2023) evaluated the performance of the iLet bionic pancreas (BP) in non-Hispanic White individuals (here referred to as "Whites") and in Black, Hispanic, and other individuals

(here collectively referred to as "Minorities").[42] This multicenter, RCT evaluated glycemic management with the BP versus standard of care (SC) in 161 adult and 165 pediatric participants with T1D over 13 weeks. In Whites (n = 240), the mean baseline-adjusted difference in 13-week HbA1c between the BP and SC groups was -0.45% (95% CI -0.61 to -0.29 [-4.9 mmol/mol; -6.6 to -3.1]; P < 0.001), while this difference among Minorities (n = 84) was -0.53% (-0.83 to -0.24 [-6.0 mmol/mol; -9.2 to -2.8]; p < 0.001). In Whites, the mean baseline-adjusted difference in time in range between the BP and SC groups was 10% (95% CI 7-12; p < 0.001) and in Minorities was 14% (10-18; p < 0.001). The authors conclude that the BP improves glycemic control in both Whites and Minorities and offers promise in decreasing health care disparities.

Ekhlaspour (2023) published the results of a six-month, multicenter RCT evaluating the benefits of automated insulin delivery (AID) among individuals with T1D in sub-populations of baseline device use determined by continuous glucose monitor (CGM) use status and insulin delivery via multiple daily injections (MDI) or insulin pump.[43] Participants (n = 168) were assigned to closed-loop control (CLC, Control-IQ, Tandem Diabetes Care), or sensor-augmented pump (SAP) therapy. The trial included a two- to eight-week run-in phase to train participants on study devices. The participants were stratified into four subgroups: insulin pump and CGM (pump+CGM), pump-only, MDI and CGM (MDI+CGM), and MDI users without CGM (MDI-only) users. We compared glycemic outcomes among four subgroups. At baseline, 61% were pump+CGM users, 18% pump-only users, 10% MDI+CGM users, and 11% MDI-only users. Mean time in range 70-180 mg/dL (TIR) improved from baseline in the four subgroups using CLC: pump+CGM, 62% to 73%; pump-only, 61% to 70%; MDI+CGM, 54% to 68%; and MDI-only, 61% to 69%. The reduction in time below 70 mg/dL from baseline was comparable among the four subgroups. No interaction effect was detected with baseline device use for TIR (P = .67) or time below (p = 0.77). On the System Usability Questionnaire, scores were high at 26 weeks for all subgroups: pump+CGM: 87.2 ± 12.1, pump-only: 89.4 ± 8.2, MDI+CGM 87.2 ± 9.3, MDI: 78.1 ± 15. The authors conclude that there was a consistent benefit in patients with T1D when using CLC, regardless of baseline insulin delivery modality or CGM use. Suggesting that this CLC system can be considered across a wide range of patients.

Mauras (2023) published the results of a RCT evaluating the bionic pancreas (BP) generated backup insulin dose for injection for pump users (including long-acting insulin dose, a four period basal insulin profile, short acting meal doses and a glucose correction factor) provided in case of device malfunction.[44] Following a 13-week trial in T1D, participants using the BP (6-83 years) completed 2-4 days, in which they were randomly assigned to their prestudy insulin regimen (n = 147) or to follow BP-provided guidance (n = 148). Glycemic outcomes with BP guidance were similar to those reinstituting their prestudy insulin regimen, with both groups having higher mean glucose and lower time-in-range than while using the BP during the 13-week trial. In conclusion, a backup insulin regimen automatically generated by the BP can be safely implemented if need arises to discontinue use of the BP. Clinical Trial Registry: clinicaltrials.gov; NCT04200313.

The iLet Bionic Pancreas System was compared to standard care in a multicenter RCT (NCT04200313) enrolling 219 individuals ages 6 to 79 years with type 1 diabetes.[45] Comparator group participants continued their pre-study subcutaneous insulin delivery (either multiple daily injections, an insulin pump without automation of insulin delivery, an insulin pump with predictive low glucose suspend feature, or an insulin pump as part of an HCL system)

plus real-time CGM. The primary outcome was glycated hemoglobin level at 13 weeks and the key secondary outcome was the percent time A1c was below < 54 mg/dL at 13 weeks.

The main results for the full group (n = 326) were reported by Russell (2022).[45] Mean glycated hemoglobin decreased from 7.9% to 7.3% in the closed-loop insulin delivery system group while it did not change (7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5%; 95% CI −0.6% to −0.3%; p <0.001). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the closed-loop insulin delivery system group and 10.8 events per 100 participant-years in the standard-care group (p = 0.39). No episodes of diabetic ketoacidosis occurred in either group.

The trial results for the subgroups of adults (ages 18 and older) and youth (ages 6 to 17 years) have additionally been reported and were similar to the main results for the full cohort (see Table 6). Kruger (2022) reported results for adults ages 18 and over (n= 161).[46] In this subgroup, mean glycated hemoglobin decreased from 7.6% (± 1.2%) at baseline to 7.1% (± 0.6%) at 13 weeks in the intervention group versus 7.6% (± 1.2%) to 7.5% (± 0.9%) with standard care (adjusted difference -0.5%, 95% confidence interval [CI] -0.6% - -0.3%, p <.001). Time below 54 mg/dL was low at baseline (median 0.2%) and not significantly different between groups over 13 weeks (p = 0.24). The incidence of severe hypoglycemia did not differ between groups. Messer (2022) reported results for children and youth ages 6 to 17 years (n = 165).[47] Mean glycated hemoglobin decreased from 8.1% (± 1.2%) at baseline to 7.5% (± 0.7%) at 13 weeks in the intervention group versus 7.8% (± 1.1%) at both baseline and 13 weeks with standard care (adjusted difference -0.5%; 95% CI -0.7% - -0.2%).

Following the 13-week randomized portion of the trial, comparator group participants (n = 90 of 107) crossed over and received the closed-loop insulin delivery system for 13 weeks.[48] In this extension phase, improvement in glycemic control was of a similar magnitude to that observed during the randomized trial. Results were similar in the adult (n = 42) and pediatric (n = 48) cohort

Section Summary: Closed-Loop Insulin Delivery System

The evidence includes a SR (nine studies), including a 13-week multicenter RCT of the iLet Bionic Pancreas System compared to usual care in 219 individuals ages 6 to 79 years with type 1 diabetes. Comparator group participants continued their pre-study subcutaneous insulin delivery (either multiple daily injections, an insulin pump without automation of insulin delivery, an insulin pump with predictive low glucose suspend feature, or an insulin pump as part of an HCL system) plus real-time CGM. The glycated hemoglobin level decreased from 7.9% to 7.3% in the closed-loop insulin delivery system group and did not change (7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5%; 95%CI −0.6 to −0.3; p <0.001). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the closed-loop insulin delivery system group and 10.8 events per 100 participant-years in the standard-care group (p = 0.39). No episodes of diabetic ketoacidosis occurred in either group. The trial's results for the subgroups of adults (ages 18 and older) and youth (ages 6 to 17 years) have additionally been reported and were similar to the main results for the full cohort. The evidence supports the bionic pancreas may improve health outcomes by preventing complications of T1D by improving the TIR and decreasing the HbA1c and mean glucose levels. Furthermore, serious adverse events with the use of a bionic pancreas and standard of care show insignificant results, suggesting a good safety profile.

PRACTICE GUIDELINE SUMMARY

AMERICAN DIABETES ASSOCIATION

The 2023 American Diabetes Association Standards of Medical Care in Diabetes provides the following recommendations on controlling diabetes:[49]

> Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or automated insulin delivery systems should be offered for diabetes management to youth and adults on multiple daily injections with type 1 diabetes (Level of Evidence A) or other types of insulin-deficient diabetes (Level of Evidence E) who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an automated insulin delivery system. The choice of device should be made based on the individual's circumstances, preferences, and needs. (Level of Evidence A)
>
> Individuals with diabetes may be using systems not approved by the U.S. Food and Drug Administration, such as do-it yourself closed-loop systems and others; health care professionals cannot prescribe these systems but should assist in diabetes management to ensure the safety of people with diabetes. (Level of Evidence E)

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY

The American Association of Clinical Endocrinologists published a 2022 update of their Clinical Practice Guideline: Developing a Diabetes Mellitus (DM)Comprehensive Care Plan.[50] The guideline includes the following recommendations:

> Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM. (Grade B, Best Evidence Level 1)
>
> Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. (Grade A, Best Evidence Level 1)

The American Association of Clinical Endocrinologists and American College of Endocrinology (2018) published a joint position statement on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes.**[51]** The statement emphasized the use of continuous glucose monitoring and insulin pump therapy for T1D patients who are not in glycemic target ranges despite intensive attempts at self-blood glucose monitoring and multiple insulin injection therapy.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

In 2021, the American Association of Clinical Endocrinologists published a clinical practice guideline for the use of advanced technology in the management of individuals with diabetes.[52] The guideline included the following statements:

"Low-glucose suspend (LGS) is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia, whereas predictive low glucose suspend (PLGS) is strongly recommended for all persons with T1D to mitigate hypoglycemia. Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia awareness, and those who fear hypoglycemia leading to permissive hyperglycemia should be considered for this method of insulin delivery. "Grade A; High Strength of Evidence

"Automated insulin delivery (AID) systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and the reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia, significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered." Grade A; High Strength of Evidence

SUMMARY

There is enough research to show that the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) improves health outcomes for select patients with diabetes mellitus or preconception/pregnancy related suboptimal glycemic control. Clinical practice guidelines based on research recommend these devices in certain populations and clinical scenarios. Therefore, the use of an external insulin infusion pump or an FDA-approved automated insulin delivery system (artificial pancreas device) may be considered medically necessary when policy criteria are met.

There is not enough research to show that an insulin pump or FDA-approved automated insulin delivery system (artificial pancreas device) improve health outcomes in all other situations. No clinical practice guidelines based on research recommend these devices for patients not addressed in the policy criteria. Therefore, the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) is investigational when the policy criteria are not met.

All or part of an insulin pump or automated insulin delivery system (artificial pancreas device) may warrant replacement or upgrade when the current device is no longer able to perform its basic function and cannot be repaired or adapted adequately to meet the patient's medical needs. Therefore, a replacement or upgrade may be considered medically necessary when policy criteria are met. A replacement or upgrade is considered not medically necessary when the device is adequately functioning and can meet the patient's medical needs.

REFERENCES

1. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific

statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation.* 2009;119(2):351-7. PMID: 19095622
2. FDA website. MiniMed® 530G System by Medtronic©. [cited 11/02/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf12/p120010b.pdf.
3. FDA website. MiniMed® 630G System by Medtronic©. [cited 11/02/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf15/p150001a.pdf.
4. FDA website. MiniMed® 670G System by Medtronic©. [cited 11/02/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017b.pdf.
5. FDA website. MiniMed® 770G System by Medtronic©. [cited 11/02/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S076B.pdf.
6. FDA website. t:slim X2 Insulin Pump with Basal-IQ Technology. [cited 11/02/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180008A.pdf.
7. FDA website. FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system. [cited 11/02/2023]. 'Available from:' https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-interoperable-automated-insulin-dosing-controller-designed-allow-more-choices.
8. FDA Website. Insulet SmartAdjust™ technology 510k. [cited 11/02/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/reviews/K220394.pdf.
9. FDA Website. Omnipod 5 ACE Pump (Pod) 510k approval. [cited 11/02/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf20/K203774.pdf.
10. FDA Website. iLet ACE Pump (K223846). [cited 11/02/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf22/K223846.pdf.
11. Beta Bonics: iLET user manual. . [cited 11/02/2023]. 'Available from:' https://www.betabionics.com/wp-content/uploads/LA000081_A-iLet-User-Guide.pdf.
12. Ly TT, Nicholas JA, Retterath A, et al. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA.* 2013;310(12):1240-7. PMID: 24065010
13. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes care.* 2006;29(1):44-50. PMID: 16373894
14. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med.* 2013;368(9):824-33. PMID: 23445093
15. Hirsch IB. Reducing hypoglycemia in type 1 diabetes: an incremental step forward. *Diabetes Technol Ther.* 2013;15(7):531-2. PMID: 23789651
16. Bergenstal RM, Welsh JB, Shin JJ. Threshold insulin-pump interruption to reduce hypoglycemia. *N Engl J Med.* 2013;369(15):1474. PMID: 24106952
17. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med.* 2013;369(3):224-32. PMID: 23789889
18. Alotaibi A, Al Khalifah R, McAssey K. The efficacy and safety of insulin pump therapy with predictive low glucose suspend feature in decreasing hypoglycemia in children with type 1 diabetes mellitus: A systematic review and meta-analysis. *Pediatric diabetes.* 2020. PMID: 32738022
19. Collyns OJ, Meier RA, Betts ZL, et al. Improved Glycemic Outcomes With Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results From a Randomized Crossover Trial Comparing Automated Insulin Delivery With Predictive Low Glucose Suspend in People With Type 1 Diabetes. *Diabetes care.* 2021;44(4):969-75. PMID: 33579715

20. Breton MD, Kanapka LG, Beck RW, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. *N Engl J Med.* 2020;383(9):836-45. PMID: 32846062
21. Kanapka LG, Wadwa RP, Breton MD, et al. Extended Use of the Control-IQ Closed-Loop Control System in Children With Type 1 Diabetes. *Diabetes care.* 2021;44(2):473-78. PMID: 33355258
22. Cobry EC, Kanapka LG, Cengiz E, et al. Health-Related Quality of Life and Treatment Satisfaction in Parents and Children with Type 1 Diabetes Using Closed-Loop Control. *Diabetes Technol Ther.* 2021;23(6):401-09. PMID: 33404325
23. Garg S, Brazg RL, Bailey TS, et al. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. *Diabetes Technol Ther.* 2012;14(3):205-9. PMID: 22316089
24. Gomez AM, Marin Carrillo LF, Munoz Velandia OM, et al. Long-Term Efficacy and Safety of Sensor Augmented Insulin Pump Therapy with Low-Glucose Suspend Feature in Patients with Type 1 Diabetes. *Diabetes Technol Ther.* 2017;19(2):109-14. PMID: 28001445
25. Agrawal P, Zhong A, Welsh JB, et al. Retrospective analysis of the real-world use of the threshold suspend feature of sensor-augmented insulin pumps. *Diabetes Technol Ther.* 2015;17(5):316-9. PMID: 25611577
26. Michou P, Gkiourtzis N, Christoforidis A, et al. The efficacy of automated insulin delivery systems in children and adolescents with type 1 diabetes Mellitus: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* 2023;199:110678. PMID: 37094750
27. Peacock S, Frizelle I, Hussain S. A Systematic Review of Commercial Hybrid Closed-Loop Automated Insulin Delivery Systems. *Diabetes Ther.* 2023;14(5):839-55. PMID: 37017916
28. Karageorgiou V, Papaioannou TG, Bellos I, et al. Effectiveness of artificial pancreas in the non-adult population: A systematic review and network meta-analysis. *Metabolism: clinical and experimental.* 2019;90:20-30. PMID: 30321535
29. Edd SN, Castañeda J, Choudhary P, et al. Twelve-month results of the ADAPT randomized controlled trial: Reproducibility and sustainability of advanced hybrid closed-loop therapy outcomes versus conventional therapy in adults with type 1 diabetes. *Diabetes Obes Metab.* 2023;25(11):3212-22. PMID: 37551542
30. Brown SA, Forlenza GP, Bode BW, et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes. *Diabetes care.* 2021;44(7):1630-40. PMID: 34099518
31. Sherr JL, Bode BW, Forlenza GP, et al. Safety and Glycemic Outcomes With a Tubeless Automated Insulin Delivery System in Very Young Children With Type 1 Diabetes: A Single-Arm Multicenter Clinical Trial. *Diabetes care.* 2022;45(8):1907-10. PMID: 35678724
32. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. *JAMA.* 2016;316:1407-08. PMID: 27629148
33. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. *Diabetes Technol Ther.* 2017;19(3):155-63. PMID: 28134564
34. Forlenza GP, Deshpande S, Ly TT, et al. Application of Zone Model Predictive Control Artificial Pancreas During Extended Use of Infusion Set and Sensor: A Randomized

Crossover-Controlled Home-Use Trial. *Diabetes care.* 2017;40:1096-102. PMID: 28584075
35. Pinsker JE, Dassau E, Deshpande S, et al. Outpatient Randomized Crossover Comparison of Zone Model Predictive Control Automated Insulin Delivery with Weekly Data Driven Adaptation Versus Sensor-Augmented Pump: Results from the International Diabetes Closed-Loop Trial 4. *Diabetes Technol Ther.* 2022;24(9):635-42. PMID: 35549708
36. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet.* 2018;392(10155):1321-29. PMID: 30292578
37. Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-term Randomized Controlled Trial in Adolescents With Type 1 Diabetes. *Diabetes care.* 2018;41:303-10. PMID: 29191844
38. Abraham MB, Smith GJ, Nicholas JA, et al. Effect of frequency of sensor use on glycaemic control in individuals on sensor-augmented pump therapy with and without Predictive Low Glucose Management System. *Diabetes Res Clin Pract.* 2020;159:107989. PMID: 31866529
39. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety Evaluation of the MiniMed 670G System in Children 7-13 Years of Age with Type 1 Diabetes. *Diabetes Technol Ther.* 2019;21(1):11-19. PMID: 30585770
40. Wood MA, Shulman DI, Forlenza GP, et al. In-Clinic Evaluation of the MiniMed 670G System "Suspend Before Low" Feature in Children with Type 1 Diabetes. *Diabetes Technol Ther.* 2018;20(11):731-37. PMID: 30299976
41. Messer LH, Forlenza GP, Sherr JL, et al. Optimizing Hybrid Closed-Loop Therapy in Adolescents and Emerging Adults Using the MiniMed 670G System. *Diabetes care.* 2018;41:789-96. PMID: 29444895
42. Castellanos LE, Russell SJ, Damiano ER, et al. The Insulin-Only Bionic Pancreas Improves Glycemic Control in Non-Hispanic White and Minority Adults and Children With Type 1 Diabetes. *Diabetes care.* 2023;46(6):1185-90. PMID: 37000680
43. Ekhlaspour L, Raghinaru D, Forlenza GP, et al. Outcomes in Pump- and CGM-Baseline Use Subgroups in the International Diabetes Closed-Loop Trial. *J Diabetes Sci Technol.* 2023;17(4):935-42. PMID: 35473359
44. Mauras N, Damiano ER, El-Khatib FH, et al. Utility and Safety of Backup Insulin Regimens Generated by the Bionic Pancreas: A Randomized Study. *Diabetes Technol Ther.* 2023;25(6):437-41. PMID: 36877259
45. Russell SJ, Beck RW, Damiano ER, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *N Engl J Med.* 2022;387(13):1161-72. PMID: 36170500
46. Kruger D, Kass A, Lonier J, et al. A Multicenter Randomized Trial Evaluating the Insulin-Only Configuration of the Bionic Pancreas in Adults with Type 1 Diabetes. *Diabetes Technol Ther.* 2022;24(10):697-711. PMID: 36173236
47. Messer LH, Buckingham BA, Cogen F, et al. Positive Impact of the Bionic Pancreas on Diabetes Control in Youth 6-17 Years Old with Type 1 Diabetes: A Multicenter Randomized Trial. *Diabetes Technol Ther.* 2022;24(10):712-25. PMID: 36173237
48. Lynch J, Kanapka LG, Russell SJ, et al. The Insulin-Only Bionic Pancreas Pivotal Trial Extension Study: A Multi-Center Single-Arm Evaluation of the Insulin-Only Configuration of the Bionic Pancreas in Adults and Youth with Type 1 Diabetes. *Diabetes Technol Ther.* 2022;24(10):726-36. PMID: 36173238

49. ElSayed NA, Aleppo G, Aroda VR, et al. 7. Diabetes Technology: Standards of Care in Diabetes-2023. *Diabetes care.* 2023;46(Suppl 1):S111-s27. PMID: 36507635
50. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. *Endocr Pract.* 2022;28(10):923-1049. PMID: 35963508
51. Grunberger G, Handelsman Y, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology 2018 Position Statement on Integration of Insulin Pumps and Continuous Glucose Monitoring in Patients with Diabetes Mellitus. *Endocr Pract.* 2018;24(3):302-08. PMID: 29547046
52. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. *Endocr Pract.* 2021;27(6):505-37. PMID: 34116789

CODES

Codes	Number	Description
CPT	None	
HCPCS	A4226	Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week
	A9999	Miscellaneous DME supply or accessory, not otherwise specified
	E0784	External ambulatory infusion pump, insulin
	E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
	E1399	Durable medical equipment, miscellaneous
	S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
	S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
	S1036	Transmitter; external, for use with artificial pancreas device system
	S1037	Receiver (monitor); external, for use with artificial pancreas device system

Date of Origin: *September 2000*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 80

Myoelectric Prosthetic and Orthotic Components for the Upper Limb

Effective: August 1, 2023

Next Review: June 2024
Last Review: June 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Myoelectric prostheses and orthotics are powered by electric motors with an external power source. The joint movement of upper limb prostheses or orthoses (e.g., hand, wrist, and/or elbow) is driven by microchip-processed electrical activity in the muscles of the remaining limb or limb stump.

MEDICAL POLICY CRITERIA

I. Myoelectric upper limb prostheses may be **medically necessary** when all of the following criteria are met (A. – F.):

A. The patient has an amputation or missing limb at the wrist or above (forearm, elbow, etc.); and

B. Standard body-powered prosthetic devices cannot be used or are insufficient to meet the functional needs of the individual in performing activities of daily living; and

C. The remaining musculature of the arm(s) contains the minimum microvolt threshold to allow operation of a myoelectric prosthetic device, as demonstrated by functional testing using a physical or computer model prosthesis; and

D. The patient has demonstrated sufficient neurological and cognitive function to operate the prosthesis effectively; and

E. The patient is free of comorbidities that could interfere with function of the prosthesis (neuromuscular disease, etc.); and

F. Functional evaluation by a qualified professional (e.g., prosthetist) indicates that with training, use of a myoelectric prosthesis and associated components is necessary to meet the functional needs of the individual (e.g., automatic grasp features, microprocessor control features, or other components to aid gripping, releasing, holding, and coordinating movement of the prosthesis) when performing activities of daily living. This evaluation should consider the patient's needs for control, durability (maintenance), function (speed, work capability), and usability. Both of the following criteria must be met (1. and 2.):

1. The device is necessary for the patient to perform instrumental activities of daily living including job functioning; and

2. The device is *not* primarily for the purpose of allowing the patient to perform leisure or recreational activities.

II. The replacement of all or part of an existing myoelectric upper limb prosthesis is considered **medically necessary** when the existing myoelectric upper limb prosthesis is malfunctioning, cannot be repaired, and is no longer under warranty OR when the current prosthetic can no longer meet the patient's medical needs due to a significant change in the patient's physiological condition.

III. Replacement of all or part of an existing myoelectric upper limb prosthesis is considered **not medically necessary** when Criterion II. is not met.

IV. Myoelectric upper limb prosthetic components are considered **not medically necessary** under all other conditions.

V. Upper-limb prosthetic components with both sensor and myoelectric control are considered **investigational**.

VI. Myoelectric controlled upper-limb orthoses are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of amputation or missing limb at the wrist or above
- Documentation that standard body-powered devices can't be used or are not efficient including the ADLs that cannot be accomplished currently
- Documentation that the remaining musculature in the limb contains the minimum microvolt threshold to allow operation of the device including a functional test using a physical or computer model prosthesis

- Documentation the patient is cognitively and neurologically able to operate the prosthetic
- Documentation the patient doesn't have any comorbidities that might interfere with the use of the prosthetic
- An evaluation by a qualified professional such as a prosthetist that show the patient will be able to use the prosthetic for ADLs including the patient's ability to control, maintain, function, and use the prosthetic including why it is necessary for the patient to perform ADLs or job functions and evidence it is not being requested only for leisure or recreational activities
- Documentation that the prosthetic is not being requested to replace a functioning prosthetic

CROSS REFERENCES

1. Definitive Lower Limb Prostheses, Durable Medical Equipment, Policy No. 18
2. Powered Knee Prosthesis, or Powered Ankle-Foot Prosthesis, and Microprocessor-Controlled Ankle-Foot Prosthesis, Durable Medical Equipment, Policy No. 81
3. Powered Exoskeleton for Ambulation, Durable Medical Equipment, Policy No. 89

BACKGROUND

Upper limb prostheses are used following amputation at any level from the hand to the shoulder. The need for a prosthesis can occur for a number of reasons, including trauma, surgery, or congenital anomalies. The primary goals of the upper limb prosthesis are to restore natural appearance and function. Achieving these goals also requires sufficient comfort and ease of use for continued acceptance by the wearer. The difficulty of achieving these diverse goals with an upper limb prosthesis increases as the level of amputation (digits, hand, wrist, elbow, and shoulder), and thus the complexity of joint movement, increases.

Upper limb prostheses are classified based on the means of generating movement at the joints as follows:

PASSIVE PROSTHESIS:

- The lightest weight upper extremity prosthesis
- Patients generally describe this as the most comfortable of the three types
- Must be repositioned manually, typically by moving it with the opposite arm
- Cannot restore function.

BODY-POWERED PROSTHESIS

- Uses a body harness and cable system to provide functional manipulation of the elbow and hand. Voluntary movement of the shoulder and/or limb stump extends the cable and transmits the force to the terminal device.
- Prosthetic hand attachments, which may be claw-like devices that allow good grip strength and visual control of objects or latex-gloved devices that provide a more natural appearance at the expense of control, can be opened and closed by the cable system.
- Patient complaints with body-powered prostheses include harness discomfort, particularly the wear temperature, wire failure, and the unattractive appearance.

MYOELECTRIC PROSTHESIS

Uses muscle activity from the remaining limb for the control of joint movement.

- Electromyographic (EMG) signals from the limb stump are detected by surface electrodes, amplified, and then processed by a controller to drive battery-powered motors that move the hand, wrist, or elbow.
- Implantable EMG sensors with wireless signal transmission (e.g., Implantable Myoelectric Sensors [IMES®]) are being studied as alternatives to surface electrodes to improve prosthetic hand function. These implantable sensors may eliminate the limitations inherent in surface electrodes such as issues related to poor skin contact (e.g., skin sweating) and the ability to detect signals only from superficial muscles.
- Although upper arm movement may be slow and limited to one joint at a time, myoelectric control of movement may be considered the most physiologically natural.
- Myoelectric hand attachments are similar in form to those offered with the body-powered prosthesis, but are battery powered.
- Patient dissatisfaction with myoelectric prostheses includes the increased cost, maintenance (particularly for the glove), and weight.
- Examples of available technologies:
    - The SensorHand™ by Advanced Arm Dynamics, which is described as having an AutoGrasp feature, an opening/closing speed of up to 300 mm/second, and advanced EMG signal processing.
    - The Utah Arm 3 by Motion Control has a microprocessor interface that allows individualized adjustments to achieve maximum performance.
    - The i-LIMB™ hand (Touch Bionics), sometimes referred to as the bionic hand, is the first commercially available myoelectric hand prosthesis with individually powered digits.
    - ProDigits™, also from Touch Bionics, are prosthetic digits for one or more fingers in patients with amputation at a transmetacarpal level or higher.
    - Otto Bock has a number of myoelectric hand and elbow prostheses including the AutoGrasp feature, the Michelangelo® Hand, and the Electrohand 2000 designed for children.
    - LTI Boston Digital Arm™ System by Liberating Technologies Inc. is marketed as having greater torque than any other powered prosthetic elbows
    - These devices may be covered by LIVINGSKIN™, a high-definition silicone prosthesis created to resemble a patient's natural skin.

SENSOR AND MYOELECTRIC PROSTHESIS

The LUKE Arm (previously known as the DEKA Arm System) can perform complex tasks with multiple simultaneous powered movements (e.g., movement of the elbow, wrist, and hand at the same time). In addition to the EMG electrodes, the LUKE Arm contains a combination of mechanisms including switches, movement sensors, and force sensors. The Luke Arm is the same shape and weight as an adult arm.

HYBRID SYSTEM, A COMBINATION OF BODY-POWERED AND MYOELECTRIC COMPONENTS

- May be used for high-level amputations (at or above the elbow).
- Allows control of two joints at once (i.e., one body-powered and one myoelectric)
- Generally lighter weight and less expensive than a prosthesis composed entirely of myoelectric components.

- An example of a hybrid system is the ErgoArm by Otto Bock which has a myoelectric hand and a cable-controlled elbow joint

Technology in this area is rapidly changing, driven by advances in biomedical engineering and by the U.S. Department of Defense Advanced Research Projects Agency (DARPA), which is funding a public and private collaborative effort on prosthetic research and development. Areas of development include the use of skin-like silicone elastomer gloves, “artificial muscles,” and sensory feedback. Smaller motors, microcontrollers, implantable myoelectric sensors, and re-innervation of remaining muscle fibers are being developed to allow fine movement control. Lighter batteries and newer materials are being incorporated into myoelectric prostheses to improve comfort.

MYOELECTRIC ORTHOSES

The MyoPro (Myomo) is a myoelectric powered upper-extremity orthotic. This orthotic device weighs about 1.8 kilograms (4 pounds), has manual wrist articulation, and myoelectric initiated bi-directional elbow movement. The MyoPro detects weak muscle activity from the affected muscle groups. A therapist or prosthetist/orthoptist can adjust the gain (amount of assistance), signal boost, thresholds, and range of motion. Potential users include patients with traumatic brain injury, spinal cord injury, brachial plexus injury, amyotrophic lateral sclerosis, and multiple sclerosis. Use of robotic devices for therapy has been reported. The MyoPro is the first myoelectric orthotic available for home use.

Regulatory Status

Prostheses are class I devices that are exempt from U.S. Food and Drug Administration (FDA) marketing clearance, but manufacturers must register prostheses with the restorative devices branch of the FDA and keep a record of any complaints.

Examples of available myoelectric devices are listed above.

The MyoPro® (Myomo) is registered with the FDA as a class 1 limb orthosis.

EVIDENCE SUMMARY

In evaluating the effects of the increased sophistication of myoelectric upper limb prostheses compared with body-powered prostheses, passive prostheses, or no prosthesis, the most informative data are from prospective comparative studies with objective and subjective measures that directly address function and health-related quality of life.

In light of the magnitude of functional loss in upper extremity amputation, evaluation of the evidence is based on two assumptions:

1. Use of any prosthesis confers clinical benefit, and

2. Self-selected use is an acceptable measure of the perceived benefit (combination of utility, comfort, and appearance) of a prosthesis for that individual.

It should be considered that the upper limb amputee’s needs may depend on their situation. For example, increased functional capability may be needed with heavy work or domestic duties, while a more natural appearing prosthesis with reduced functional capability may be acceptable for an office, school, or another social environment.

MYOELECTRIC UPPER LIMB PROSTHESIS

Systematic Reviews

A 2015 systematic review (SR) by Carey evaluated differences between myoelectric and body-powered prostheses. The SR included 31 studies.[1] The evidence was conflicting for functional performance between the two prostheses. The authors concluded that there is insufficient evidence to show that one system provides a significant advantage over the other and that prosthetic selection should be based on patient preference and functional needs.

A 2007 SR by Biddis of 40 articles published over the previous 25 years assessed upper limb prosthesis acceptance and abandonment.[2] For pediatric patients the mean rejection rate was 38% for passive prostheses (one study), 45% for body-powered prostheses (three studies), and 32% for myoelectric prostheses (12 studies). For adults there was considerable variation between studies, with mean rejection rates of 39% (six studies), 26% (eight studies), and 23% (10 studies) for passive, body-powered and myoelectric prostheses, respectively. The authors found no evidence that the acceptability of passive prostheses had declined over the period from 1983 to 2004, “despite the advent of myoelectric devices with functional as well as cosmetic appeal.” Body-powered prostheses were also found to have remained a popular choice, with the type of hand-attachment being the major factor in acceptance. Body-powered hooks were considered acceptable by many users, but body-powered hands were frequently rejected (80% to 87% rejection rates) due to slowness in movement, awkward use, maintenance issues, excessive weight, insufficient grip strength, and the energy needed to operate. Rejection rates of myoelectric prostheses tended to increase with longer follow-up. There was no evidence of a change in rejection rates over the 25 years of study, but the results are limited by sampling bias from isolated populations and the generally poor quality of the studies included.

Randomized Controlled Trials

Touillett (2023) published the results of a monocentric, randomized, controlled, cross-over trial evaluating shoulder abduction and manual dexterity in transradial amputees (N = 8) fitted with two prosthetic myoelectric hooks, the Greifer and the Axon-Hook.[3] They also made comparisons with the non-affected (NA) side. Shoulder abduction was significantly higher with the Greifer (60.9 ± 20.3, $p = 0.03$) than with the Axon-Hook (39.8 ± 16.9) and also than with the NA side (37.6 ± 19.4, $p = 0.02$). Shoulder abduction on the NA side (37.6 ± 19.4) was close to that of the Axon-Hook (39.8 ± 16.9). There was no difference between devices or with the NA side in the percentage of time spent with shoulder abduction > 60 during the Box Block Test (BBT). A significant strong negative correlation was found between shoulder abduction and wrist position with the Axon-Hook ($r = -0.86$; $p < 0.01$), but not with the Greifer. Manual dexterity and satisfaction did not differ significantly between the two devices.

In comparative studies of prostheses, subjects served as their own control. Since these studies included use by all subjects of both a myoelectric and a body-powered prosthesis, randomization was directed at the order in which each amputee used the prostheses. Two trials were found in which a total of 196 children used both a myoelectric and a body-powered hand prosthesis, in randomized order, for a period of three months each.[4, 5] No clinically relevant objective or subjective difference was found between the two types of prostheses.

Nonrandomized Studies

A number of small (n<50) non-randomized case series[6-8] and online, telephone, or mailed surveys[9-13] were found, but few studies directly addressed whether myoelectric prostheses improved function and health-related quality of life. Most of the studies identified described amputees' self-selected use or rejection rates. The results were usually presented as hours worn at work or school, hours worn at home, and hours worn in social situations. Amputees' self-reported reasons for use and abandonment were also frequently reported. The limited evidence available suggests that, in comparison with body-powered prostheses, myoelectric components may improve range of motion to some extent, have similar capability for light work, but may have reduced performance under heavy working conditions. The literature also indicated that the percentage of amputees who accepted use of a myoelectric prosthesis was about the same as those who prefer to use a body-powered prosthesis, and that self-selected use depended at least in part on the individual's activities of daily living. Appearance was most frequently cited as an advantage of myoelectric prostheses. Nonuse of any prosthesis was associated with lack of functional need, discomfort (excessive weight and heat), and impediment to sensory feedback.

Section Summary: Myoelectric Upper-Limb Prosthesis

The identified literature focuses primarily on patient acceptance and rejection; data are limited or lacking in the areas of function and functional status. The limited evidence suggests that the percentage of amputees who accept a myoelectric prosthesis is approximately the same as those who prefer to use a body-powered prosthesis, and that self-selected use depends partly on the individual's activities of daily living. When compared with body-powered prostheses, myoelectric components possess similar capability to perform light work, and myoelectric components may improve range of motion. The literature has also indicated that appearance is most frequently cited as an advantage of myoelectric prostheses, and for patients who desire a restorative appearance, the myoelectric prosthesis can provide greater function than a passive prosthesis with equivalent function to a body-powered prosthesis for light work.

SENSOR AND MYOELECTRIC UPPER LIMB COMPONENTS

Investigators from three Veterans Administration medical centers and the Center for the Intrepid at Brooke Army Medical Center published a series of reports on home use of the LUKE prototype (DEKA Gen 2 and DEKA Gen 3) in 2017 and 2018.[14-18] Participants were included in the in-laboratory training if they met criteria and had sufficient control options (e.g., myoelectric and/or active control over one or both feet) to operate the device. In-lab training included a virtual reality training component. At the completion of the in-lab training, the investigators determined, using a priori criteria, which participants were eligible to continue to the 12-week home trial. The criteria included the independent use of the prosthesis in the laboratory and community setting, fair, functional performance, and sound judgment when operating or troubleshooting minor technical issues.

One of the publications (Resnick, 2017) reported on the acceptance of the LUKE prototype before and after a 12-week trial of home use.[16] Of 42 participants enrolled at the time, 32 (76%) participants completed the in-laboratory training, 22 (52%) wanted to receive a LUKE Arm and proceeded to the home trial, 18 (43%) completed the home trial, and 14 (33%) expressed a desire to receive the prototype at the end of the home trial. Over 80% of those who completed the home trial preferred the prototype arm for hand and wrist function, but as many preferred the weight and look of their own prosthesis. One-third of those who completed the home training thought that the arm was not ready for commercialization. Participants who

completed the trial were more likely to be prosthesis users at study onset (p=0.03), and less likely to have musculoskeletal problems (p=0.047).[14] Reasons for attrition during the in-laboratory training were reported in a separate publication by Resnik and Klinger (2017).[17] Attrition was related to the prosthesis entirely or in part by 67% of the participants, leading to a recommendation to provide patients with an opportunity to train with the prosthesis before a final decision about the appropriateness of the device.

Functional outcomes of the Gen 2 and Gen 3 arms, as compared with participants' prostheses, were reported by Resnick et al (2018).[15] At the time of the report, 23 regular prosthesis users had completed the in-lab training, and 15 had gone on to complete the home use portion of the study. Outcomes were both performance-based and self-reported measures. At the end of the lab training, dexterity was similar, but performance was slower with the LUKE prototype than with their conventional prosthesis. At the end of the home study, activity speed was similar to the conventional prostheses, and one of the performance measures (Activities Measure for Upper-Limb Amputees) was improved. Participants also reported that they were able to perform more activities, had less perceived disability, and less difficulty in activities, but there were no differences between the two prostheses on many of the outcome measures including dexterity, prosthetic skill, spontaneity, pain, community integration, or quality of life. Post hoc power analysis suggested that evaluation of some outcomes might not have been sufficiently powered to detect a difference.

In a separate publication, Resnick (2017) reported that participants continued to use their prosthesis (average, 2.7 h/d) in addition to the LUKE prototype, concluding that availability of both prostheses would have the greatest utility.[18] This conclusion is similar to those from earlier prosthesis surveys, which found that the selection of a specific prosthesis type (myoelectric, powered, or passive) could differ depending on the specific activity during the day. In the DEKA Gen 2 and Gen 3 study reported here, 29% of participants had a body-powered device, and 71% had a conventional myoelectric prosthesis.

Section Summary: Sensor and Myoelectric Upper-Limb Components

The LUKE Arm was cleared for marketing in 2014 and is now commercially available. The prototypes for the LUKE Arm, the DEKA Gen 2 and Gen 3, were evaluated by the U.S. military and Veteran's Administration in a 12-week home study, with study results reported in a series of publications. Acceptance of the advanced prosthesis in this trial was mixed, with one-third of enrolled participants desiring to receive the prototype at the end of the trial. Demonstration of improvement in function has also been mixed. After several months of home use, activity speed was shown to be similar to the conventional prosthesis. There was an improvement in the performance of some, but not all, activities. Participants continued to use their prosthesis for part of the day, and some commented that the prosthesis was not ready for commercialization. There were no differences between the LUKE Arm prototype and the participants' prostheses for many outcome measures. Study of the current generation of the LUKE Arm is needed to determine whether the newer models of this advanced prosthesis lead to consistent improvements in function and quality of life.

MYOELECTRIC ORTHOTIC

Page (2020) compared the efficacy of a myoelectric orthosis combined with repetitive task-specific practice to repetitive task-specific practice alone in improving performance for subjects with post-stroke upper extremity hemiparesis.[19] A total of 34 patients with chronic, moderate, stable, post-stroke, upper extremity hemiparesis were randomly assigned to Myomo +

repetitive, task-specific practice; repetitive, task-specific practice only; or Myomo only. The primary outcome was the upper extremity section of the Fugl-Meyer Impairment Scale and the secondary outcome was the Arm Motor Activity Test. The groups all increased on the Fugl-Meyer Impairment Scale and the Arm Motor Activity Test, with no significant differences between groups.

Peters (2017) evaluated the immediate effect (no training) of a myoelectric elbow-wrist-hand orthosis on paretic upper-extremity impairment.[20] Participants (n=18) were stable and moderately impaired with a single stroke 12 months or later before study enrollment. They were tested using a battery of measures without, and then with the device; the order of testing was not counterbalanced. The primary measure was the upper-extremity section of the Fugl-Meyer Assessment, a validated scale that determines active movement. Upper-extremity movement on the Fugl-Meyer Assessment was significantly improved while wearing the orthotic (a clinically significant increase of 8.71 points, $p<0.001$). The most commonly observed gains were in elbow extension, finger extension, grasping a tennis ball, and grasping a pencil. The Box and Block test (moving blocks from one side of a box to another) also improved ($p<0.001$). Clinically significant improvements were observed for raising a spoon and cup, and there were significant decreases in the time taken to grasp a cup and gross manual dexterity. Performance on these tests changed from unable to able to complete. The functional outcome measures (raising a spoon and cup, turning on a light switch, and picking up a laundry basket with two hands) were developed by the investigators to assess these moderately impaired participants. The authors noted that performance on these tasks was inconsistent, and proposed a future study that would include training with the myoelectric orthosis before testing.

Page (2013) compared the efficacy of a myoelectric orthosis combined with repetitive task-specific practice to repetitive task-specific practice alone in improving performance following stroke.[21] Sixteen subjects at a mean of 75 months post-stroke were divided into two groups. Both groups received therapist-supervised repetitive task-specific practice for three days a week for eight weeks. One group used the orthotic during practice. After intervention, there was no significant difference between groups in Fugl-Meyer score increases, six measures of the Stroke Impact Scale, or Canadian Occupational Performance Measure Performance. There was a significant difference in the Stroke Impact Scale Total ($p=0.027$).

Section Summary: Myoelectric Orthotic

The largest study identified tested participants with and without the orthosis. This study evaluated the function with and without the orthotic in stable poststroke participants who had no prior experience with the device. Outcomes were inconsistent. Studies are needed that show consistent improvements in relevant outcome measures. Results should also be replicated in a larger number of patients.

PRACTICE GUIDELINE SUMMARY

No practice guidelines identified.

SUMMARY

There is enough research to show that myoelectric upper limb prostheses improve health outcomes for people with an amputation or missing limb at the wrist or above when the

medical policy criteria are met. Therefore, myoelectric upper limb prostheses may be considered medically necessary when policy criteria are met.

In certain situations, a myoelectric upper limb prosthesis may no longer be able to perform its basic function due to damage or wear. When it is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a myoelectric upper limb prosthesis may be considered medically necessary when device replacement Criteria are met.

When a myoelectric upper limb prosthesis is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a myoelectric upper limb prosthesis is considered not medically necessary when device replacement Criteria are not met.

There is enough research to show that myoelectric upper limb prostheses do not improve health outcomes when policy criteria are not met. Therefore, myoelectric upper limb prostheses, under all other conditions including but not limited to replacement of an existing functioning prostheses are considered not medically necessary when policy criteria are not met.

There is not enough research to show that upper-limb prosthetic components with both sensor and myoelectric control improve health outcomes compared with conventional prostheses. Therefore, upper-limb prosthetic components with both sensor and myoelectric control are considered investigational.

There is not enough research to show that myoelectric controlled upper-limb orthoses improve health outcomes for people with upper limb weakness or paresis. Only two comparative studies have been published examining myoelectric orthoses. They had small sample sizes and demonstrated inconsistent performance. Therefore, myoelectric controlled upper-limb orthoses are considered investigational.

REFERENCES

1. Carey SL, Lura DJ, Highsmith MJ. Differences in myoelectric and body-powered upper-limb prostheses: Systematic literature review. *J Rehabil Res Dev.* 2015;52(3):247-62. PMID: 26230500
2. Biddiss EA, Chau TT. Upper limb prosthesis use and abandonment: a survey of the last 25 years. *Prosthet Orthot Int.* 2007;31(3):236-57. PMID: 17979010
3. Touillet A, Billon-Grumillier C, Pierret J, et al. Comparison of compensatory shoulder movements, functionality and satisfaction in transradial amputees fitted with two prosthetic myoelectric hooks. *PloS one.* 2023;18(2):e0272855. PMID: 36730223
4. Kruger LM, Fishman S. Myoelectric and body-powered prostheses. *J Pediatr Orthop.* 1993;13(1):68-75. PMID: 8416358
5. Edelstein JE, Berger N. Performance comparison among children fitted with myoelectric and body-powered hands. *Arch Phys Med Rehabil.* 1993;74(4):376-80. PMID: 8466418

6. Silcox DH, 3rd, Rooks MD, Vogel RR, et al. Myoelectric prostheses. A long-term follow-up and a study of the use of alternate prostheses. *J Bone Joint Surg Am.* 1993;75(12):1781-9. PMID: 8258548
7. Egermann M, Kasten P, Thomsen M. Myoelectric hand prostheses in very young children. *Int Orthop.* 2009;33(4):1101-5. PMID: 18636257
8. James MA, Bagley AM, Brasington K, et al. Impact of prostheses on function and quality of life for children with unilateral congenital below-the-elbow deficiency. *J Bone Joint Surg Am.* 2006;88(11):2356-65. PMID: 17079391
9. Biddiss E, Chau T. Upper-limb prosthetics: critical factors in device abandonment. *Am J Phys Med Rehabil.* 2007;86(12):977-87. PMID: 18090439
10. Pylatiuk C, Schulz S, Doderlein L. Results of an Internet survey of myoelectric prosthetic hand users. *Prosthet Orthot Int.* 2007;31(4):362-70. PMID: 18050007
11. Berke GM, Fergason J, Milani JR, et al. Comparison of satisfaction with current prosthetic care in veterans and servicemembers from Vietnam and OIF/OEF conflicts with major traumatic limb loss. *J Rehabil Res Dev.* 2010;47(4):361-71. PMID: 20803404
12. McFarland LV, Hubbard Winkler SL, Heinemann AW, et al. Unilateral upper-limb loss: satisfaction and prosthetic-device use in veterans and servicemembers from Vietnam and OIF/OEF conflicts. *J Rehabil Res Dev.* 2010;47(4):299-316. PMID: 20803400
13. Resnik L, Borgia M, Clark M. Function and Quality of Life of Unilateral Major Upper Limb Amputees: Effect of Prosthesis Use and Type. *Arch Phys Med Rehabil.* 2020. PMID: 32437692
14. Resnik L, Cancio J, Klinger S, et al. Predictors of retention and attrition in a study of an advanced upper limb prosthesis: implications for adoption of the DEKA Arm. *Disability and rehabilitation Assistive technology.* 2018;13(2):206-10. PMID: 28375687
15. Resnik LJ, Borgia ML, Acluche F, et al. How do the outcomes of the DEKA Arm compare to conventional prostheses? *PloS one.* 2018;13(1):e0191326. PMID: 29342217
16. Resnik LJ, Borgia ML, Acluche F. Perceptions of satisfaction, usability and desirability of the DEKA Arm before and after a trial of home use. *PloS one.* 2017;12(6):e0178640. PMID: 28575025
17. Resnik L, Klinger S. Attrition and retention in upper limb prosthetics research: experience of the VA home study of the DEKA arm. *Disability and rehabilitation Assistive technology.* 2017;12(8):816-21. PMID: 28098513
18. Resnik L, Acluche F, Lieberman Klinger S, et al. Does the DEKA Arm substitute for or supplement conventional prostheses. *Prosthet Orthot Int.* 2017:309364617729924. PMID: 28905665
19. Page S, Griffin C, White S. Efficacy of myoelectric bracing in moderately impaired stroke survivors: A randomized, controlled trial. *Journal of rehabilitation medicine.* 2020;52(2). PMID: 31960066
20. Peters HT, Page SJ, Persch A. Giving them a hand: wearing a myoelectric elbow-wrist-hand orthosis reduces upper extremity impairment in chronic stroke. *Annals of rehabilitation medicine.* 2017;98(9):1821-27. PMID: 28130084
21. Page SJ, Hill V, White S. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy: a randomized controlled pilot trial. *Clin Rehabil.* 2013;27(6):494-503. PMID: 23147552

CODES

Codes	Number	Description
CPT	None	
HCPCS	E1399	Durable medical equipment, miscellaneous
	L6026	Transcarpal/metacarpal or partial hand disarticulation prosthesis, external power, self-suspended, inner socket with removable forearm section, electrodes and cables, two batteries, charger, myoelectric control of terminal device, excludes terminal device(s)
	L6693	Upper extremity addition, locking elbow, forearm counterbalance
	L6715	Terminal device, multiple articulating digit, includes motor(s), initial issue or replacement
	L6880	Electric hand, switch or myoelectric controlled, independently articulating digits, any grasp pattern or combination of grasp patterns, includes motor(s)
	L6881	Automatic grasp feature, addition to upper limb electric prosthetic terminal device
	L6882	Microprocessor control feature, addition to upper limb prosthetic terminal device
	L6925	Wrist disarticulation, external power, self-suspended inner socket, removable forearm shell, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L6935	Below elbow, external power, self-suspended inner socket, removable forearm shell, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L6945	Elbow disarticulation, external power, molded inner socket, removable humeral shell, outside locking hinges, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L6955	Above elbow, external power, molded inner socket, removable humeral shell, internal locking elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L6965	Shoulder disarticulation, external power, molded inner socket, removable shoulder shell, shoulder bulkhead, humeral section, mechanical elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L6975	Interscapular-thoracic, external power, molded inner socket, removable shoulder shell, shoulder bulkhead, humeral section, mechanical elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
	L7007	Electric hand, switch or myoelectric controlled, adult
	L7008	Electric hand, switch or myoelectric controlled, pediatric
	L7009	Electric hook, switch or myoelectric controlled, adult
	L7045	Electric hook, switch or myoelectric controlled, pediatric
	L7180	Electronic elbow, microprocessor sequential control of elbow and terminal device
	L7181	Electronic elbow, microprocessor simultaneous control of elbow and terminal device
	L7190	Electronic elbow, adolescent, Variety Village or equal, myoelectronically controlled
	L7191	Electronic elbow, child, Variety Village or equal, myoelectronically controlled
	L7259	Electronic wrist rotator, any type
	L7499	Upper extremity prosthesis, not otherwise specified
	L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated

Codes	Number	Description
	L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated

Date of Origin: *June 2010*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 81

Powered and Microprocessor-Controlled Knee and Ankle-Foot Prostheses and Microprocessor-Controlled Knee-Ankle-Foot Orthoses

Effective: January 1, 2024

Next Review: September 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Microprocessor-controlled prostheses and orthoses use feedback from sensors to adjust joint movement on a real-time as-needed basis and powered prostheses are designed to replace muscle activity in the affected limb.

MEDICAL POLICY CRITERIA

I. Microprocessor-controlled knee may be considered **medically necessary** in amputees when all of the following criteria are met (A. – E.):

   A. At least one of the following criteria are met:

      1. Demonstrated need for ambulation at variable rates or for long distances such that the patient would benefit from a device that may reduce energy consumption. (Use of the limb only in the home and/or for basic community ambulation does not establish medical necessity of the computerized limb over standard limb applications); or

      2. Demonstrated daily activities or job tasks that do not permit full focus of concentration on knee control and stability, including but not limited to

ambulation on uneven terrain, curbs, ramps, regular use on stairs or repetitive lifting and/or carrying. (Use of the limb for limited stair climbing in the home or employment environment does not establish medical necessity of the computerized limb over standard prosthetic application).

B. All of the following criteria must be met to demonstrate adequate physical ability:
    1. Adequate cardiovascular and pulmonary reserve for ambulation at faster than normal walking speed; and
    2. Adequate stride strength and balance to activate the knee unit; and
    3. Classified as one of the following Medicare Functional Levels:
        a. Select Level K2—Patients capable of limited community ambulation, but only if improved stability in stance permits increased independence, decreased risk of falls, and potential to advance to a less restrictive walking device. The microprocessor is required to enable fine-tuning and adjustment of the hydraulic mechanism to accommodate the unique motor skills and demands of the functional level K2 ambulator; or
        b. Level K3—Patients who have the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion; or
        c. Level K4—Patients who have the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete.

C. Adequate cognitive ability to master use and care requirements for the technology; and

D. Patients with amputation from hemi-pelvectomy through knee-disarticulation level including bilateral lower extremity; and

E. All of the following criteria must also be met:
    1. Stable or absent wound; and
    2. The request is for either a microprocessor-controlled knee or a non-microprocessor-controlled mechanical prosthesis but not both for a single knee; and
    3. Adequate socket fitting with the potential to return to active lifestyle.

II. The replacement of all or part of an existing microprocessor-controlled knee is considered **medically necessary** when either of the following are met:

A. The existing microprocessor-controlled knee is malfunctioning, cannot be repaired, and is no longer under warranty; or

B. The current prosthetic can no longer meet the patient's medical needs due to a significant change in the patient's physiological condition.

III. Replacement of all or part of an existing microprocessor-controlled knee is considered **not medically necessary** when Criterion II. is not met.

IV. A microprocessor-controlled knee is considered **not medically necessary** when Criterion I. is not met or when any of the following apply:

   A. Medicare Functional Levels K0, K1, and the subset of K2 patients capable of limited community ambulation who do not have the cardiovascular reserve, strength, and balance to improve stability in stance to permit increased independence, decreased risk of falls and potential to advance to a less restrictive walking device

   B. When the primary benefit is to allow the patient to perform leisure or recreational activities

   C. Inability to tolerate the weight of the prosthesis

   D. Significant hip flexion contracture (over 20 degrees)

   E. Patient falls outside of recommended weight or height guidelines of manufacturer

V. A powered knee or ankle-foot is considered **investigational**.

VI. A microprocessor-controlled ankle-foot *prosthesis* or knee-ankle-foot *orthosis* is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of need at variable rates or for long distance ambulation from a device that reduces energy consumption
- Documentation of specific ADLS including job tasks that call do not permit full focus of concentration on knee control and stability
- Documentation of adequate ability to ambulate faster than normal walking speed including cardiovascular/pulmonary reserve, stride length, balance, Medicare Functional Level, and cognitive ability
- Type of amputation
- Wound status if applicable
- If a replacement is requested, documentation that the device is malfunctioning, cannot be repaired, and is no longer under warranty OR documentation of a significant change in the patient's physiological condition that makes the current prosthetic no longer able to meet the patient's medical needs

CROSS REFERENCES

1. Definitive Lower Limb Prostheses, Durable Medical Equipment, Policy No. 18
2. Myoelectric Prosthetic and Orthotic Components for the Upper Limb, DME, Policy No. 80
3. Powered Exoskeleton for Ambulation, DME, Policy No. 89

BACKGROUND

MICROPROCESSOR-CONTROLLED PROSTHETIC KNEES

Microprocessor-controlled prosthetic knees have been developed, including the Intelligent Prosthesis (IP) (Blatchford, England), the Adaptive (Endolite, England), the Rheo Knee® (Össur, Iceland), the C-Leg®, Genium™ Bionic Prosthetic System, and the X2 and X3 prostheses (Otto Bock Orthopedic Industry, Minneapolis, MN), and Seattle Power Knees (3 models include Single Axis, 4-bar and Fusion, from Seattle Systems). These devices are equipped with a sensor that detects when the knee is in full extension and adjusts the swing phase automatically, permitting a more natural walking pattern of varying speeds. For example, the prosthetist can specify several different optimal adjustments that the computer later selects and applies according to the pace of ambulation. In addition, these devices (with the exception of the IP) use microprocessor control in both the swing and stance phases of gait. (The C-Leg Compact provides only stance control). By improving stance control, they may provide increased safety, stability, and function. For example, the sensors are designed to recognize a stumble and stiffen the knee, thus avoiding a fall. Other potential benefits of microprocessor-controlled knee prostheses are improved ability to navigate stairs, slopes, and uneven terrain and reduction in energy expenditure and concentration required for ambulation. The C-Leg was cleared for marketing in 1999 through the 510(k) process of the U.S. Food and Drug Administration (FDA; K991590). Next-generation devices such as the Genium Bionic Prosthetic system and the X2 and X3 prostheses utilize additional environmental input (e.g., gyroscope and accelerometer) and more sophisticated processing that is intended to create more natural movement. One improvement in function is step-over-step stair and ramp ascent. They also allow the user to walk and run forward and backward. The X3 is a more rugged version of the X2 that can be used, for example, in water, sand, and mud. The X2 and X3 were developed by Otto Bock as part of the Military Amputee Research Program.

MICROPROCESSOR-CONTROLLED ANKLE-FOOT PROSTHESES

Microprocessor-controlled ankle-foot prostheses are being developed for transtibial amputees. These include the Proprio Foot® (Össur), the iPED (developed by Martin Bionics and licensed to College Park Industries), and the Elan Foot (Endolite). With sensors in the feet that determine the direction and speed of the foot's movement, a microprocessor controls the flexion angle of the ankle, allowing the foot to lift during the swing phase and potentially adjust to changes in force, speed, and terrain during the step phase. The intent of the technology is to make ambulation more efficient and prevent falls in patients ranging from the young active amputee to the elderly diabetic patient. The Proprio Foot™ and Elan Foot are microprocessor-controlled foot prostheses that are commercially available and considered class I devices that are exempt from 510(k) marketing clearance. Information on the Össur website indicates use of the Proprio Foot™ for low- to moderate-impact for transtibial amputees who are classified as level K3 (i.e., community ambulatory, with the ability or potential for ambulation with variable cadence). The Meridium and Empower are microprocessor ankle-feet available from Otto Bock, and the Kinnex is a microprocessor ankle-foot available from Freedom Innovations.

POWERED PROSTHESES

In development are lower-limb prostheses that also replace muscle activity in order to bend and straighten the prosthetic joint. For example, the PowerFoot BiOM® (developed at the Massachusetts Institute of Technology and licensed to iWalk) is a myoelectric prosthesis for transtibial amputees that uses muscle activity from the remaining limb for the control of ankle

movement. This prosthesis is designed to propel the foot forward as it pushes off the ground during the gait cycle, which in addition to improving efficiency, has the potential to reduce hip and back problems arising from an unnatural gait with use of a passive prosthesis. This technology is limited by the size and the weight required for a motor and batteries in the prosthesis. The Power Knee™ (Össur), which is designed to replace muscle activity of the quadriceps, uses artificial proprioception with sensors similar to the Proprio Foot in order to anticipate and respond with the appropriate movement required for the next step.

REGULATORY STATUS

Microprocessor-controlled prostheses are categorized as class I, exempt devices. Manufacturers must register prostheses with the restorative devices branch of FDA and keep a record of any complaints but do not have to undergo a full FDA review. FDA product codes include ISW and KFX.

EVIDENCE SUMMARY

Evaluating the effects of the increased sophistication of powered knee, powered ankle-foot, and microprocessor-controlled ankle-foot prostheses requires comparison with body-powered prostheses, passive prostheses, or no prosthesis. The most informative data are prospective comparative studies with objective measures that directly address function, safety, and health-related quality of life.

The evidence review below does not address microprocessor-controlled knees, which have been shown to improve function measures and decrease the cognitive burden associated with monitoring the prosthesis.

MICROPROCESSOR-CONTROLLED ANKLE-FOOT PROSTHESES

Systematic Reviews

A 2004 Cochrane review of ankle-foot prostheses (updated in 2008 with search dates through June 2006) concluded that there is insufficient evidence from high quality comparative studies to determine the overall superiority of any individual type of prosthetic ankle-foot mechanism.[1] The review included 26 cross-over studies with 3 to 16 participants in each study (n=245). Only one study was considered to be of high methodological quality while the remainders were considered of moderate quality. The vast majority of clinical studies on human walking have used standardized gait assessment protocols (e.g., treadmills) with limited “ecological validity”. The authors recommended that for future research, functional outcomes should be assessed for various aspects of mobility such as making transfers, maintaining balance, level walking, stair climbing, negotiating ramps and obstacles, and changes in walking speed.

Randomized Controlled Trials

Colas-Ribas (2022) conducted a cross-over study in 45 patients with ankle prosthesis at two centers in France.[2] Participants had a prosthetic foot for more than three months and were able to walk outdoors. After randomization, each foot (Proprio Foot or non-microprocessor) was worn for a total of 34 days which included two weeks of adaptation and adaptation confirmation and 20 days in everyday life. Energy expenditure was similar between prostheses (19.4 mL/kg/min with Proprio Foot and 19.1 mL/kg/min with other prostheses). Mean Short Form 36 (SF-36) physical scores with Proprio Foot were significantly better than with other prostheses (68.5 vs. 62.1; p=0.005) as were mental scores (72.0 vs. 66.2; p=0.006).

Gailey (2012) published a randomized, within-subject crossover study that compared self-reported and objective performance outcomes for four types of prosthetic feet, including the SACH (solid ankle cushion heel), SAFE (stationary attachment flexible endoskeletal), Talux mechanical foot, and the Proprio Foot microprocessor-controlled ankle prosthesis.[3] Ten patients with transtibial amputation were tested with their own prosthesis and then, in random order, each of the other prostheses after training and a two week acclimation period. No differences between prostheses were detected for the following measures:

- Prosthesis Evaluation Questionnaire (PEQ) (self-reported subjective rating of ease of use, social and emotional issues, and function over different surfaces)
- Locomotor Capabilities Index (self-reported subjective rating of capability to perform certain activities such as walking in various environments on various surfaces, sitting, standing, bending)
- Six-minute walk test (objective distance measurement)
- Steps per day
- Hours of daily activity

In 2014, the same investigators reported the effects of these prosthetic feet on ramp ambulation in 10 unilateral transtibial amputees.[4] Higher symmetry was reported with the Talux mechanical foot and the Proprio Foot during ramp descent, while no significant difference was found between the prostheses during ramp ascent.

Due to the limited sample sizes in these studies, conclusions cannot be reached about the comparisons between the various types of foot prostheses.

Nonrandomized Comparative Studies

Riveras (2020) reported on minimum toe clearance and tripping probability in 13 transtibial amputees using three prosthetic ankle-foot designs.[5] The participants tested a non-articulating ankle (NAA), an articulating hydraulic ankle (AHA), and an articulating hydraulic ankle with microprocessor (AHA-MP). Statistically significant differences were found for minimum toe clearance for ramp ascending ($p \leq 0.001$) and descending ($p=0.003$), with larger median values in the prosthetic limb when using the AHA-MP. The coefficient of variation was also significantly lower on the prosthetic limb for both types of articulating hydraulic ankle compared to the non-articulating ankle during ramp descent ($p=0.014$). The lowest tripping probability was reported for the AHA-MP.

Two comparative trials of the microprocessor-controlled ankle from the same investigators investigated the Proprio Foot. Its use was evaluated in 16 transtibial amputees during stair ascent and descent[6] or while walking up and down a ramp[7]. These studies were limited to the effect of flexion angles (flexion versus neutral angle). Healthy controls were also used for comparison. The outcomes of these studies were mixed. For example, the adapted mode (ankle flexion) resulted in more normal gait analysis results during ramp ascent but not during descent; however, some patients reported feeling safer with the adaptive mode ankle than with the Proprio Foot.

Thomas-Pohl (2021) compared three different types of ankle-foot prostheses, including the Proprio Foot, in a within-subject crossover study.[8] The primary outcome was to evaluate the ability of these prostheses to adapt to ground inclination. Six patients tested each of the three devices; each data acquisition was preceded with a two-week acclimation period and was

followed by a three-week wash-out period with the patient's energy storing and returning foot. Overall, the study found that microprocessor prostheses allowed for better posture and a reduction of residual knee moment on positive and/or negative slope when compared to the patients' energy storing and returning feet. Patients exhibited the most symmetric balance when they wore the Proprio Foot compared to the other microprocessor feet, but clinical functional tests between microprocessor prostheses and other feet did not differ greatly.

Other small studies have reported on these devices, including a study on ankle flexion using individuals as their own comparison group.[9] A within-subject study of six patients reported no benefit of an active Proprio Foot compared with the same prosthesis turned off with level walking or with slope ascent or descent.[10] An additional study reported a lower energy cost of floor walking with the Proprio Foot compared with a dynamic carbon fiber foot in 10 transtibial amputees.[11]

Section Summary

These studies do not permit conclusions about the clinical benefits and risks of the microprocessor-controlled foot compared with mechanical prostheses due to methodological limitations. These limitations included, among others, the small sample size, which limits the ability to rule out chance as an explanation of the study findings.

POWERED KNEE AND/OR ANKLE-FOOT PROSTHESES

Cacciola (2022) conducted a survey of 57 individuals who were current or (n=41) or former (n=16) users of a powered ankle-foot. All survey respondents were male with an average age of 53.5 years and an average of 13.1 years since amputation.[12] Among the current users, numeric rating scale pain scores were significantly improved with Empower compared with a passive foot in terms of sound knee pain (one vs. two; p=0.001), amputated side knee pain (one vs. two; p=0.001), and low-back pain (one vs. three; p<0.001). Limitations of this study include the use of recall data for pain and pain-related function since individuals tend to overestimate past pain, and other factors that may impact musculoskeletal pain, such as prosthetic alignment or concurrent medical treatments, were not accounted for in the study comparisons.

Kim (2021) reported results of a randomized trial of twelve participants that compared the BiOM powered ankle prosthesis with the participants' prescribed, unpowered prostheses.[13] Seven participants were randomly allocated to the powered prosthesis first group and five to the unpowered prosthesis first. Ten participants completed the study. No significant differences were identified in metabolic costs (p=0.585), daily step count (p=0.995), walking speed in-lab (p=0.145) and in daily life (p=0.226), or perception of mobility between prostheses (p≥0.058).

Ferris compared the BiOM powered ankle-foot prosthesis with an energy-storing and –returning (ESR) foot in 11 transtibial amputees. These results were also compared with 11 matched controls with intact limbs.[14] Compared with the ESR foot, the powered ankle-foot increased walking speed, but there were no significant differences in physical performance measure or conditions on the PEQ. Compared with the intact limb, the powered ankle-foot had increased step length and greater ankle peak power but had reduced range of motion. There appeared to be an increase in compensatory strategies at proximal joints with the powered prosthesis; the authors noted that normalization of gait kinematics and kinetics may not be

possible with a uniarticular device. Seven patients preferred the PowerFoot BiOM and four preferred the ESR prosthesis.

In another small study of seven amputees and seven intact controls, Herr (2012) reported gross metabolic cost and preferred walking speed to be more similar to non-amputee controls with the powered foot than with the ESR prosthesis.[15]

Mancinelli (2011) compared the PowerFoot BiOM with a passive-elastic foot in five transtibial amputees.[16] At the time of this study the powered prosthesis was a prototype and subjects' exposure to the prosthesis was limited to the laboratory. Laboratory assessment of gait biomechanics showed an average increase of 54% in the peak ankle power generation during late stance. Metabolic cost measured by oxygen consumption while walking on an indoor track was reduced by an average of 8.4% (p=0.06). This study did not report the impact of these measurements on patient function.

Section Summary

The current evidence is insufficient to permit conclusions about the benefits of powered lower extremity prostheses compared with other prostheses. These small studies mainly report on the feasibility of various prototypes. Larger, higher quality studies are needed to determine the impact of these devices on functional outcomes with greater certainty.

MICROPROCESSOR-CONTROLLED ORTHOSES

Randomized Controlled Trials

A randomized crossover trial of a microprocessor swing- and stance-controlled knee-ankle-foot orthosis was reported by Deems-Dluhy in 2021.[17] A total of 18 community-dwelling adults were assigned to receive a C-brace orthosis and a stance-control-orthosis in a randomized order. The C-brace controls with a microprocessor-controlled knee throughout stance and swing phases of gait. All participants received six sessions of training over a one-month period. Statistically significant differences were reported between post-microprocessor orthosis and post-stance-control orthosis in the six-minute walk test, with longer times post-microprocessor orthosis. Higher quality of life scores were reported in the Modified Falls Efficacy Scale, Orthotic and Prosthetic User's Survey (OPUS) (p=0.02) and physical health domain of the World Health Organization Quality of Life (WHOQOL-BREF) (p=0.037) after using the microprocessor-controlled orthosis. There were also fewer participant-reported falls when wearing the microprocessor-controlled orthosis versus a stance-control-orthosis or locked knee-ankle-foot orthosis.

Nonrandomized Comparative Studies

Pröbsting (2017) reported results of a questionnaire filled out by 13 patients at baseline (regarding their current locked knee ankle foot orthosis or stance control orthosis) and following use of a microprocessor stance and swing control orthosis.[18] The patients completed the Orthosis Evaluation Questionnaire, a new self-reported outcome measure created by modifying the Prosthesis Evaluation Questionnaire for use in lower limb orthotics and the Activities of Daily Living Questionnaire. There were statistically significant differences in the total score and the domains of ambulation (p=0.001), paretic limb health (p=0.04), sounds (p =0.02), and well-being (p=0.01), with superior results reported for the microprocessor orthosis.

Section Summary

The current evidence is insufficient to permit conclusions about the benefits of microprocessor-controlled lower extremity orthoses compared with other orthoses. These limitations include, among others, the small sample size. Larger, higher quality studies are needed to determine the impact of these devices on functional outcomes with greater certainty.

PRACTICE GUIDELINE SUMMARY

A 2019 clinical practice guideline from the Department of Veterans Affairs and the Department of Defense (VA/DoD) included the following recommendation with a weak strength of evidence:[19]

> We suggest offering microprocessor knee units over non-microprocessor knee units for ambulation to reduce risk of falls and maximize patient satisfaction. There is insufficient evidence to recommend for or against any particular socket design, prosthetic foot categories, and suspensions and interfaces.

The VAs' Prosthetic and Sensory Aids Strategic Healthcare Group was directed by the Under Secretary for Health to establish a Prosthetic Clinical Management Program to coordinate the development of clinical practice recommendations for prosthetic prescriptive practices. The following are guidelines from the Veterans Health Administration Prosthetic Clinical Management program:[20]

A. Contraindications for use of the microprocessor knee should include:
   - Any condition that prevents socket fitting, such as a complicated wound or intractable pain which precludes socket wear.
   - Inability to tolerate the weight of the prosthesis.
   - Medicare Level K 0—no ability or potential to ambulate or transfer.
   - Medicare Level K 1—limited ability to transfer or ambulate on level ground at fixed cadence.
   - Medicare Level K 2—limited community ambulator that does not have the cardiovascular reserve, strength, and balance to improve stability in stance to permit increased independence, less risk of falls, and potential to advance to a less-restrictive walking device.
   - Inability to use swing and stance features of the knee unit.
   - Poor balance or ataxia that limits ambulation.
   - Significant hip flexion contracture (over 20 degrees).
   - Significant deformity of remaining limb that would impair ability to stride.
   - Limited cardiovascular and/or pulmonary reserve or profound weakness.
   - Limited cognitive ability to understand gait sequencing or care requirements.
   - Long distance or competitive running.
   - Falls outside of recommended weight or height guidelines of manufacturer.
   - Specific environmental factors—such as excessive moisture or dust, or inability to charge the prosthesis.
   - Extremely rural conditions where maintenance ability is limited.

B. Indications for use of the microprocessor knee should include:
   - Adequate cardiovascular and pulmonary reserve to ambulate at variable cadence.
   - Adequate strength and balance in stride to activate the knee unit.

- Should not exceed the weight or height restrictions of the device.
- Adequate cognitive ability to master technology and gait requirements of device.
- Hemi-pelvectomy through knee-disarticulation level of amputation, including bilateral; lower extremity amputees are candidates if they meet functional criteria as listed
- Patient is an active walker and requires a device that reduces energy consumption to permit longer distances with less fatigue.
- Daily activities or job tasks that do not permit full focus of concentration on knee control and stability—such as uneven terrain, ramps, curbs, stairs, repetitive lifting, and/or carrying.
- Medicare Level K 2—limited community ambulator, but only if improved stability in stance permits increased independence, less risk of falls, and potential to advance to a less restrictive walking device, and patient has cardiovascular reserve, strength, and balance to use the prosthesis. The microprocessor enables fine-tuning and adjustment of the hydraulic mechanism to accommodate the unique motor skills and demands of the functional level K2 ambulator.
- Medicare Level K 3—unlimited community ambulator.
- Medicare Level K 4—active adult, athlete who has the need to function as a K 3 level in daily activities.
- Potential to lessen back pain by providing more secure stance control, using less muscle control to keep knee stable.
- Potential to unload and decrease stress on remaining limb.
- Potential to return to an active lifestyle.

C. Physical and Functional Fitting Criteria for New Amputees:
- New amputees may be considered if they meet certain criteria as outlined above.
- Premorbid and current functional assessment important determinant.
- Requires stable wound and ability to fit socket.
- Immediate postoperative fit is possible.
- Must have potential to return to active lifestyle.

SUMMARY

Research has shown that microprocessor-controlled knees improve function for some amputees and decrease the cognitive burden associated with monitoring the prosthesis. Those considered most likely to benefit from these prostheses have both the potential and need for frequent movement at a variable pace, uneven ground, or on stairs. Therefore, a microprocessor-controlled knee may be considered medically necessary when policy criteria are met.

In certain situations, a microprocessor-controlled knee may no longer be able to perform its basic function due to damage or wear or because of a change in the patient's physiological condition. When this occurs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a microprocessor-controlled knee may be considered medically necessary when device replacement Criteria are met.

When a microprocessor-controlled knee is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not

medically appropriate. Therefore, replacement of all or part of a microprocessor-controlled knee is considered not medically necessary when device replacement Criteria are not met.

There is not enough research to show if or how well microprocessor-controlled knees improve health outcomes when criteria are not met. Therefore, microprocessor-controlled knees are not medically necessary when policy criteria are not met.

There is not enough research to show that there are improved health outcomes for microprocessor-controlled ankle-foot prostheses compared with conventional prostheses. Therefore, microprocessor-controlled ankle-foot prostheses are considered investigational.

There is not enough research to evaluate the health benefits and risks of powered lower limb prostheses. Therefore, powered knee and/or powered ankle-foot prostheses are considered investigational.

There is not enough research to show that microprocessor-controlled knee-ankle-foot orthoses improve health outcomes compared with conventional orthoses. Therefore, microprocessor-controlled knee-ankle-foot orthoses are considered investigational.

REFERENCES

1. Hofstad C, Linde H, Limbeek J, et al. Prescription of prosthetic ankle-foot mechanisms after lower limb amputation. *Cochrane Database Syst Rev.* 2004(1):CD003978. PMID: 14974050
2. Colas-Ribas C, Martinet N, Audat G, et al. Effects of a microprocessor-controlled ankle-foot unit on energy expenditure, quality of life, and postural stability in persons with transtibial amputation: An unblinded, randomized, controlled, cross-over study. *Prosthetics and orthotics international.* 2022;46(6):541-48. PMID: 36515900
3. Gailey RS, Gaunaurd I, Agrawal V, et al. Application of self-report and performance-based outcome measures to determine functional differences between four categories of prosthetic feet. *Journal of rehabilitation research and development.* 2012;49(4):597-612. PMID: 22773262
4. Agrawal V, Gailey RS, Gaunaurd IA, et al. Comparison of four different categories of prosthetic feet during ramp ambulation in unilateral transtibial amputees. *Prosthetics and orthotics international.* 2014. PMID: 24925671
5. Riveras M, Ravera E, Ewins D, et al. Minimum toe clearance and tripping probability in people with unilateral transtibial amputation walking on ramps with different prosthetic designs. *Gait Posture.* 2020;81:41-48. PMID: 32663775
6. Alimusaj M, Fradet L, Braatz F, et al. Kinematics and kinetics with an adaptive ankle foot system during stair ambulation of transtibial amputees. *Gait Posture.* 2009;30(3):356-63. PMID: 19616436
7. Fradet L, Alimusaj M, Braatz F, et al. Biomechanical analysis of ramp ambulation of transtibial amputees with an adaptive ankle foot system. *Gait Posture.* 2010;32(2):191-8. PMID: 20457526
8. Thomas-Pohl M, Villa C, Davot J, et al. Microprocessor prosthetic ankles: comparative biomechanical evaluation of people with transtibial traumatic amputation during standing on level ground and slope. *Disabil Rehabil Assist Technol.* 2021;16(1):17-26. PMID: 31535903

9. Struchkov V, Buckley JG. Biomechanics of ramp descent in unilateral trans-tibial amputees: Comparison of a microprocessor controlled foot with conventional ankle-foot mechanisms. *Clin Biomech (Bristol, Avon).* 2016;32:164-70. PMID: 26689894
10. Darter BJ, Wilken JM. Energetic consequences of using a prosthesis with adaptive ankle motion during slope walking in persons with a transtibial amputation. *Prosthetics and orthotics international.* 2014;38:5-11. PMID: 23525888
11. Delussu AS, Brunelli S, Paradisi F, et al. Assessment of the effects of carbon fiber and bionic foot during overground and treadmill walking in transtibial amputees. *Gait Posture.* 2013;38(4):876-82. PMID: 23702342
12. Cacciola CE, Kannenberg A, Hibler KD, et al. Impact of a Powered Prosthetic Ankle-Foot Component on Musculoskeletal Pain in Individuals with Transtibial Amputation: A Real-World Cross-Sectional Study with Concurrent and Recalled Pain and Functional Ratings. *JPO: Journal of Prosthetics and Orthotics.* 2022:10.1097/JPO.0000000000000442. PMID:
13. Kim J, Wensman J, Colabianchi N, et al. The influence of powered prostheses on user perspectives, metabolics, and activity: a randomized crossover trial. *J Neuroeng Rehabil.* 2021;18(1):49. PMID: 33726802
14. Ferris AE, Aldridge JM, Rabago CA, et al. Evaluation of a powered ankle-foot prosthetic system during walking. *Archives of physical medicine and rehabilitation.* 2012;93(11):1911-8. PMID: 22732369
15. Herr HM, Grabowski AM. Bionic ankle-foot prosthesis normalizes walking gait for persons with leg amputation. *Proceedings Biological sciences / The Royal Society.* 2012;279(1728):457-64. PMID: 21752817
16. Mancinelli C, Patritti BL, Tropea P, et al. Comparing a passive-elastic and a powered prosthesis in transtibial amputees. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference.* 2011;2011:8255-8. PMID: 22256259
17. Deems-Dluhy S, Hoppe-Ludwig S, Mummidisetty CK, et al. Microprocessor Controlled Knee Ankle Foot Orthosis (KAFO) vs Stance Control vs Locked KAFO: A Randomized Controlled Trial. *Archives of physical medicine and rehabilitation.* 2021;102(2):233-44. PMID: 32976844
18. Pröbsting E, Kannenberg A, Zacharias B. Safety and walking ability of KAFO users with the C-Brace(®) Orthotronic Mobility System, a new microprocessor stance and swing control orthosis. *Prosthetics and orthotics international.* 2017;41(1):65-77. PMID: 27151648
19. Webster JB, Crunkhorn A, Sall J, et al. Clinical Practice Guidelines for the Rehabilitation of Lower Limb Amputation: An Update from the Department of Veterans Affairs and Department of Defense (2019). Sep [cited 9/19/2023]. 'Available from:' https://journals.lww.com/ajpmr/fulltext/2019/09000/clinical_practice_guidelines_for_the.13.aspx.
20. VHA Prosthetic Clinical Management Program (PCMP). Clinical practice recommendations: microprocessor knees, 2004. See: Berry D. Microprocessor prosthetic knees. Phys Med Rehabil Clin N Am. 2006;17:91-113.

CODES

Codes	Number	Description
CPT	None	

Codes	Number	Description
HCPCS	~~K1014~~	~~Addition, endoskeletal knee-shin system, 4 bar linkage or multiaxial, fluid swing and stance phase control~~ (Deleted 01/01/2024)
	L2006	Knee ankle foot device, any material, single or double upright, swing and/or stance phase microprocessor control with adjustability, includes all components (e.g., sensors, batteries, charger), any type activation, with or without ankle joint(s), custom fabricated
	L5615	Addition, endoskeletal knee-shin system, 4 bar linkage or multiaxial, fluid swing and stance phase control
	L5856	Addition to lower extremity prosthesis, endoskeletal knee-shin system, microprocessor control feature, swing and stance phase, includes electronic sensor(s), any type
	L5857	;swing phase only, includes electronic sensor(s), any type
	L5858	;stance phase only, includes electronic sensor(s), any type
	L5859	Addition to lower extremity prosthesis, endoskeletal knee-shin system, powered
	L5969	Addition, endoskeletal ankle-foot or ankle system, power assist, includes any type motor(s)
	L5973	Endoskeletal ankle foot system, microprocessor controlled feature, dorsiflexion and/or plantar flexion control, include power source
	L5999	Lower extremity prosthesis, not otherwise specified

Date of Origin: *May 2010*

Regence

Medical Policy Manual Durable Medical Equipment, Policy No. 87

Noninvasive Ventilators in the Home Setting

Effective: September 1, 2023

Next Review: July 2024
Last Review: July 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Noninvasive ventilation (NIV) assistance or noninvasive positive pressure ventilation (NPPV) uses a nasal mask, face mask, or mouthpiece, connected to a ventilator to provide ventilation support during sleep or intermittently throughout the day.

MEDICAL POLICY CRITERIA

Notes: This policy only addresses home ventilators with a *noninvasive* interface (HCPCS code E0466). It does not address the use of other types of home ventilators, including those with an *invasive* interface (HCPCS E0465) or a multi-function home ventilator (HCPCS E0467).

I. Use of a noninvasive ventilator in the home setting may be considered **medically necessary** when both of the following criteria are met (A. and B.):

A. The device is being requested to treat any of the following indications:

1. Neuromuscular disease, or
2. Thoracic restrictive disease, or

3. Chronic respiratory failure consequent to chronic obstructive pulmonary disease.

B. There is sufficient documentation in the medical record to support the condition is life-threatening where interruption of respiratory support would quickly lead to serious harm or death.

II. Use of a noninvasive ventilator in the home setting is considered **not medically necessary** when Criterion I. is not met, including but not limited to the following situations:

A. The patient's condition is such that treatment may be adequately provided by a bilevel positive airway pressure device; or

B. Severity of the patient's condition is not severe and life-threatening.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

VENTILATOR WITH NOINVASIVE INTERFACES

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determinations Manual (Internet-Only Manual, Publ. 100-03) in Chapter 1, Part 4, Section 280.1 stipulates that ventilators (E0465, E0466) are covered for the following conditions:[1]

"[N]euromuscular diseases, thoracic restrictive diseases, and chronic respiratory failure consequent to chronic obstructive pulmonary disease."

Each of these disease categories are comprised of conditions that can vary from severe and life-threatening to less serious forms. These ventilator-related disease groups overlap conditions described in this Respiratory Assist Devices LCD used to determine coverage for bi-level PAP devices. Each of these disease categories are conditions where the specific presentation of the disease can vary from patient to patient. For conditions such as these, the specific treatment plan for any individual patient will vary as well. Choice of an appropriate treatment plan, including the determination to use a ventilator vs. a bi-level PAP device, is made based upon the specifics of each individual beneficiary's medical condition. In the event of a claim review, there must be sufficient detailed information in the medical record to justify the treatment selected.

Ventilators fall under the Frequent and Substantial Servicing (FSS) payment category, and payment policy requirements preclude FSS payment for devices used to deliver continuous and/or intermittent positive airway pressure, regardless of the illness treated by the device. (Social Security Act 1834(a)(3)(A)) This means that products currently classified as HCPCS code E0465 or E0466 when used to provide CPAP or bi-level PAP (with or without backup rate) therapy, regardless of the underlying medical condition, shall not be paid in the FSS payment category. A ventilator is not eligible for reimbursement for any of the conditions described in this RAD LCD even though the ventilator equipment may have the capability of operating in a bi-level PAP (E0470, E0471) mode. Claims for ventilators used to provide CPAP or bi-level CPAP therapy for conditions described in this RAD policy will be denied as not reasonable and necessary.

General principles of correct coding require that products assigned to a specific HCPCS code only be billed using the assigned code. Thus, using the HCPCS codes for CPAP (E0601) or bi-level PAP (E0470, E0471) devices for a ventilator (E0465, E0466) used to provide CPAP or bi-level PAP therapy is incorrect coding. Claims for ventilators billed using the CPAP or bi-level PAP device HCPCS codes will be denied as incorrect coding.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- All chart notes and medical records pertinent to the request (e.g., supporting documentation of neuromuscular disease, thoracic restrictive disease, and/or chronic respiratory failure consequent to COPD).
- Documentation must demonstrate that the condition is life-threatening where interruption of respiratory support would quickly lead to serious harm or death.

CROSS REFERENCES

1. Phrenic Nerve Stimulation for Central Sleep Apnea, Surgery, Policy No. 212

BACKGROUND

This policy is based on the Centers for Medicare & Medicaid Services (CMS) National Coverage Determinations Manual (Internet-Only Manual, Publ. 100-03) in Chapter 1, Part 4, Section 280.1; and Local Coverage Determination (LCD): Respiratory Assist Devices (L33800).[1, 2]

NONINVASIVE VENTILATORS

Ventilators, also known as respirators, are medical devices used to mechanically assist with a patients' breathing. Mechanical ventilation is often categorized by the interface used, such as a tracheostomy tube for invasive ventilation, or a mask for non-invasive ventilation. Non-invasive ventilation (NIV) assistance or non-invasive positive pressure ventilation (NPPV) uses a nasal mask, face mask, or mouthpiece, connected to a ventilator to provide ventilation support during sleep or intermittently throughout the day. In the hospital setting, a trial of NPPV may be attempted prior to invasive treatment. Ventilation support rests the lung muscles and improves breathing performance during the day. At night, ventilation may be used to treat sleep-associated hypoventilation. If use is at night only, this is referred to as nocturnal NPPV. If use is intermittent, this may be referred to as "Mouthpiece" or "Sip and Puff" ventilation. Supplemental oxygen may also be added to this type of system.

In recent decades, NPPV has been used for treatment in the home setting. BPAP are portable pressure-limited ventilators, which are more commonly used than portable volume-limited ventilators. In some populations, efficacy is similar with both types of devices according to comparative studies, thus the portable pressure-limited ventilators are usually preferred over portable volume-limited ventilators, because of lower cost, better portability, and often greater comfort.[3]

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved numerous portable home ventilators through the 510(k) process. A non-exhaustive list of examples includes the following:

- Servo-u Ventilator system 4.1 (Rontgenvagen)
- Trilogy™ (Philips Respironics)
- Newport® (Newport Medical Instruments)
- IVent (GE Healthcare)
- Puritan™ (Covidien)
- LTV® (Carefusion)

FDA Product Code: CBK.

SUMMARY

There is enough research to show that use of a noninvasive ventilator in the home setting improves health outcomes for patients with neuromuscular disease, thoracic restrictive disease, or chronic respiratory failure consequent to chronic obstructive pulmonary disease. Clinical guidelines based on research recommend noninvasive ventilators for use in the home setting for these populations. Therefore, the use of a noninvasive ventilator in the home setting may be considered medically necessary when policy criteria are met.

In all other situations, the use of a noninvasive ventilator in the home setting is not associated with improvements in health outcomes. Therefore, the use of a noninvasive ventilator in the home setting is considered not medically necessary when policy criteria are not met.

REFERENCES

1. U.S. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Durable Medical Equipment Reference List (280.1). Version number: 2. Publication Number 100-3. Implementation Date 7/5/2005. [cited 07/24/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=190&ncdver=2&DocID=280.1&bc=gAAAABAAAAAA&.
2. U.S. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): Respiratory Assist Devices (L33800). For services performed on or after 01/01/2020. [cited 07/24/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=33800&ver=26&Date=&DocID=L33800&bc=hAAAAAgAAAAA&=.
3. Noridian Healthcare Solutions. Correct Coding and Coverage of Ventilators - Revised July 2020. [cited 07/24/2023]. 'Available from:' https://med.noridianmedicare.com/web/jddme/policies/dmd-articles/2020/correct-coding-and-coverage-of-ventilators-revised-july-2020.

CODES

NOTE: Home ventilator codes requiring prior authorization are listed on the "Commercial Pre-authorization List" web page. Home ventilators not listed on the pre-authorization website do not require prior approval. There may be codes related to home ventilator systems that are not included in this medical policy.

Codes	Number	Description
CPT	None	
HCPCS	E0466	Home ventilator, any type, used with non-invasive interface, (e.g., mask, chest shell)

Date of Origin: *July 2019*

HTCC Decision: Negative Pressure Wound Therapy

Implementation 1/1/18

Definition of "Complete Wound Therapy Program"

A minimum of the following measures must be addressed and documented:
a. Evaluation, care and wound measurements by a licensed medical professional, and
b. Application of dressings to maintain a moist wound environment, and
c. Debridement of necrotic tissue if present, and
d. Evaluation of and provision for adequate nutritional status, and
e. Standard forms of treatment specific to the type of wound.

Regence

Medical Policy Manual Surgery, Policy No. 01

Endometrial Ablation

Effective: May 1, 2024

Next Review: October 2024
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Endometrial ablation involves ablation or destruction of the endometrium using a variety of techniques to treat people with menorrhagia when standard therapy is ineffective.

MEDICAL POLICY CRITERIA

I. Endometrial ablation, with or without hysteroscopic guidance, may be considered **medically necessary** when the clinical records document all of the following criteria (I.A. - D.) are met:

A. There is a diagnosis of abnormally heavy uterine bleeding in a patient who is not post-menopausal; *and*

B. Hysteroscopy, sonohysterography (SIS), pelvic ultrasound, or other pelvic imaging (e.g. pelvic MRI, pelvic CT) has been performed and clinical documentation of the results is provided; *and*

C. Clinical documentation confirms counseling regarding hormonal treatment options has been addressed (see Policy Guidelines); *and*

D. Endometrial sampling or dilation and curettage (D&C) has been performed or is planned according to either of the following:

1. Endometrial sampling or D&C has been performed to evaluate the current

abnormal bleeding episode and clinical documentation of the results is provided, either showing absence of endometrial hyperplasia or uterine cancer OR inadequate tissue was obtained for diagnosis; *or*

2. Cervical stenosis documented in the clinical record precludes endometrial sampling, and D&C is planned concomitantly with ablation procedure.

II. Repeat endometrial ablation may be considered **medically necessary** when all of the following (A. - C.) criteria are met:

A. There is a recurrent diagnosis of abnormally heavy uterine bleeding in a patient who is not post-menopausal; *and*

B. The initial endometrial ablation procedure was performed at least six months prior; *and*

C. Endometrial sampling or D&C has been performed or is planned according to either of the following:

1. Endometrial sampling or D&C has been performed to evaluate the current abnormal bleeding episode since the previous ablation procedure, and the clinical documentation of the results is provided, either showing absence of endometrial hyperplasia or uterine cancer OR inadequate tissue was obtained for diagnosis; *or*

2. Cervical stenosis documented in the clinical record precludes endometrial sampling, and D&C is planned concomitantly with ablation procedure.

III. Endometrial ablation using *any* technique is considered **not medically necessary** for all other indications not meeting the criteria in I.A.-D., or II.A.-C.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

HORMONAL THERAPY OPTIONS

Counseling regarding hormonal treatment options has occurred, or uterine intracavitary abnormality (i.e., endometrial polyps, submucosal fibroids) is found on hysteroscopy, sonohysterography, pelvic ultrasound, or endometrial biopsy/curettings and endometrial ablation is to be performed concomitantly with surgical treatment of the uterine intracavitary abnormality.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical chart notes
- Clinical documentation that affirms:

    - Endometrial sampling or D&C was completed with date performed, and description of the results, OR
    - Cervical stenosis; AND
- Clinical documentation that affirms:
    - Hysteroscopy, sonohysterography (SIS), pelvic ultrasound, or other pelvic imaging (e.g. pelvic MRI, pelvic CT) was completed with date performed, and description of the results, OR
    - Repeat endometrial ablation is planned at least six months after the initial procedure
- When relevant, clinical documentation of counseling regarding hormonal treatment options

CROSS REFERENCES

1. Gender Affirming Interventions for Gender Dysphoria, Medicine, Policy No. 153
2. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
3. Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants, Surgery, Policy No. 40
4. Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells, Surgery, Policy No. 182
5. Hysterectomy, Surgery, Policy No. 218

BACKGROUND

Ablation or destruction of the endometrium is used to treat abnormal uterine bleeding in premenopausal women when standard medical therapy is ineffective. Standard medical management typically includes a trial of nonhormonal therapy with adequate doses of nonsteroidal anti-inflammatory medication and oral tranexamic acid. If this fails, management with hormonal treatment to thin the endometrium may be tried. Hormonal treatment may include oral contraceptive pills, patch, vaginal ring, or progestin-only hormonal therapy (oral, IUD, implant, or injection). Ablation is considered a less invasive alternative to hysterectomy; however, as with hysterectomy, the procedure is not recommended for women who wish to preserve their fertility.

Techniques for endometrial ablation are generally divided into two categories:

HYSTEROSCOPIC TECHNIQUES

Hysteroscopic techniques require skilled surgeons and, due to the requirement for cervical dilation, use of general or regional anesthesia. In addition, the need for the instillation of hypotonic distension media creates a risk of pulmonary edema and hyponatremia such that very accurate monitoring of fluids is required.

The initial hysteroscopic technique involved photovaporization of the endometrium using an Nd-YAG laser. This was followed by electrosurgical ablation using an electrical rollerball or electrical wire loop. The latter technique is also known as transcervical resection of the endometrium, or TCRE. Hydrothermal ablation is another technique involving hysteroscopy.

NON-HYSTEROSCOPIC TECHNIQUES

Non-hysteroscopic techniques can be performed without general anesthesia and do not involve use of a fluid distention medium. Techniques include thermal fluid-filled balloon, cryosurgical endometrial ablation, instillation of heated saline, and radio frequency (RF) ablation.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) indicated that endometrial devices are for use in premenopausal women with menorrhagia due to benign causes for whom childbearing is complete. FDA-approved devices for endometrial ablation include, but may not be limited to, laser therapy, electrical wire loop, rollerball using electric current, and thermal ablation using a liquid-filled balloon, microwave, electrode array, or a cryosurgical device. Examples of devices for endometrial ablation are listed below. FDA product code: MNB.

- The Genesys HTA™ system (Boston Scientific), This system involves the instillation and circulation of heated saline into the uterus using hysteroscopic guidance and includes features such as a smaller console and simplified set-up requirements, was approved by the FDA in May 2010.
- The Microwave Endometrial Ablation (MEA) system (Microsulis Medical): This delivers fixed-frequency microwave energy and may be performed in a physician's office but does require use of the hysteroscope.
- The ThermaChoice® device (J&J Ethicon Gynecare): This device ablates endometrial tissue by thermal energy heating of sterile injectable fluid within a silicone balloon. Endometrial ablation will only work when there is direct contact between the endometrial wall and the fluid-filled balloon. Therefore, patients with uteri of abnormal shape, resulting from tumors such as myomas or polyps, or large size, due to fibroids, are generally not considered candidates for this procedure.
- The NovaSure® impedance-controlled endometrial ablation system (Hologic®): The system delivers RF energy to the endometrial surface. The device consists of an electrode array on a stretchable porous fabric that conforms to the endometrial surface.
- Her Option™ Uterine Cryoablation Therapy™ system (American Medical Systems): The system consists of, in part, a cryoprobe that is inserted through the cervix into the endometrial cavity. When cooled, an ice ball forms around the probe, which permanently destroys the endometrial tissue. Cryoablation is typically monitored by abdominal ultrasound.

EVIDENCE SUMMARY

SYSTEMATIC REVIEWS

Several published systematic reviews have evaluated the accumulated evidence for endometrial ablation. These reviews address both first- generation techniques (laser ablation, electrical wire loop, rollerball, or vaporizing electrode procedure) and second-generation techniques (newer techniques that generally do not require hysteroscopy such as balloon ablation, microwave ablation, and electrode ablation).

Oderkerk (2022) published a systematic review to assess whether previous endometrial ablation affects future endometrial cancer (EC) risk.[1] The review involved 29,102 patients from 11 studies and found that previous endometrial ablation is associated with a reduced risk for EC (0.0% - 1.6% vs.3.1% average lifetime risk of EC). The review is limited by follow-up times of fewer than 15 years in nine of the studies.

Vitale (2022) published a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare quality of life after endometrial ablation or hysteroscopic endometrial resection (ER/GEA) to hysterectomy.[2] Twelve RCTs involving 2773 premenopausal women

were included. Outcomes were post-operative scores on the 36-Item Short Form Health Survey (SF-36), post-operative anxiety and depression, and the rate of surgical complications. The overall risk of bias was intermediate. SF-36 scores for general health perception ($p<0.00001$), social function ($p=0.02$), emotional role limitation ($p=0.02$), and vitality ($p=0.02$) were lower in the ER/GEA group, but the groups were similar in perception of physical functioning ($p=0.19$), pain ($p=0.08$), and mental health ($p=0.06$). Anxiety and depression, measured with the Hospital Anxiety and Depression Scale (HADS) were not different ($p=0.26$, $p=0.85$). The rate of post-operative complications was also not significantly different ($p=0.13$). Limitations include the studies were not blinded and the use of outdated ablation techniques.

Oderkerk (2023) conducted a systematic review and meta-analysis assessing the risk of hysterectomy at least one year after non-rectoscopic endometrial ablation.[3] The analysis involved 48,071 patients from 53 studies. Hysterectomy rates increased with time, and the study found a 12% risk of hysterectomy five years after endometrial ablation, but study design and ablation technique did not significantly affect hysterectomy rates.

Bergeron (2020) performed a systematic review and meta-analysis of the efficacy and safety of endometrial ablation or resection compared with the levonorgestrel intra-uterine system (LNG-IUS) in the treatment of premenopausal women with heavy menstrual bleeding.[4] A total of 13 randomized controlled trials met inclusion criteria. The meta-analysis identified no significant differences between groups for subsequent hysterectomy, satisfaction, quality of life, amenorrhea and treatment failure. Based on data from 10 studies, there was a statistically significant difference between groups for side effects, which were less common in the endometrial ablation/resection group (RR = 0.52, 95% CI 0.37 to 0.71, $p<0.001$, $I^2=0\%$). There was significant heterogeneity between studies for mean age of the included population ($p=0.01$). When age was limited to 42 years or younger, there was higher risk of subsequent hysterectomy for the endometrial ablation/resection group compared to the LNG-IUS group (RR=5.26, 95% CI 1.21 to 22.91, $p=0.03$, $I^2=0\%$).

In 2018, an updated Cochrane systematic review and meta-analysis compared the efficacy and safety of different endometrial ablation techniques.[5-7] The review included RCTs that compared ablation techniques and assessed amenorrhea and patient satisfaction.

A total of 28 studies with 4,287 premenopausal women were eligible for the review. Five of the trials compared two “first generation” ablation methods (laser ablation, electrical wire loop, rollerball, or vaporizing electrode procedure) to one another and five trials compared “second generation” techniques to one another. Fifteen trials compared first- to second-generation procedures. Eighteen trials had adequate randomization methods, but in most trials blinding was not performed or was not reported. Of the studies that compared among second generation techniques, three described triple blinding and two described double blinding.

The investigators also conducted a meta-analysis that combined studies comparing first- and second-generation techniques. A pooled analysis of 12 studies (total n=2,085) did not find a significant difference in the rate of amenorrhea at one year (OR 0.94; 95% CI 0.74 to 1.20). Eleven studies (total n=1,690) reported satisfaction rates at one year, and there was not a significant difference between first-and second-generation techniques (OR 1.00; 95% CI, 0.97 to 1.02). Pooled analysis of adverse effects did not find any significant differences in the rate of perforation (eight studies), endometritis (four studies), or hemorrhage (four studies) using first- versus second-generation ablation techniques. Rates of fluid overload (three studies) and

cervical lacerations (seven studies) and hematometra (five studies) were significantly higher with first-generation techniques than with second-generation techniques.

The authors of the Cochrane review concluded that, overall, the existing evidence suggests that success rates and complications profiles of second-generation techniques compare favorably with the first generation hysteroscopic techniques.

In 2011, the Health Technology Assessment (HTA) program in the U.K. conducted a meta-analysis of individual patient data from RCTs evaluating second-line treatments for menorrhagia.[8] They identified data on 2,448 women from 14 trials comparing first- and second-generation endometrial ablation devices and data on 1,127 women from seven trials comparing first-generation devices to hysterectomy. A limitation of the review is that individual patient data were not available for approximately 35% of women randomized in the trials. The most frequently measured outcome in the studies was patient satisfaction/dissatisfaction and this was used as the primary outcome of the meta-analysis. After 12 months of follow-up, 7.3% (57/454) of women treated with first-generation endometrial ablation devices and 5.3% (23/432) of women who had a hysterectomy were dissatisfied with their treatment outcome. This difference was statistically significant, favoring hysterectomy (OR 2.46, 95% CI 1.54 to 3.93, p=0.0002). Rates of dissatisfaction were similar among women treated with first-generation endometrial ablation devices (123/1,006 [12.2%]) and second-generation devices (110/1,034 [10.6%], p=0.20). The authors noted that rates of dissatisfaction were low for all treatments.

The HTA also conducted meta-analyses on several clinical outcomes. For example, when first- and second-generation endometrial ablation devices were compared, there was not a significant difference between groups in the rate of amenorrhea after 12 months. When findings from 13 studies were pooled, rates of amenorrhea were 326/899 (36%) with first-generation devices and 464/1,261 (37%) with second-generation devices (OR 1.12; 95% CI 0.93 to 1.35). There were insufficient data to conduct meta-analyses of longer-term amenorrhea rates. Similarly, the rates of menorrhagia after 12 months did not differ between groups. In a pooled analysis of 12 studies, rates were 111/899 (12.3%) with first-generation devices and 151/1,281 (11.8%) after second-generation devices (pooled OR 0.97, 95% CI 0.74 to 1.28). In addition, a pooled analysis of 6 studies did not find a significant difference in repeat endometrial ablations over 12 months after initial treatment with first-generation devices (4/589, 0.7%) or second-generation devices (4/880, 0.5%) (OR 0.71, 95% CI 0.17 to 2.94). The proportion of women requiring hysterectomy within 12 months after endometrial ablation did not differ significantly when first-generation devices (39/933 [4.2%]) or second-generation devices (35/1,343 [2.6%]) were used (OR 0.77; 95% CI 0.47 to 1.24 [11 studies]).

In addition to the meta-analyses of data from published studies, the HTA included an analysis of individual patient data from national databases in Scotland to evaluate long-term outcomes after hysterectomy or endometrial ablation. The investigators identified a total of 37,120 women who underwent hysterectomy and 11,299 women who underwent endometrial ablation for dysfunctional uterine bleeding between 1989 and 2006. Women who received endometrial ablation were significantly older (mean of 42.5 years) compared to those receiving hysterectomy (mean of 41.0 years). The type of endometrial ablation device could not be determined. The median duration of follow-up was 6.2 years in the endometrial ablation group and 11.6 years in the hysterectomy group. During follow-up, 962 (8.5%) women who received endometrial ablation had additional gynecologic surgery compared to 1,446 (3.9%) women who had hysterectomy; this difference was statistically significant (adjusted hazard ratio [HR]:

3.56, 95% CI 3.26 to 3.89). The most common types of additional surgery after endometrial ablation were intrauterine procedures (n=577, 5.1%) and repeat endometrial ablation (n=278, 2.5%). However, women who had initial endometrial ablation procedures were significantly less likely than those with initial hysterectomies to have surgery for pelvic floor repair (0.9% vs. 2.2%, respectively, adjusted HR 0.50 to 0.77). Women were also less likely to have tension-free vaginal tape surgery for stress urinary incontinence after endometrial ablation than after hysterectomy (0.5% vs. 1.1%, respectively, adjusted HR 0.55, 95% CI 0.41 to 0.74).

In 2012, Daniels compared first- and second-generation methods using 14 trials previously addressed in the HTA assessment.[9] A pooled analysis of these studies yielded conclusions that were similar to the HTA group, in that no significant difference in amenorrhea rates was observed with the two types of techniques (OR 0.72, 95% CI 0.52 to 1.101). In addition, three studies compared the second-generation techniques, thermal balloon ablation and bipolar radiofrequency (RF) (total n=264). A pooled analysis showed a higher rate of amenorrhea with bipolar RF (OR 4.56; 95% CI 2.24 to 9.26).

In 2013, Kroft also reported no difference in amenorrhea rates when comparing first- and second-generation methods as a treatment for menorrhagia in premenopausal women (11 randomized controlled trials[10] were included in the review). However, authors did note a decrease in complication rates (seven studies with 1272 patients, rate ratio 0.52, 95% CI 0.35 to 0.76; p<0.001), operating time (16.6 minutes three studies with 486 patients, 95% CI 12.1 to 21.2 minutes; p<0.001) and improved compatibility with anaesthesia (three studies with 558 patients, rate ratio 1.87, 95% CI 1.04 to 3.37; p=0.04) in second-generation devices compared to first-generation methods. In addition, authors reported higher rates of amenorrhea in patients treated with Novasure compared to other second-generation devices (four studies with 407 patients, rate ratio 2.60, 95% CI 1.63 to 4.14; p<0.001).

Several medium and large nonrandomized studies have reported time to surgical reoperation rates, including repeat endometrial ablation, in women who fail initial procedure.[11-13] The majority of surgical reoperations occurred at least one year after the initial procedure.

Section Summary

Evidence from these large systematic reviews do not demonstrate that one ablation technique is superior to another. Overall, these studies continue to report similar amenorrhea rates in first-generation and second-generation techniques.

SAFETY

In 2012, Brown published an analysis of adverse events associated with endometrial ablation procedures that were reported in the U.S. Food and Drug Administration (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database.[14] There were a total of 829 reported adverse events between 2005 and 2011. Nearly two-thirds of the adverse events (540 of 829, 65%) were genital tract or skin burns and 529 of these events (98%) were associated with hydrothermal endometrial ablation. The next two most frequent types of adverse events were thermal bowel injury (93 of 820, 11%) and transmural uterine thermal activity (89 of 820, 11%). Of the 182 thermal injuries, 140 (77%) were associated with radiofrequency endometrial ablation. In addition, 47 instances of sepsis or bacteremia were reported, and 43 of these cases (91%) were associated with radiofrequency endometrial ablation. There were four reported deaths, two associated with radiofrequency ablation and one each associated with thermal balloon ablation and cryoablation. Sixty-six of the 829 events (8%) occurred when

endometrial ablation was performed outside of the labeled instructions for use of the procedure. The authors did not report the total number of endometrial ablations performed during this time period, therefore the proportion of procedures with adverse events cannot be determined from these data.

A 2014 study by Dood examined whether women who undergo endometrial ablation are at increased risk of endometrial cancer compared with those with abnormal uterine bleeding that is managed with medication.[15] The data were collected from a population-based cohort in the U.S. and included a total of 234,721 women with abnormal bleeding, 4776 of whom underwent endometrial ablation. During a median follow-up period of 4.1 years, three women with a history of endometrial ablation and 601 women who were treated medically developed endometrial cancer. There was not a statistically significant difference in endometrial cancer rates between groups (age-adjusted HR=0.61, 95% CI, 0.20 to 1.89, p=0.17). Moreover, the median time to endometrial cancer diagnosis, 237 days after ablation and 299 days with medical management, did not differ significantly between groups.

Section Summary

Adverse events have been associated with endometrial ablation procedures. Certain types of adverse events are more likely to occur with specific approaches to endometrial ablation. Due to lack of information about the total number of procedures and the number of each type of endometrial ablation procedure performed, conclusions cannot be drawn from these data about the relative safety of different types of endometrial ablation procedures.

PRACTICE GUIDELINE SUMMARY

PRACTICE COMMITTEE OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2008, the American Society for Reproductive Medicine (ASRM) reviewed their 2006 Practice Committee report and reissued their statement on indications and options for endometrial ablation.[16] Conclusions were:

- “Endometrial ablation is an effective therapeutic option for the management of menorrhagia.
- Hysteroscopic and nonhysteroscopic techniques for endometrial ablation offer similar rates of symptom relief and patient satisfaction.
- Later definitive surgery may be required in 6% to 20% of women after endometrial ablation.
- Women who undergo hysterectomy after a failed endometrial ablation report significantly more satisfaction after 2 years of follow-up.
- Endometrial ablation generally is more effective when the endometrium is relatively thin.
- Ideally, hysteroscopic methods for endometrial ablation should be performed using a fluid monitoring system to reduce the risks and complications relating to fluid overload and electrolyte imbalance.
- Nonhysteroscopic methods for endometrial ablation require less skill and operating time.”

A 2015 patient fact sheet from the ASRM states that women who meet the following criteria should not have endometrial ablation:

> "Women who are pregnant, who would like to have children in the future, or have gone through menopause should not have this procedure."[17]

AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

The American Congress of Obstetricians and Gynecologists (ACOG) published a practice bulletin on endometrial ablation in 2007, which was later reaffirmed in 2013, 2015, and 2018.[18] ACOG made the following recommendations, as being based on good and consistent evidence:

> "For women with normal endometrial cavities, resectoscopic endometrial ablation and nonresectoscopic endometrial ablation systems appear to be equivalent with respect to successful reduction in menstrual flow and patient satisfaction at 1 year following index surgery."

> "Resectoscopic endometrial ablation is associated with a high degree of patient satisfaction but not as high as hysterectomy."

In addition, the ACOG practice bulletin regarding endometrial ablation included the following statement regarding preoperative evaluation:

> "The structure and histology of the endometrial cavity should be thoroughly evaluated, both to assess for malignancy or endometrial hyperplasia and to ensure that the length and configuration is suitable for endometrial ablation. These parameters will vary depending on the technique or system used. Endometrial sampling, typically with an outpatient technique, can be used to evaluate all women for hyperplasia or malignancy, and results should be reviewed before ablation is scheduled. Women with endometrial hyperplasia or uterine cancer should not undergo endometrial ablation."

In 2013, ACOG published committee opinion number 557 (reaffirmed in 2020) regarding the management of acute abnormal uterine bleeding (AUB) in nonpregnant reproductive-aged women.[19] Recommendations regarding laboratory testing and imaging of these patients are as follows:

> "Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first-line test. Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in patients with obesity or polycystic ovary syndrome), failed medical management, and persistent AUB."

Recommendations regarding surgical management of women who do not respond to medical management of symptoms are as follows:

> "Surgical options include dilation and curettage (D&C), endometrial ablation, uterine artery embolization, and hysterectomy."

> "Endometrial ablation, although readily available in most centers, should be considered only if other treatments have been ineffective or are contraindicated, and it should be performed only when a woman does not have plans for future childbearing and when the possibility of endometrial or uterine cancer has been reliably ruled out as the cause of the acute AUB."

The 2013, ACOG practice bulletin regarding the management of abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O) was reaffirmed in 2018.[20] The following recommendation is made primarily based upon consensus and expert opinion:

> "Endometrial ablation is not recommended as a first-line therapy for AUB-O. Physicians must provide thorough informed consent and adequate counseling to women with AUB-O who desire endometrial ablation."

Furthermore, the practice bulletin recommends combined hormonal contraceptive therapy or progestin therapy, and other medical management depending upon age group and menopause status. The bulletin stresses that contraindications to combined hormonal contraceptive therapy should be excluded.

SOCIETY FOR GYNECOLOGIC SURGEONS

In 2012, the Society for Gynecologic Surgeons (SGS) published a clinical practice guideline on treatment of abnormal uterine bleeding.[21] The guideline recommends that, in women with bleeding caused mainly by ovulatory disorders or endometrial hemostatic disorders, any of the following treatments may be chosen depending on patient values and preferences: hysterectomy, endometrial ablation, systemic medical therapies or levonorgestrel-releasing intrauterine systems. In choosing between endometrial ablation and hysterectomy, if the patient's preference is for amenorrhea, less pain or avoiding additional therapy, hysterectomy is suggested. If the patient's preference is for lower operative and postoperative procedural risk, and a shorter hospital stay, endometrial ablation is recommended.

SUMMARY

There is enough research to show that endometrial ablation improves overall health outcomes in women with abnormally heavy uterine bleeding who are not post-menopausal. Clinical guidelines recommend endometrial ablation for clinical scenarios that generally align with the policy criteria. Therefore, endometrial ablation may be considered medically necessary when criteria are met.

Evidence and guidelines do not support the use of endometrial ablation when policy criteria are not met. Therefore, endometrial ablation for indications or using techniques other than those specified in policy criteria are considered not medically necessary.

REFERENCES

1. Oderkerk TJ, van de Kar MRD, Cornel KMC, et al. Endometrial cancer after endometrial ablation: a systematic review. *Int J Gynecol Cancer.* 2022;32(12):1555-60. PMID: 36375895
2. Vitale SG, Riemma G, Mikuš M, et al. Quality of Life, Anxiety and Depression in Women Treated with Hysteroscopic Endometrial Resection or Ablation for Heavy Menstrual Bleeding: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicina (Kaunas).* 2022;58(11). PMID: 36422203

3. Oderkerk TJ, Beelen P, Bukkems ALA, et al. Risk of Hysterectomy After Endometrial Ablation: A Systematic Review and Meta-analysis. *Obstetrics and gynecology.* 2023;142(1):51-60. PMID: 37290114
4. Bergeron C, Laberge PY, Boutin A, et al. Endometrial ablation or resection versus levonorgestrel intra-uterine system for the treatment of women with heavy menstrual bleeding and a normal uterine cavity: a systematic review with meta-analysis. *Hum Reprod Update.* 2020;26(2):302-11. PMID: 31990359
5. Lethaby A, Hickey M, Garry R, et al. Endometrial resection / ablation techniques for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2009(4):CD001501. PMID: 19821278
6. Lethaby A, Penninx J, Hickey M, et al. Endometrial resection and ablation techniques for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2013;8:CD001501. PMID: 23990373
7. Bofill Rodriguez M, Lethaby A, Grigore M, et al. Endometrial resection and ablation techniques for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews.* 2019(1). PMID: CD001501
8. Bhattacharya S, Middleton LJ, Tsourapas A, et al. Hysterectomy, endometrial ablation and Mirena(R) for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis. *Health technology assessment (Winchester, England).* 2011;15(19):iii-xvi, 1-252. PMID: 21535970
9. Daniels JP, Middleton LJ, Champaneria R, et al. Second generation endometrial ablation techniques for heavy menstrual bleeding: network meta-analysis. *BMJ.* 2012;344:e2564. PMID: 22529302
10. Kroft J, Liu G. First- versus second-generation endometrial ablation devices for treatment of menorrhagia: a systematic review, meta-analysis and appraisal of economic evaluations. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC.* 2013;35(11):1010-9. PMID: 24246401
11. Wortman M, Daggett A, Deckman A. Ultrasound-guided reoperative hysteroscopy for managing global endometrial ablation failures. *Journal of minimally invasive gynecology.* 2014;21(2):238-44. PMID: 24126259
12. Wortman M, Daggett A. Reoperative hysteroscopic surgery in the management of patients who fail endometrial ablation and resection. *The Journal of the American Association of Gynecologic Laparoscopists.* 2001;8(2):272-7. PMID: 11342737
13. Bansi-Matharu L, Gurol-Urganci I, Mahmood TA, et al. Rates of subsequent surgery following endometrial ablation among English women with menorrhagia: population-based cohort study. *BJOG : an international journal of obstetrics and gynaecology.* 2013;120(12):1500-7. PMID: 23786246
14. Brown J, Blank K. Minimally invasive endometrial ablation device complications and use outside of the manufacturers' instructions. *Obstetrics and gynecology.* 2012;120(4):865-70. PMID: 22996104
15. Dood RL, Gracia CR, Sammel MD, et al. Endometrial cancer after endometrial ablation vs medical management of abnormal uterine bleeding. *Journal of minimally invasive gynecology.* 2014;21(5):744-52. PMID: 24590007
16. Indications and options for endometrial ablation. *Fertil Steril.* 2008;90(5 Suppl):S236-40. PMID: 19007637
17. American Society for Reproductive Medicine (ASRM). Fact Sheet: Endometrial Ablation. Revised 2015. [cited 03.18.2024]. 'Available from:' https://www.reproductivefacts.org/news-and-publications/fact-sheets-and-infographics/endometrial-ablation/.

18. Endometrial Ablation. American Congress of Obstetricians and Gynecologists (ACOG) Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 81, May 2007. *Obstetrics and gynecology.* 2007;109(5):1233-48. PMID: 17470612
19. ACOG committee opinion no. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstetrics and gynecology.* 2013;121(4):891-6. PMID: 23635706
20. American Congress of Obstetricians and Gynecologists (ACOG): Practice Bulletin no. 136: Management of Abnormal Uterine Bleeding Associated with Ovulatory Dysfunction. *Obstetrics and gynecology.* 2013;122(1):176-85. PMID: 23787936
21. Wheeler TL, 2nd, Murphy M, Rogers RG, et al. Clinical practice guideline for abnormal uterine bleeding: hysterectomy versus alternative therapy. *Journal of minimally invasive gynecology.* 2012;19(1):81-8. PMID: 22078016

CODES

Codes	Number	Description
CPT	58353	Endometrial ablation, without hysteroscopic guidance
	58356	Endometrial cryoablation with ultrasonic guidance, including endometrial curettage, when performed
	58563	Hysteroscopy, surgical, with endometrial ablation (e.g., endometrial resection, electrosurgical ablation, thermoablation)
HCPCS	None	

Date of Origin: *September 2011*

Regence

Medical Policy Manual Surgery, Policy No. 08

Cochlear Implant

Effective: May 1, 2024

Next Review: March 2025
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A cochlear implant is a device for the treatment of severe-to-profound hearing loss in individuals who only receive limited benefit from amplification with hearing aids. A cochlear implant provides direct electrical stimulation to the auditory nerve, bypassing the usual transducer cells that are absent or nonfunctional in deaf cochlea.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not apply to surgically anchored bone-conduction hearing aids or externally worn air-conduction hearing aids. Cochlear implants are not hearing aids. While hearing aids function by amplifying sound, cochlear implants replace the functions of an absent or nonfunctioning cochlea.
- This policy does not address the use of the Nucleus® 24 Auditory Brain Stem Implant, which is designed to restore hearing in patients with neurofibromatosis who are deaf secondary to removal of bilateral acoustic neuromas.
- Hybrid cochlear implant/hearing aid systems are devices that include a hearing aid integrated into the external sound processor of the cochlear implant. If hearing aid components of such systems are billed separately, there may be specific member

benefit language addressing coverage of hearing aids that would be applicable. Contract language takes precedence over medical policy.

- Repeat hearing tests or trials of hearing aids are not necessary for patients who have previously met Criteria I. and II. as it is unlikely that natural hearing or the benefit from hearing aids will improve significantly over time.

I. **For individuals with bilateral hearing loss, implantation of cochlear implants (unilateral or bilateral)**, ***other than*** cochlear implant/hearing aid ***hybrid*** devices, and associated aural rehabilitation may be considered **medically necessary** when all of the following criteria (A. – D.) are met:

A. Meets one of the following age requirements:

1. Age 9 months or older for the Nucleus 24 cochlear implant system (with any of the Cochlear® sound processors); or
2. Age 12 months or older.

B. Meets one or more of the following:

1. Patients diagnosed with enlarged vestibular aqueduct (EVA) (greater than 1mm at the midpoint), as evidenced by MRI or CT imaging; or
2. Patients with both of the following (a. and b.):
   a. Patients meeting criterion (i. or ii.):
      i. Bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, defined as a pure-tone average of 70 decibels (dB) hearing threshold or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz; or
      ii. Severe to profound pre- or postlingual (sensorineural) hearing loss, defined as a pure-tone average of 70 dB hearing threshold or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz in one ear with documented progressive hearing loss (i.e., documentation of multiple audiograms demonstrating progressive hearing loss with expectation of continued progressive hearing loss) in the contralateral ear; and
   b. Limited or no benefit from hearing aids (defined below) unless hearing aids are unreasonable.
      i. **Adults:** Scores less than or equal to 50 percent correct on tape recorded sets of open-set sentence recognition in the ear to be implanted.
      ii. **Children:** Failure to develop basic auditory skills, and in older children, less than or equal to 30 percent correct on open-set tests.

C. Implanted device is FDA approved PMA or 510(k) only.

D. Patients do not have any of the following contraindications:

1. Deafness due to lesions of the acoustic nerve (eighth cranial nerve), central auditory pathways, or brain stem in the implanted ear.

2. Active or chronic infections of the external or middle ear and mastoid cavity in the implanted ear, including but not limited to otitis media.
3. Tympanic membrane perforation.
4. Radiographic evidence of absent cochlear development in the implanted ear.
5. Inability or lack of willingness to participate in post-implantation aural rehabilitation.

II. **For individuals with bilateral hearing loss, unilateral implantation of *hybrid* cochlear implant/hearing aid systems** that include the hearing aid integrated into the external sound processor of the cochlear implant may be considered **medically necessary** when all of the following criteria are met (A. – F.):

A. Age 18 years or older.

B. Bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, defined as a pure-tone average of 70 decibels (dB) hearing threshold or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz.

C. Limited or no benefit from hearing aids unless hearing aids are unreasonable, defined as scores less than 50 percent correct on tape recorded sets of open-set sentence recognition in the ear selected for implantation.

D. Meets all of the following (1. and 2.):

1. All of the following in the ear selected for implantation (a. – c.):
    a. Low frequency hearing thresholds no poorer than 60 dB hearing level up to and including 500 Hz (averaged over 125, 250, and 500 Hz; i.e., threshold average of 125, 250, and 500 Hz less than or equal to 60 dB hearing level); and
    b. Severe to profound mid-to-high frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz greater than or equal to 75 dB hearing level); and
    c. Aided consonant-nucleus-consonant word recognition score from 10 percent to 60 percent in the preoperative aided condition.
2. All of the following for the contralateral ear (a and b):
    a. Moderately severe to profound mid-to-high frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz greater than or equal to 60 dB hearing level); and
    b. Aided consonant-nucleus-consonant word recognition score equal to or better than that of the ear selected for implantation but not more than 80 percent correct.

E. Implanted device is FDA approved PMA or 510(k) only.

F. Does not have any of the following contraindications:

1. Deafness due to lesions of the acoustic nerve (eighth cranial nerve), central auditory pathways, or brain stem in the implanted ear
2. Active or chronic infections of the external or middle ear and mastoid cavity in

the implanted ear, including but not limited to otitis media

3. Tympanic membrane perforation
4. Radiographic evidence of absent cochlear development in the implanted ear
5. Inability or lack of willingness to participate in post-implantation aural rehabilitation
6. A duration of severe to profound hearing loss of 30 years or greater.

III. **For individuals with unilateral hearing loss (single sided deafness), unilateral implantation of cochlear implant, *other than*** cochlear implant/hearing aid ***hybrid*** devices, and associated rehabilitation may be considered **medically necessary** when all of the following criteria (A. - F.) are met:

A. Five years of age or older.

B. Profound sensorineural hearing loss in one ear (defined as having a pure-tone average of 90dB hearing loss or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.)

C. One of the following in the contralateral ear (1. or 2.):

1. Normal hearing or mild sensorineural hearing loss in the contralateral ear. Normal hearing is defined as having a PTA of up to 15 dB Hearing Loss at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. (i.e., single sided deafness); or
2. Mild to moderately severe sensorineural hearing loss in the contralateral ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears (i.e., asymmetric hearing loss).

D. Documented limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted.

E. Implanted device is FDA approved - PMA or 510(k) only.

F. Does not have any of the following contraindications:

1. Deafness due to lesions of the acoustic nerve (eighth cranial nerve), central auditory pathways, or brain stem in the implanted ear.
2. Active or chronic infections of the external or middle ear and mastoid cavity in the implanted ear, including but not limited to otitis media.
3. Tympanic membrane perforation.
4. Radiographic evidence of absent cochlear development in the implanted ear.
5. Inability or lack of willingness to participate in post-implantation aural rehabilitation.

IV. Implantation of cochlear implants is considered **not medically necessary** when one of Criterion I. II. or III. above is not met.

V. **Implant replacement, including replacement parts or upgrades** to existing cochlear implants and/or components, may be considered **medically necessary** when components are no longer functional, or for functional devices only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work.

VI. **Implant replacement, including replacement parts or upgrades** to existing cochlear implants and/or components, are considered **not medically necessary** when Criterion V. is not met, including but not limited to upgrades of existing, functioning external systems to achieve aesthetic improvement, such as smaller profile components, or a switch from a body-worn external sound processor to a behind-the-ear (BTE) model.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

A Pure Tone Average (PTA) is determined by averaging the hearing threshold levels at a set of specified frequencies: for example, 500, 1000, and 2000 Hz (PTA = 500 Hz (T)+ 1000 Hz (T) + 2000Hz (T) ÷ 3).

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Manufacturer and Model Name of Cochlear Implant being requested
- Audiology test results

CROSS REFERENCES

1. Transcutaneous Bone-Conduction and Bone-Anchored Hearing Aids, Surgery, Policy No. 121

BACKGROUND

Hearing loss is rated on a scale based on the threshold of hearing sounds, measured in decibels (dB). The generally accepted range for human hearing is 0 -120 dB (where 0 dB is no sound, 120 dB is very loud). Severe hearing loss is defined as a hearing threshold of 70-90 decibels (dB) and profound hearing loss is defined as a hearing threshold of 90 dB and above. Profound unilateral sensorineural hearing loss (UHL) or single-sided deafness (SSD), is clinically unaidable hearing defined by severe-to-profound hearing thresholds with a poor word recognition ability.

A cochlear implant provides direct electrical stimulation to the auditory nerve, bypassing the usual transducer cells that are absent or nonfunctional in deaf cochlea. The basic components of a cochlear implant include both external and internal components. The external components include a microphone, an external sound processor, and an external transmitter. The internal components are implanted surgically and include an internal receiver implanted within the temporal bone, and an electrode array that extends from the receiver into the cochlea through a surgically created opening in the round window of the middle ear.

Sounds that are picked up by the microphone are carried to the external signal processor, which transforms sound into coded signals that are then transmitted transcutaneously to the

implanted internal receiver. The receiver converts the incoming signals to electrical impulses that are then conveyed to the electrode array, ultimately resulting in stimulation of the auditory nerve.

Cochlear implants may be implanted in one or both ears. Implantation in both ears can be done sequentially or simultaneously. A post-cochlear implant rehabilitation program is necessary to achieve benefit from the cochlear implant. The rehabilitation program includes development of skills in understanding running speech, recognition of consonants and vowels, and tests of speech perception ability.

REGULATORY STATUS

Note: Full FDA approval includes only Premarket Approval (PMA) and 510k approval. Devices with Investigational Device Exemption (IDE) or Humanitarian Device Exemption (HDE) are not considered fully FDA approved.

Several cochlear implants are commercially available in the United States. The FDA-labeled indications for currently marketed electrode arrays are summarized in the table below. Over the years, subsequent generations of the various components of the devices have been FDA approved, focusing on improved electrode design and speech-processing capabilities. Furthermore, smaller devices and the accumulating experience in children have resulted in broadening of the selection criteria to include children as young as 9 months.

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
CONVENTIONAL COCHLEAR IMPLANTS	
Advanced Bionics® • HiRes™ Ultra implant • HiResolution Bionic Ear System (HiRes 90K*) Sound Processors: • ClearVoice • HiRes Fidelity 120 • HiRes Optima Predecessors: • Clarion Multi-Strategy • HiFocus CII Bionic Ear	<u>Adults</u>: • ≥ 18 years of age • Post-lingual onset of severe to profound bilateral sensorineural hearing loss [≥70 decibels (dBs)] • Limited benefit from appropriately fitted hearing aids, defined as scoring ≤ 50% on a test of open-set Hearing in Noise Test (HINT) sentence recognition <u>Children:</u> • 12 months to 17 years of age • Profound bilateral sensorineural deafness (>90dB) • Use of appropriately fitted hearing aids for at least 6 months in children 2 to 17 years of age or at least 3 months in children 12 to 23 months of age. • Lack of benefit in children <4 years of age is defined as a failure to reach developmentally-appropriate auditory milestones (e.g., spontaneous response to name in quiet or to environmental sounds) measured using the Infant-Toddler Meaningful Auditory Integration Scale or Meaningful Auditory Integration Scale or < 20% correct on a simple open-set word recognition test (Multisyllabic Lexical Neighborhood Test) administered using monitored live voice [70 dB SPL (sound pressure level)] • Lack of hearing aid benefit in children >4 years of age is defined as scoring < 12% on a difficult open-set word recognition test (Phonetically Balanced-Kindergarten Test) or < 30% on an open-

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
	set sentence test (HINT for Children) administered using recorded materials in the soundfield (70 dB SPL)
Cochlear® • Nucleus CI600 series • Nucleus CI500 series • Nucleus CI24RE series • Nucleus 24 series Sound Processors: • Kanso® 2 • Kanso® • Nucleus® 8 • Nucleus® 7 • Nucleus® 6 • Nucleus® 5* • Nucleus Freedom Predecessors: • Nucleus 22, 24	<u>Adults</u>: • ≥ 18 years old • Pre- or post-lingual onset of moderate to profound bilateral sensorineural hearing loss • ≤50% sentence recognition in the ear to be implanted • ≤60% sentence recognition in the opposite ear or binaurally • Adults with Severe to profound unilateral SNHL (SSD or AHL) o PTA at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz of > 80 dB HL o Normal or near normal hearing in the contralateral ear defined as PTA at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz of ≤ 30 dB HL o Limited benefit from an appropriately fitted unilateral hearing device <u>Children 9 months to 24 months:</u> • Profound sensorineural hearing loss bilaterally • Limited benefit from appropriate binaural hearing aids • Lack of progress in the development of auditory skills <u>Children 25 months to 17 years 11 months</u>: • Severe to profound bilateral sensorineural hearing loss • Multi-syllabic Lexical Neighborhood Test (MLNT) scores of ≤30% in best-aided condition in children 25 months to 4 years 11 months • Lexical Neighborhood Test (LNT) scores of ≤30% in best-aided condition in children 5 years to 17 years and 11 months • Lack of progress in the development of auditory skills • Children 5 y to 18 y of age with severe to profound unilateral SNHL (SSD or AHL) o PTA at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz of > 80 dB HL o Normal or near normal hearing in the contralateral ear defined as PTA at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz of ≤ 30 dB HL o Limited benefit from an appropriately fitted unilateral hearing device
Med El® • Maestro system • Synchrony Implant • Synchrony 2 Implant • Concerto Implant	<u>Bilateral Hearing Loss</u> <u>Adults</u>: • ≥ 18 years old • Severe to profound bilateral sensorineural hearing loss (≥70dB) • ≤40% correct Hearing in Noise test (HINT) sentences with best-sided listening condition

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
Sound Processors: • Sonnet • Sonnet 2 • Concerto implant • Opus • Opus 2 • Rondo 2 Predecessors: • Combi 40+ • Sonata • Pulsar	<u>Children:</u> • 12 months to 18 years with profound sensorineural hearing loss (≥90dB) • In younger children, little or no benefit is defined by lack of progress in the development of simple auditory skills with hearing aids over a 3-6 month period • In older children, lack of aided benefit is defined as <20% correct on the MLNT or LNT depending upon the child's cognitive ability and linguistic skills • A 3-6 month trial with hearing aids is required if not previously experienced <u>Single-Sided Deafness and Asymmetric Hearing Loss</u> • ≥ 5 years old • Single-sided deafness (SSD) or asymmetric hearing loss (AHL), where: o SSD is defined as profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear. o AHL is defined as a profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears. • Limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted. • For ages 18 years-old and above, limited benefit from unilateral amplification is defined by test scores of 5% correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. • For ages between 5 and 18 years-old, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone • At least 1 month experience wearing a Contra Lateral Routing of Signal (CROS) hearing aid or other relevant device and not show any subjective benefit
Oticon Medical Neuro Cochlear Implant System (Neuro 2 sound processor and Neuro Zti implant)	<u>Adults:</u> • Severe-to-profound bilateral SNHL (≥70 dB at 500, 1000, and 2000 Hz) • Limited benefit from appropriately fit hearing aids, defined as scoring ≤50% correct HINT sentences in quiet or noise with best-sided listening condition
HYBRID COCHLEAR IMPLANTS	
Cochlear®	<u>Adults:</u> • ≥ 18 years old • Residual low-frequency hearing sensitivity

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
• Nucleus® Hybrid™ L24 Cochlear Implant (Nucleus 6)	• Severe to profound high-frequency sensorineural hearing loss • Limited benefit from appropriately fit bilateral hearing aids
Med El® • Med EL EAS™	Adults: • ≥ 18 years old • Residual low-frequency hearing sensitivity • Severe to profound high-frequency sensorineural hearing loss • Candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids
RECENTLY FDA-APPROVED DEVICES	
• New devices that come onto the market are added to the policy at policy updates. In the interim, new devices may be approved for coverage for FDA-approved indications when applicable criteria are met.**	

*Note: Cochlear, Ltd. voluntarily recalled the Nucleus CI500 range in September 2011 for device malfunction in the CI512 implant. The external Nucleus 5 sound processor is not a part of the recall. Advanced Bionics HiRes90K was voluntarily recalled in November 2010 and given FDA-approval for re-entry to market the device in September 2011.
** FDA-approved indications can be found by searching by device name in the FDA 510(k) Premarket Notification Database or the De Novo Database and viewing the Summary.

While cochlear implants have typically been used mono laterally, in recent years, interest in bilateral cochlear implantation has arisen. The proposed benefits of bilateral cochlear implants are to improve understanding of speech in noise and localization of sounds. Improvements in speech intelligibility may occur with bilateral cochlear implants through binaural summation; i.e., signal processing of sound input from two sides may provide a better representation of sound and allow one to separate out noise from speech. Speech intelligibility and localization of sound or spatial hearing may also be improved with head shadow and squelch effects, i.e., the ear that is closest to the noise will be received at a different frequency and with different intensity, allowing one to sort out noise and identify the direction of sound. Bilateral cochlear implantation may be performed independently with separate implants and speech processors in each ear or with a single processor. However, no single processor for bilateral cochlear implantation has been FDA approved for use in the United States. In addition, single processors do not provide binaural benefit and may impair localization and increase the signal to noise ratio received by the cochlear implant.

In March 2014, FDA approved the Nucleus® Hybrid™ L24 Cochlear Implant System (Cochlear Corporation) through the premarket approval process.[1] This system is a hybrid cochlear implant and hearing aid, with the hearing aid integrated into the external sound processor of the cochlear implant. It is indicated for unilateral use in patients aged 18 years and older who have residual low-frequency hearing sensitivity and severe to profound high-frequency sensorineural hearing loss, and who obtain limited benefit from appropriately fit bilateral hearing aid. The electrode array inserted into the cochlea is shorter than conventional cochlear implants. According to the FDA's premarket approval notification, labeled indications for the device include:

- Preoperative hearing in the range from normal to moderate hearing loss (HL) in the low frequencies (thresholds no poorer than 60 dB HL up to and including 500 Hz).

- Preoperative hearing with severe to profound mid- to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz ≥75 dB HL) in the ear to be implanted.
- Preoperative hearing with moderately severe to profound mid- to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz ≥60 dB HL) in the contralateral ear.
- Consonant-Nucleus-Consonant (CNC) word recognition score between 10% to 60% (inclusively) in the ear to be implanted in the preoperative aided condition and in the contralateral ear equal to or better than that of the ear to be implanted but not more than 80% correct.

In January 2022, the FDA approved to expand the indication for the Nucleus 24 Cochlear Implant System to individuals aged 5 years and older with single-sided deafness (SSD) or asymmetrical hearing loss (AHL).[2]

> According to the FDA's summary of safety and effectiveness data, approval was based on unpublished data in 42 adults from a feasibility study (n=10) and real-world data from two cochlear implantation centers (n=32). Study interpretation is limited by small sample size in adult subjects only, unclear rationale for the efficacy threshold, and missing data. The FDA has required Cochlear Americas to conduct a postmarketing study to continue to assess the safety and efficacy of the implant in a new enrollment cohort of adults and children. (P970051/S205).

In September 2016, FDA approved the Med EL EAS™ (Electric Acoustic Stimulation) Hearing Implant System (Med EL Corp.).[3] This system is a hybrid cochlear implant and hearing aid, with the hearing aid integrated into the external sound processor of the cochlear implant. It is the combination of the SYNCHRONY cochlear implant and the SONNET EAS audio processor. According to the FDA's premarket approval notification:[4]

> The MED-EL EAS System is indicated for partially deaf individuals aged 18 years and older who have residual hearing sensitivity in the low frequencies sloping to a severe/profound sensorineural hearing loss in the mid to high frequencies, and who obtain minimal benefit from conventional acoustic amplification. Typical preoperative hearing of candidates ranges from normal hearing to moderate sensorineural hearing loss in the low frequencies (thresholds no poorer than 65 dB HL up to and including 500 Hz) with severe to profound mid- to high-frequency hearing loss (no better than 70 dB HL at 2000 Hz and above) in the ear to be implanted. For the non-implanted ear, thresholds may be worse than the criteria for the implanted ear, but may not be better. The CNC word recognition score in quiet in the best-aided condition will be 60% or less, in the ear to be implanted and in the contralateral ear. Prospective candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids.

In July 2019, the FDA expanded indications for the MED-EL Cochlear Implant System to include SSD and AHL.[5]

> The indications for use are as follows: The MED-EL Cochlear Implant System is indicated for evoking auditory sensations via electrical stimulation of the auditory pathways for individuals ages 5 years and above with single-sided deafness (SSD) or asymmetric hearing loss (AHL), where: SSD is defined as profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear. AHL is defined as a profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears. Profound hearing loss is

defined as having a PTA of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Normal hearing is defined as having a PTA of up to 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild hearing loss is defined as having a PTA of up to 30 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild to moderately severe hearing loss is defined as having a PTA ranging from 31 to up to 55 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Individuals with SSD or AHL must obtain limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted. For individuals ages 18 years-old and above, limited benefit from unilateral amplification is defined by test scores of five (5) percent correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. For individuals between 5 and 18 years-old, insufficient functional access to sound in the ear to be implanted.

EVIDENCE SUMMARY

Cochlear implants (CI) are recognized effective treatment of sensorineural deafness in select patient, as noted in a 1995 National Institutes of Health Consensus Development conference, which offered the following conclusions:[6]

- Cochlear implantation has a profound impact on hearing and speech reception in postlingually deafened adults with positive impacts on psychological and social functioning.
- The results are more variable in children. Benefits are not realized immediately but rather are manifested over time, with some children continuing to show improvement over several years.
- Prelingually deafened adults may also benefit, although to a lesser extent than postlingually deafened adults. These individuals achieve minimal improvement in speech recognition skills. However, other basic benefits, such as improved sound awareness, may meet safety needs.
- Training and educational intervention are fundamental for optimal post implant benefit.
- Cochlear implants in children under two years old are complicated by the inability to perform detailed assessment of hearing and functional communication. However, a younger age of implantation may limit the negative consequences of auditory deprivation and may allow more efficient acquisition of speech and language. Some children with post-meningitis hearing loss have been implanted under the age of two years due to the risk of new bone formation associated with meningitis, which may preclude a cochlear implant at a later date.

ENLARGED VESTIBULAR AQUEDUCTS (EVA)

Enlarged vestibular aqueduct (also known as enlarged vestibular aqueduct syndrome (EVAS), large vestibular aqueduct, large vestibular aqueduct syndrome (LVAS), or dilated vestibular aqueduct) is a condition which is associated with childhood hearing loss. According to the NIH National Institute on Deafness and other Communication Disorders (NIDCD):[7] most children with enlarged vestibular aqueducts (EVA) will develop some amount of hearing loss, and approximately 5 to 15% of children with sensorineural hearing loss (hearing loss caused by damage to sensory cells inside the cochlea) have EVA.

Systematic Reviews

Alahmadi (2022) published a systematic review (SR) evaluating the surgical and clinical outcomes of cochlear implant among patients with EVA.[8] Of the 4035 subjects (34 studies)

included, 853 (21.14%) underwent cochlear implantation. Unilateral implantation was performed in 258 cases while bilateral in 119 subjects. Postoperative complications included CSF/perilymph gusher (n = 112), CSF oozing (n = 18), and partial electrode insertion (n = 6). Closing the cochleostomy with temporalis fascia, muscle, connective tissue, or fibrin glue was the most frequently reported approach to manage CSF/perilymph gusher (n = 67, 56.7%) while packing was performed in six patients. The authors conclude that patients with EVA demonstrated audiometric and speech performance improvement after CI. However, many patients had intra- or postoperative complications.

Hansen (2022) published a SR to evaluate the age at implantation, improvement in hearing and speech perception outcomes, as well as surgical complications in pediatric cochlear implant recipients with Pendred Syndrome (PS) or non-syndromic enlarged vestibular aqueduct (NSEVA). A total of 55 studies were included in the analysis. The authors reported that the four-frequency pure-tone audiogram average improved by 60 to 78 dB HL due to cochlear implantation (in 46 studies with audiogram results). Auditory performance and speech intelligibility scores increased by 44%. The overall average implantation age was 60 months. Perilymph gusher/oozing was the most common surgical incident reported, occurring in 187 of 1572 implantations. The authors conclude that in children with PS/NSEVA, cochlear implantation improves pure-tone average by 60 to 78 dB HL and capacity of auditory performance/speech intelligibility by 44%. The implantation age for these children has decreased during the last two decades but is still somewhat higher than reported for unselected pediatric cochlear implantation.

Pan (2022) reported a SR and meta-analysis of the safety and effectiveness of cochlear implantation for patients with large vestibular aqueduct deformity.[9] A total of five randomized controlled trials met inclusion criteria. There was low to high risk of bias for blinding of participants and personnel and low or unclear risk of bias for the other evaluated biases. Meta-analysis evaluated postoperative hearing ability and speech intelligibility rate between EVA patients and those with normal inner ear structure. No significant differences between groups were identified.

In 2014, Xu conducted a SR in Chinese to assess the efficacy and safety of cochlear implantation in deaf patients with inner ear malformations compared to deaf patients with normal inner ear structure, including 11 RTCs (n=655 patients).[10] In terms of postoperative complications, electrode impedance, behavior T-level, hearing abilities and speech discrimination; patients with mixed inner ear malformations, Mondini syndrome or EVA were not significantly different than controls. However, the reviewers concluded that additional larger controlled studies with longer follow-up may help to evaluate the efficacy of cochlear implantation for deaf patients with inner ear malformation more reliably.

Pakdaman (2012) conducted a SR to determine if abnormal cochleovestibular anatomy influences surgical and audiologic outcomes following cochlear implant (CI) surgery in children, including 22 studies.[11] Out of the 311 children included, 89 (29%) were diagnosed with EVA, considered to be a mild/moderate anomaly. Outcomes of CI surgery were analyzed based on the severity of the ear malformation (mild/moderate anomaly versus severe), and subgroup analyses were not performed based on the different malformations observed. The reviewers reported that severe inner ear dysplasia was associated with increased surgical difficulty and lower speech perception.

Nonrandomized Studies

There have been a number of case series and retrospective analyses published on the efficacy of cochlear implants in patients with EVA, all generally reporting an improvement of outcomes including various clinical scores for hearing improvement and scores measuring quality of life. These studies range in size from three to 47 cases.[12-22] Some of these studies have focused on pediatric patients, while others have included mixed patient populations and have not analyzed pediatric patients from adults in terms of outcomes. Overall, these studies report that outcomes in EVA patients are comparable to cochlear implant patients with no malformations, including similar risk of cerebrospinal fluid (CSF) gusher during cochlear implantation.

There is research indicating that the age of cochlear implantation for patients with EVA affects health outcomes. In 2013, Ko conducted a study (1) to assess health outcomes of Mandarin-speaking patients with EVA after cochlear implantation (CI); (2) to compare their performance with a group of CI users without EVA; (3) to understand the effects of age at implantation and duration of implant use on the CI outcomes.[23] Forty-two patients with EVA participating in this study were divided into two groups: the early group received CI before five years of age and the late group after five years of age. The patients with EVA with more than five years of implant use (18 cases) achieved a mean score higher than 80% on the most recent speech perception tests and reached the highest level on the CAP/SIR scales. The early group developed speech perception and intelligibility steadily over time, while the late group had a rapid improvement during the first year after implantation. The two groups, regardless of their age at implantation, reached a similar performance level. These patients do not necessarily need to wait until their hearing thresholds are higher than 90 dB HL or PB word score lower than 40% to receive CI. Similar results have been reported in small pediatric case series, indicating that if patients receive cochlear implants prior to becoming severely to profoundly deaf, that residual hearing is preserved.[12, 24]

In contrast to studies reporting favorable outcomes, one small retrospective study performed by Bichy in 2002 that reported better hearing outcomes in patients with EVA using hearing aid than those who had undergone cochlear implantation.[25] The analysis in this study included 16 children and adults with EVA that had undergone cochlear implantation and 10 children and adults undergoing treatment of progressive or fluctuant sensorineural hearing loss with the use of a hearing aid alone. Although the hearing aid group had a better mean pure-tone average (70.8 dB; SD 24.4) versus (107.0 dB; SD 21.7) for the cochlear implant group, the use of health utility indexes determined that greater net health benefit (including quality of life) was derived from cochlear implantation over hearing aids.

INFANTS UNDER AGE 12 MONTHS

The literature review focused on studies comparing the impact on hearing, speech development and recognition, and complication rates of implantation in infants younger than 12 months with those of older age groups. This includes the question of whether any early benefits that may occur in these very young patients later converge with those in older patients.

Systematic Reviews

Sbeih (2022) reported a SR that assessed the safety of cochlear implantation in children 12 months and younger.[26] A total of 18 studies met inclusion criteria. Major and minor complications were reported in 3.1% and 2.4% of patients, respectively. The authors noted that this is similar to rates of complications in older cohorts.

Two older SRs were identified that addressed CI in children under 12 months of age. The reviews, summarized below, reported few studies of CI in this age group compared with CI in children over one year of age. Both systematic reviews ranked the available studies as poor to fair due to heterogeneity in study participants and study designs, and high risk for potential bias. In addition, differences in outcomes between the age groups did not reach statistical significance.

In 2011 Forli reported similar findings in seven studies comparing CI implanted prior to one year of age with implantations performed after one year of age.[27] The studies precluded meta-analysis due to heterogeneity of age ranges analyzed and outcomes evaluated. While studies suggested improvements in hearing and communicative outcomes in children receiving implants prior to one year of age, between-group differences did not reach statistical significance. In addition, it is not certain whether any improvements were related to duration of cochlear implant usage rather than age of implantation. Nor is it clear whether any advantages of early implantation are retained over time.

In 2010, Vlastarakos conducted a SR of studies on bilateral cochlear implants in a total of 125 children implanted before one year of age.[28] The authors noted that follow-up times ranged from a median duration of 6 to 12 months and, while results seemed to indicate accelerated rates of improvement in implanted infants, the evidence available was limited and of lower quality. Additionally, the lack of reliable outcome measures for infants demonstrated the need for further research before cochlear implantation prior to one year of age becomes widespread.

Nonrandomized Studies

In March 2020, the FDA approved an expansion of the indications for Cochlear Americas' Nucleus 24 cochlear implant system for infants aged 9 to 12 months of age with bilateral profound sensorineural deafness who demonstrate limited benefit from appropriate binaural hearing aids. Previously, this device was approved for ages 12 months and older. According to the FDA's summary of safety and effectiveness data, approval was based on supporting evidence from a comprehensive literature review and a clinical feasibility study. The clinical feasibility study was a retrospective clinical analysis of 84 subjects implanted with cochlear implants between the ages of 9 and 12 months. Descriptive statistics were reported for time under anesthesia (unilateral: 2hrs 34min, bilateral: 4hrs 15min), estimated blood loss (unilateral: 10.75 cc, bilateral: 19.88 cc), time in recovery (unilateral: 2hr 18min, bilateral: 1hr 59min), and adverse events (Percent of subjects: 2.4% cerebral spinal fluid leak; 2.4% facial weakness; 2.4% infection; 7.1% minor post-op complication; 3.6% minor skin irritation; 3.6% otitis media; 2.4% seroma; 7.1% temperature regulation during procedure).

The supporting literature review identified 49 articles including 750 total (not necessarily unique) patients implanted with cochlear implants prior to 12 months of age. Safety results were reported on a per-study basis with no meta-analysis. Complication rates were reported between 1.5% and 10% except for two studies. One reported a rate of 29%, and the other reported on two techniques, one of which had a rate of 20.6% and the other 61.5%. Two studies compared complications across different age ranges. One reported similar complication rates across ages and the other reported higher rates for younger ages. The summary section states that the study findings support that the safety profile for cochlear implantation in pediatric patients who are implanted between 9 and 12 months of age is comparable to that of the currently approved population of age 12 months and older. Effectiveness results were reported on a per-study basis with no meta-analysis. No study

reported worse hearing outcomes for the early-implanted group and many reported significantly better outcomes for this group.

A 2017 retrospective study by Kalejaiye assessed surgical complications, operative times, and reoperation rates in 73 patients under one year of age.[30] They compared these patients, identified from the American College of Surgeons National Surgical Quality Improvement Program Pediatric database (2012-2013), with pediatric patients in the database above the age of one. They found that the patients under one year had higher readmission rates (6.9% vs. 2.7%) and longer mean operative times (191 minutes vs. 160 minutes), but no significant differences were noted in complication rate, postoperative length of stay, or reoperation rate.

In 2015, Guerzoni conducted a prospective study of 28 children with profound sensorineural hearing loss who were implanted early with cochlear implants (mean age at device activation: 13.3 months).[31] The investigators reported that at one-year follow-up, assertiveness and responsiveness scores were within the normal range of normal-hearing age-matched peers. Age at cochlear implant activation exerted a significant impact, with the highest scores associated to the youngest patients.

In 2011, Colletti reported on the 10-year results comparing 19 children with cochlear implants received between the ages of 2 to 11 months to 21 children implanted between 12-23 months and 33 children implanted between 24 to 35 months.[32] Within the first six months post-implantation, there was no significant difference among groups in Category of Auditory Performance testing but differences became significantly better in the infant group (early implantation) at the 12 and 36 month testing. Previously, Colletti reported on findings from 13 infants who had implants placed before 12 months.[33] The procedures were performed between 1998 and 2004. In this small study, the rate of receptive language growth for these early implant infants overlapped scores of normal-hearing children. This overlap was not detected for those implanted at 12 to 23 or 24 to 36 months.

In 2009 Ching published an interim report on early language outcomes of children with cochlear implants.[34] This study evaluated 16 children who had implants before 12 months of age compared to 23 who had implants after 12 months (specific time of implantation was not provided). The preliminary results demonstrated that children who received an implant before 12 months of age developed normal language skills at a rate comparable to normal-hearing children, while those with later implants performed at two standard deviations below normal. The authors noted that these results are preliminary, as there is a need to examine the effect of multiple factors on language outcomes and the rate of language development.

Johr (2008) highlighted the surgical and anesthetic considerations when performing cochlear implant surgery in very young infants.[35] This was an observational study and literature review by pediatricians at a tertiary children’s hospital in Switzerland. Surgical techniques and anesthetic management aspects of elective surgeries in small infants were analyzed in patients younger than one year of age undergoing cochlear implant surgeries. The results demonstrated that the age of the patient and the pediatric experience of the anesthesiologist, but not the duration of the surgery, are relevant risk factors. The authors concluded, “Further research is needed to provide more conclusive evidence that the performance outcome for children implanted before 12 months of age does not converge with the results of children implanted between 12 and 18 months.”

ADULTS AND CHILDREN OVER AGE 12 MONTHS; BILATERAL HEARING LOSS

Since there is sufficient evidence that bilateral and unilateral cochlear implants are safe and lead to improvements in health outcomes in adults and children over the age of twelve months with bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, the evidence reviewed below will be focused on systematic reviews and randomized studies. Nonrandomized studies will not be described in detail.

Systematic Reviews

The following is a summary of the most recent SRs related to CI. These reviews included a critical analysis of the quality of the included studies. While noting the heterogeneity of the studies, and the potential for bias, these reviews found that the studies consistently reported beneficial outcomes for both bilateral and unilateral CI in select children and adults compared with no hearing devices or with conventional hearing aids.

Adults

A technology assessment published by Health Quality Ontario in 2018 evaluated bilateral cochlear implantation in adults and children in separate analyses.[36] The literature search conducted through March 2017 identified 10 studies on bilateral cochlear implantation in adults: three RCTs and seven prospective observational studies. Two of the three RCTs included data from a single RCT and compared simultaneous bilateral with unilateral cochlear implantation for severe bilateral sensorineural hearing loss. The third RCT randomized 24 adult patients with severe bilateral sensorineural hearing loss to receive bilateral implantation immediately or after a six-month waiting period. The observational studies performed within- or between-patient comparisons of bilateral cochlear implantation with unilateral cochlear implantation with or without hearing aids in the nonimplanted ear. Study quality was evaluated using the GRADE system. The quality of the RCTs was high, medium, and low and the quality of the prospective observational studies ranged from very low to low. The GRADE of evidence for adults overall was rated moderate to high. Overall, the authors concluded that bilateral cochlear implantation improved sound localization, speech perception in noise, and subjective benefits of hearing and that the safety profile was acceptable.

In a meta-analysis, McRackan (2018) examined the impact of cochlear implantation on quality of life (QOL).[37] From 14 articles with 679 CI patients who met the inclusion criteria, pooled analyses of all hearing-specific QOL measures revealed a very strong improvement in QOL after cochlear implantation (standardized mean difference [SMD]=51.77). Subset analysis of CI-specific QOL measures also showed very strong improvement (SMD=51.69). Thirteen articles with 715 patients met the criteria to evaluate associations between QOL and speech recognition. Pooled analyses showed a low positive correlation between hearing-specific QOL and word recognition in quiet (r=50.213), sentence recognition in quiet (r=50.241), and sentence recognition in noise (r=50.238). A subset analysis of CI-specific QOL showed similarly low positive correlations with word recognition in quiet (r=50.213), word recognition in noise (r=50.241), and sentence recognition in noise (r=50.255) between QOL and speech recognition ability. Using hearing-specific and CI-specific measures of QOL, patients report significantly improved QOL after cochlear implantation. This study is limited in that widely used clinical measures of speech recognition are poor predictors of patient-reported QOL with CIs.

In a meta-analysis, McRackan (2018) aimed to determine the change in general health-related quality of life (HRQOL) after cochlear implantation and association with speech recognition.[38] Twenty-two articles met criteria for meta-analysis of HRQOL improvement, but 15 (65%) were

excluded due to incomplete statistical reporting. From the seven articles with 274 CI patients that met inclusion criteria, pooled analyses showed a medium positive effect of cochlear implantation on HRQOL (SMD=0.79). Subset analysis of the HUI-3 measure showed a large effect (SMD=0.84). Nine articles with 550 CI patients met inclusion criteria for meta-analysis of correlations between non-disease specific PROMs and speech recognition after cochlear implantation (word recognition in quiet [r=0.35], sentence recognition in quiet [r=0.40], and sentence recognition in noise [r=0.32]). Some limitations are, though regularly used, HRQOL measures are not intended to measure nor do they accurately reflect the complex difficulties facing CI patients. Only a medium positive effect of cochlear implantation on HRQOL was observed along with a low correlation between non-disease specific PROMs and speech recognition. The use of such instruments in this population may underestimate the benefit of cochlear implantation.

In 2013, the authors of the 2011 AHRQ technology assessment reported the following findings of an updated systematic review of studies published through May 2012:[39]

- Unilateral cochlear implants

  Sixteen (of 42) studies were of unilateral cochlear implants. Most unilateral implant studies showed a statistically significant improvement in mean speech scores as measured by open-set sentence or multi-syllable word tests. A meta-analysis of four studies revealed a significant improvement in cochlear-implant relevant quality of life (QOL) after unilateral implantation. However, these studies varied in design and there was considerable heterogeneity observed across studies, making it difficult to compare outcomes across studies.

- Bilateral cochlear implants

  Thirteen studies reported improvement in communication-related outcomes with bilateral implantation compared with unilateral implantation and additional improvements in sound localization compared with unilateral device use or implantation only. The risk of bias varied from medium to high across studies. Based on results from at least two studies, the QOL outcomes varied across tests after bilateral implantation. A meta-analysis was not performed because of heterogeneity in design between the studies.

In 2012 and 2013 Crathorne and van Schoonhoven, respectively, published updated SRs for the National Institute for Health and Care Excellence (NICE). Included studies were from the U.S. and Europe and compared bilateral with unilateral cochlear implants. In two studies the unilateral implant group also had an acoustic hearing aid for the contralateral ear. Neither systematic review was able to conduct a meta-analysis due to the heterogeneity of the studies and the level of evidence of the studies which was rated as moderate-to-poor.

In October 2011, Berrettini published results of a systematic review of unilateral and bilateral cochlear implant effectiveness in adults.[40]

- Unilateral cochlear implants

  Eight articles on unilateral cochlear implants in advanced age patients were included. All of the studies reported benefits with cochlear implantation despite advanced age at time of implant (age 70 years or older). In six studies, results were not significantly different between younger and older patients. However, two studies reported statistically significant

inferior perceptive results (e.g., hearing in noise test and consonant nucleus consonant test) in older patients. This systematic review also examined three studies totaling 56 adults with pre-lingual deafness who received unilateral cochlear implants. The authors concluded unilateral cochlear implants provided hearing and quality-of-life benefits in prelingually deaf patients, but results were variable.

- Bilateral cochlear implants

  Thirteen articles on bilateral cochlear implants were reviewed. Sound localization improved with bilateral cochlear implants compared with monaural hearing in six studies. Significant improvements in hearing in noise and in quiet environments with bilateral implants compared with unilateral implants were reported in ten studies and seven studies, respectively. Five of the studies reviewed addressed simultaneous implantation, five studies reviewed sequential implantation, and three studies included a mix of simultaneous and sequential implantation. However, no studies compared simultaneous to sequential bilateral implantation results, and no conclusions could be made on the timing of bilateral cochlear implantation.

In June 2011 the most recent technology assessment, by the Tufts Evidence-based Practice Center for the Agency for Health Care Research and Quality (AHRQ), reported the following findings on the effectiveness of unilateral and bilateral cochlear implants (CIs) in adults:[41]

- Unilateral cochlear implants

  The assessment examined 22 studies with 30 or more patients and concluded that, while the studies reviewed were rated as poor to fair quality, unilateral cochlear implants are effective in adults with sensorineural hearing loss. Pre- and post-cochlear implant scores on multi-syllable tests and open-set sentence tests demonstrated significant gains in speech perception regardless of whether a contralateral hearing aid was used along with the cochlear implant. Additionally, the assessment found generic and disease-specific health-related quality of life improved with unilateral cochlear implants. However, the available evidence was insufficient to draw conclusions on improvements in open-set sentence test scores (i.e., >40% and ≤50% or >50% and ≤60%), and any relationship between pre-implantation patient characteristics and outcomes [e.g., age, duration of hearing impairment, Hearing in Noise Test (HINT) scores and pre- or post-linguistic deafness.]

- Bilateral cochlear implants

  The technology assessment examined 16 studies published since 2004 which were determined to be of fair to moderate quality. The assessment concluded that bilateral cochlear implants provided greater benefits in speech perception test scores, especially in noise, when compared with unilateral cochlear implants with or without contralateral hearing aids. Significant binaural head shadow benefits were noted along with some benefit in binaural summation, binaural squelch effects, and sound localization with bilateral cochlear implants. However, it was unclear if these benefits were experienced under quiet conditions, although benefits increased with longer bilateral cochlear implant usage indicating a need for longer term studies. Hearing-specific quality of life could not be assessed because only one study evaluated this outcome. Additionally, although gains were experienced in speech perception using open-set sentences or multi-syllable tests

compared with unilateral cochlear implants or unilateral listening conditions, the evidence available on simultaneous bilateral implantation was found to be insufficient. The assessment noted longer term studies are needed to further understand the benefits with bilateral cochlear implantation and identify candidacy criteria given the risks of a second surgery and the destruction of the cochlea preventing future medical intervention.

Children

Vanstrum (2023) published a SR to characterize cochlear implant (CI) outcomes in patients with a confirmed clinical diagnosis of Waardenburg Syndrome (WS) which is a genetic condition associated with moderate to profound sensorineural hearing loss.[42] Twenty articles meeting inclusion criteria provided data on 192 WS patients and 210 CIs. The mean age at CI was 3.8 years (95% confidence interval [95%CI]; 3.1-4.5 years), and the mean duration of follow up was 5.2 years (95% CI; 3.4-7.0 years). Surgical complications were rare (11/210 implants, 5.2%) where gusher was the most common complication. Cochlear Implants yielded favorable hearing outcomes in 90% (95% CI; 84-94%) of cases and appear successful for those with temporal bone anomalies ($p = 0.04$). The authors concluded that CI had favorable hearing outcomes and low rates of surgical complications and had clinical benefits in patients with WS.

Bo (2023) evaluated 15 studies to assess the effect of cochlear implantation on auditory and speech performance outcomes of children with Auditory Neuropathy Spectrum Disorder (ANSD).[43] The evidence suggested that children with ANSD who received cochlear implants appeared to achieve similar improvements in their auditory and speaking abilities as children with non-ANSD sensorineural hearing loss. According to pooled data, the categories of auditory performance, speech recognition score, speech intelligence rating score, and open-set speech perception did not significantly differ between the ANSD and sensorineural hearing loss groups.

The technology assessment published by Health Quality Ontario in 2018 discussed above regarding its findings on adult implantation identified 14 studies (all prospective observational studies) on bilateral cochlear implantation in children.[36] Two studies included both sequential and simultaneous bilateral implantation while the rest evaluated sequential only. As for adults, overall, the authors concluded that bilateral cochlear implantation improved sound localization, speech perception in noise, and subjective benefits of hearing and that the safety profile was acceptable (GRADE of evidence: moderate to high). The authors additionally concluded that bilateral cochlear implantation allowed for better language development and more vocalization in preverbal communication in children (GRADE of evidence: moderate).

In a 2015 systematic review, Fernandes evaluated 18 published studies and two dissertations that reported hearing performance outcomes for children with ANSD and cochlear implants.[44] Studies included four nonrandomized controlled studies considered high quality, five RCTs considered low quality, and 10 clinical outcome studies. Most studies (n=14) compared the speech perception in children with ANSD and cochlear implants with the speech perception in children with sensorineural hearing loss and cochlear implants. Most of these studies concluded that children with ANSD and cochlear implants developed hearing skills similar to those with sensorineural hearing loss and cochlear implants; however, these types of studies do not allow comparisons of outcomes between ANSD patients treated with cochlear implants and those treated with usual care.

In a 2014 systematic review, Lammers summarized the evidence on the effectiveness of bilateral cochlear implantation compared with unilateral implantation among children with sensorineural hearing loss.[45] The authors identified 21 studies that evaluated bilateral cochlear implantation in children, with no RCTs identified. Due to the limited number of studies, heterogeneity in outcomes and comparison groups, and high risk for bias in the studies, the authors were unable to perform pooled statistical analyses, so a best-evidence synthesis was performed. The best-evidence synthesis demonstrated that there was consistent evidence indicating the benefit of bilateral implantation for sound localization. One study demonstrated improvements in language development, although other studies found no significant improvements. The authors noted that the currently available evidence consisted solely of cohort studies that compared a bilaterally implanted group with a unilaterally implanted control group, with only one study providing a clear description of matching techniques to reduce bias.

In 2013, Eze published a systematic review comparing outcomes for cochlear implantation for children with developmental disability with those without developmental disability.[46] The authors noted that while approximately 30% to 40% of children who receive cochlear implants have developmental disability and that evidence about outcomes in this group was limited. Their review included 13 studies that compared receptive or expressive language outcomes in children with cochlear implants with and without developmental disability. The included studies were heterogeneous in terms of comparator groups and outcome measures, precluding data pooling and meta-analysis. In a structured systematic review, the authors reported that seven of the eligible studies demonstrated a significantly poor cochlear implant outcome in children with developmental disability, while the remaining studies reported no significant difference in outcomes between the groups.

Humphriss (2013) published a systematic review evaluating outcomes after cochlear implantation among pediatric patients with auditory neuropathy spectrum disorder (ANSD), a sensorineural hearing disorder characterized by abnormal auditory brainstem response with preserved cochlear hair cell function as measured by otoacoustic emissions testing.[47] The authors identified 27 studies that included an evaluation of cochlear implantation in patients with ANSD, including 15 noncomparative studies, one that compared children with ANSD who received a cochlear implant with children with ANSD with hearing aids, and 12 that compared children with ANSD who received a cochlear implant with children with severe sensorineural hearing loss who received a cochlear implant. Noncomparative studies were limited in that most (11/15) did not include a measure of speech recognition before cochlear implantation. Among the comparative studies, those comparing cochlear implantation to “usual care”, typically a hearing aid, provided the most information about effectiveness of cochlear implantation among patients with ANSD; the one small study that used this design found no significant differences between the groups. Overall, the authors suggested that further RCT evidence is needed.

Randomized Trials

In 2016, Smulder conducted a small prospective multi-center randomized trial to evaluate the benefits of bilateral implants compared to unilateral implants in adults with postlingual deafness, including 38 patients.[48] At one-year follow-up, there were no significant differences between groups on the speech-in-noise or the consonant-vowel-consonant test. The bilaterally implanted group performed significantly better when noise came from different directions ($p < 0.001$) and was better able to localize sounds ($p < 0.001$) compared to the unilaterally

implanted group. These results were consistent with the patients' self-reported hearing capabilities. The results were consistent at a two year follow up, reported in 2017.[49]

Nonrandomized Studies

Adults

Numerous case series have been published on adult patients with bilateral cochlear implants.[50-58] Most but not all studies report slight to modest improvements in sound localization and speech intelligibility with bilateral cochlear implants especially with noisy backgrounds but not necessarily in quiet environments. In addition, depression scores improved in cochlear implant patients from pre-implantation to 12 months post-treatment (geriatric depression scale improvement: 31%, 95% CI 10% to 47%) in a prospective observational study including 113 patients with postlingual hearing loss, of whom 50 were treated with cochlear implants and 63 with hearing aids.[59]

When reported, the combined use of binaural stimulation improved hearing in the range of one to four decibels or 1 to 2%. While this improvement seems slight, any improvement in hearing can be considered beneficial in the deaf. However, this improvement may not outweigh the significant risks of a second implantation. In addition, similar binaural results can be achieved with a contralateral hearing aid, assuming the contralateral ear has speech recognition ability. A number of studies have reported benefits for patients with a unilateral cochlear implant with hearing aid (HA) in the opposite ear.

Children

Several recent publications have evaluated bilateral cochlear implants in children.[60-62] These studies, ranging in size from 91 to 961 patients, generally report improved speech outcomes with bilateral implantation, compared with unilateral implantation. In a retrospective case series of 73 children and adolescents who underwent sequential bilateral cochlear implantation with a long (>five year) interval between implants, performance on the second implanted side was worse than the primary implanted side, with outcomes significantly associated with the interimplant interval.[53, 57, 63-69]

Adults and Children

Ching (2006) subsequently reported on 29 children and 21 adults with unilateral cochlear implant and a contralateral hearing aid.[51] They noted that both children and adults localized sound better with bilateral inputs.

UNILATERAL HEARING LOSS OR SINGLE SIDED DEAFNESS WITH OR WITHOUT TINNITUS

The FDA has approved the use of two cochlear implant devices in patients with single sided deafness (SSD) or unilateral hearing loss (UHL).

Systematic Reviews

Daher (2023) completed a SR to assess spatial hearing, tinnitus, and quality-of-life outcomes in adults with single-sided deafness (SSD) with cochlear implantation. A total of 36 studies evaluating CI use in 796 unique adults with SSD (51.3 ± 12.4 yr of age at time of implantation) were included. The mean duration of deafness was 6.2 ± 9.6 years. There was evidence of

improvement for speech recognition in noise using different target-to-masker spatial configurations, with the largest benefit observed for target-to-masker configurations assessing head shadow (mean,1.87-6.2 dB signal-to-noise ratio). Sound source localization, quantified as root-mean-squared error, improved with CI use (mean difference [MD], -25.3 degrees; 95% confidence interval [95% CI], -35.9 to -14.6 degrees; $p < 0.001$). Also, CI users reported a significant reduction in tinnitus severity as measured with the Tinnitus Handicap Inventory (MD, -29.97; 95% CI, -43.9 to -16.1; $p < 0.001$) and an improvement in spatial hearing abilities as measured with the Spatial, Speech, and Qualities of Hearing questionnaire (MD, 2.3; 95% CI, 1.7 to 2.8; $p < 0.001$).The authors conclude that CI use offer improvements in speech recognition in noise, sound source localization, tinnitus, and perceived quality of life in adults with SSD.

Idriss (2022) published a SR evaluating the effectiveness of cochlear implants in single-sided deafness with disabling tinnitus when conventional treatments fail to alleviate tinnitus.[70] A total of 31 studies were included and were divided into two categories according to whether tinnitus was assessed as a primary complaint or not. In all studies, cochlear implantation, evaluated using subjective validated tools, succeeded in reducing tinnitus significantly. A short-(3 months) and long-(up to 72 months) term tinnitus suppression was reported. When the cochlear implant is disactivated, complete residual tinnitus inhibition was reported to persist up to 24 h. The results followed a similar pattern in studies where tinnitus was assessed as a primary complaint or not. The results followed a similar pattern in studies where tinnitus was assessed as a primary complaint or not. The authors conclude that cochlear implantation is effective in reducing disabling tinnitus in single-sided deafness patients. The studies included were mostly observational, there was heterogeneity of assessment tools used and a small sample size.

Oh (2022) reported on a SR and meta-analysis of cochlear implantation in adults with single-sided deafness.[71] A total of 50 studies with 674 patients (3 to 45 patients meeting inclusion criteria per study) were included. Of these, 41 were prospective cohort studies, seven were retrospective cohort studies, and two were case series. A meta-analysis of speech perception outcomes, which included five studies, found a standardized mean difference (SMD) post-versus pre-implantation of 2.8 (95% CI 2.16 to 3.43), with some evidence of publication bias. A meta-analysis of QoL, which included eight studies, found a significant improvement, with an SMD of 0.68 (95% CI 0.45 to 0.91), and no evidence of publication bias. Meta-analysis of sound localization (seven studies; SMD, -1.13 [95% CI -1.68 to -0.57]), and tinnitus score reduction (seven studies; SMD -1.32 [95% CI -1.85 to -0.80]) also reported significant improvements. Limitations include the small sample sizes of included studies, imprecise definitions of single-sided deafness used across studies, and heterogeneity in outcomes measured, follow-up time frames, and etiology of single-sided deafness.

Donato (2021) published a SR with meta-analysis evaluating the efficacy of bone conduction devices and cochlear implantation in single-sided deafness, through the evaluation of speech discrimination in noise, sound localization and tinnitus suppression.[72] As a secondary outcome, patient satisfaction is also assessed. Nineteen articles with a total of 210 patients (95 patients with bone conduction devices and 115 in the cochlear implantation group) were included. Both children and adults were included. Sound localization was significantly better with CI with an average improvement of 13.9 degrees compared to an average of 2.31 degrees with BCD. For tinnitus, symptoms were decreased an average of 37.97 points for CI patients and decreased an average of 9.89 points for patients with BCD. The CI group reported statistically significant improvements overall, in ease of communication, and in

reverberation subscales. The BCD group reported statistically significant improvements for sound discrimination in noise. The authors conclude that both CI and bone conduction devices are effective in patients with single sided deafness. They also suggest that BCD should continue to be considered in the treatment of these patients because patient satisfaction is greater in environments with background noise. And that BCD is associated with a faster and more comfortable rehabilitation process.

Assouly (2021) published a systematic review of cochlear implantation for tinnitus.[73] A total of seven prospective cohort studies, with 105 total subjects (range 10 to 26) met inclusion criteria. Two studies had a moderate risk of bias and five had serious risk of bias. Due to considerable methodological and statistical heterogeneity (I^2>75%), no meta-analysis was performed. Each included study reported a statistically significant improvement in tinnitus distress (measured via questionnaire). The only reported adverse event was worsening of tinnitus loudness following implantation in one participant.

Benchetrit (2021) published a systematic review and meta-analysis evaluating audiological and patient-reported outcomes in children <18 years with single-sided deafness (SSD).[74] Twelve observational studies evaluating 119 children (mean age [standard deviation], 6.6 [4.0] years) were included. Clinically meaningful improvements in speech perception in noise (39/49 [79.6%]) and in quiet (34/42 [81.0%]) were reported. Sound localization improved significantly following implantation (mean difference [MD], -24.78°; 95% CI, -34.16° to -15.40°; I^2 = 10%). Compared to patients with congenital SSD, patients with acquired SSD and shorter duration of deafness reported greater improvements in speech and hearing quality. Patients with longer duration of deafness were also more likely to be device nonusers (MD, 6.84; 95% CI, 4.02 to 9.58).

A health technology assessment was published in 2020 to evaluate clinical benefits and harms, cost-effectiveness, budget impact, and patient preferences and values related to implantable devices for single-sided deafness and conductive or mixed hearing loss. [75] For adults and children with single-sided deafness, cochlear implantation when compared with no treatment improves speech perception in noise (% correct responses: 43% vs. 15%, p < .01; moderate grade), sound localization (localization error: 14° vs. 41°, p < .01; moderate grade), tinnitus (Visual Analog Scale, loudness: 3.5 vs. 8.5, p < .01; moderate grade), and hearing-specific quality of life (Speech Spatial and Qualities of Hearing Scale, speech: 5.8 vs. 2.6, p = .01; spatial: 5.7 vs. 2.3, p < .01; moderate grade); for children, speech and language development also improve (moderate grade). The authors conclude that based on evidence of moderate quality, cochlear implantation implants and bone-conduction implants improve functional and patient-important outcomes in adults and children with single-sided deafness and conductive or mixed hearing loss. And that among people with single-sided deafness, cochlear implants may be cost-effective compared with no intervention, but bone-conduction implants are unlikely to be.

Levy (2020) published a systematic review of cochlear implantation for tinnitus in SSD.[76] A total of 17 studies including 247 patients met inclusion criteria. The mean age was 50.2 years (range 23 to 71). Tinnitus outcomes were measured using the Tinnitus Handicap Inventory (THI). Based on six studies, an improvement of 35.4 points (95% CI -55.8 to -15.0, p<0.001) was reported. Based on 13 studies reporting on subjective improvement, with proportions weighted based on patients per study, 14.9% (CI 6.4 to 26.1) of patients reported complete resolution of tinnitus, 74.5% (CI 63.1 to 84.5) reported partial improvement; 7.6% (CI 4.1 to

12.6) of patients had no change in severity, and 3.0% (CI 1.0 to 6.7) reported worsening of their tinnitus.

A 2019 SR published by Peter identified 13 studies that met inclusion criteria and evaluated the influence of cochlear implantation on tinnitus in patients with single-sided deafness.[77] All identified studies were cohort studies. They mainly reported tinnitus questionnaire scores using the THI. Overall, of the 153 included patients, 34.2% demonstrated complete suppression, 53.7% demonstrated an improvement, 7.3% demonstrated a stable value, and 4.9% showed an increase of tinnitus. No patients reported an induction of tinnitus.

Peters (2016) and Cabral (2016) published SRs evaluating the effectiveness of cochlear implants in all ages[78] and in children[79] with unilateral hearing loss. Both reviews were inconclusive as there was significant clinical heterogeneity within the studies, primarily prospective or case series studies with small sample sizes, and the lack of high level of evidence. Both indicate the need for further research.

In 2015, van Zon published a systematic review of studies evaluating cochlear implantation for single-sided deafness or asymmetric hearing loss.[80] The authors reviewed 15 studies, nine of which (n=112 patients) were considered high enough quality to be included in data review. The authors identified no high-quality studies of cochlear implantation in this population. Data were not able to be pooled for meta-analysis due to high between-study heterogeneity, but the authors conclude that studies generally report improvements in sound localization, quality of life scores, and tinnitus after cochlear implantation, with varying results for speech perception in noise.

In 2014, Vlastarakos published a systematic review of the evidence related to cochlear implantation for single-sided deafness.[81] The authors included 17 studies, including prospective and retrospective comparative studies, case series and case reports that included 108 patients. The authors report that sound localization is improved after cochlear implantation, although statistical analysis was not included in some of the relevant studies. In most patients (95%), unilateral tinnitus improved. The authors note that most of the studies included had short follow-up times, and evaluation protocols and outcome measurements were heterogeneous.

In 2014, Blasco and Redleaf published a systematic review and meta-analysis of studies evaluating cochlear implantation for unilateral sudden deafness.[82] The review included nine studies with a total of 36 patients. In pooled analysis, subjective improvement in tinnitus occurred in 96% of patients (of 27 assessed), subjective improvement in speech understanding occurred in 100% of patients (of 16 assessed), and subjective improvement in sound localization occurred in 87% of patients (of 16 assessed). However, the small number of patients in which each outcome was assessed limits any conclusions that may be drawn.

Randomized Trials

Marx (2021) conducted a small open-label, multicenter RCT of cochlear implantation (n=25) versus initial observation and treatment abstention (n=26) in adult patients with single-sided deafness or asymmetric hearing loss following failure of prior treatment with contralateral routing of the signal (CROS) hearing aids or bone-conduction devices.[83] Primary outcomes included HRQOL, auditory-specific quality of life, and tinnitus severity as assessed after six months of treatment. Both EQ-5D visual analog scale and auditory-specific quality of life indices significantly improved in the cochlear implant arm. However, no significant difference in

overall EQ-5D descriptive component scores were noted between groups. Mean improvement was most pronounced in subjects with associated severe tinnitus. A clinical rationale for the minimum clinical improvement in quality of life (0.8 SD) was not reported. No significant difference for speech recognition in noise or horizontal localization was noted between groups at six months, indicating no significant effect on binaural hearing within this timeframe.

Peters (2021) randomized 120 adults with single-sided deafness (median duration, 1.8 years) into three treatment groups for the "Cochlear Implantation for siNGLE-sided deafness" (CINGLE) trial: cochlear implant (n=29); first bone-conduction devices, then CROS (n=45); and first CROS, then bone-conduction devices (n=46).[84] Patients with a maximum 30 dB hearing loss in the best ear and a minimum 70 dB hearing loss in the poor ear with duration of single-sided deafness between 3 months and 10 years were eligible for inclusion. After the initial cross-over period, 25 patients were allocated to bone-conduction devices, 34 patients were allocated to CROS, and 26 patients preferred no treatment. Seven patients did not receive their allocated treatment. For the primary outcome, speech perception in noise from the front, a statistically significant improvement was noted for the cochlear implant group at three and six months compared to baseline. At three months follow-up, the cochlear implant group performed significantly better than all other groups. At six months, the cochlear implant group performed significantly better than the bone-conduction devices and no treatment groups but no significant difference was observed between the cochlear implant group and the CROS group. Sound localization improved in the cochlear implant group only. All treatment groups improved on disease-specific quality of life compared to baseline. The study is limited by small sample size, device heterogeneity, loss to follow-up, and lack of allocation concealment. Study follow-up through five years is ongoing.

Nonrandomized Studies

Arras (2022) published a study comparing spatial hearing skills in children (n=47) across three groups: 12 SSD + CI (median age 4.7 years, range 3.9 to 7.7 years), 9 SSD-no CI (median age 4.8 years, range 3.9 to 7.0 years), and 26 normal hearing (median age 5.3 years, range 3.9 to 8.1 years).[85] Most SSD + CI children had approximately 3 years of experience with their CI at the time of their first assessment (median time 3.1 years). Only the child with acquired SSD had less than 2.5 years of experience with the device when first tested (1.9 years). The authors conclude that the implanted group exhibited improved speech perception in noise abilities and better sound localization skills, compared to their non-implanted peers. On average, the children wore their device approximately nine hours a day. They recommend further follow-up to understand the long-term benefit of a cochlear implant for children with prelingual SSD. The study is limited sample size and heterogeneity of the participant groups.

Brown (2022) published results from the Childhood Unilateral Hearing Loss (CUHL) prospective, single-arm trial.[86] Twenty children aged 3-12 with moderate to profound sensorineural hearing loss and poor speech perception (word score <30%) in one ear and normal hearing in the contralateral ear were enrolled. CNC word score perception in quiet improved significantly from 1% to 50% (p<.0001) at 12 months after activation. Speech perception in noise by BKB-SIN score also significantly improved by 3.6 dB in head shadow (p<.0001), 1.6 dB in summation (p=.003), and 2.5 dB in squelch (p=.0001). By 9 months, localization improved by 26°. Significant improvements were also found in SSQ speech (p=.0012), qualities of hearing (p=.0056), and spatial hearing subscales (p<.0001). Improvements in fatigue were not statistically significant. Study limitations include use of a

single-arm study design, small sample size, and incomplete comparison to best-aided hearing at baseline, including enrollment of never aided subjects.

In January of 2022, the FDA approved to expand the indication for the Nucleus 24 Cochlear Implant system to include individuals aged five years and older with single-sided deafness (SSD) or asymmetric hearing loss (AHL).[87] Data were combined from a feasibility study (n=10) and RWE (n = 32) conducted across four sites. There were 23 subjects with post-operative data available for the first co-primary endpoint, and 38 with data available for the second co-primary endpoint. The authors concluded that the effectiveness data demonstrated that for most subjects, the cochlear implant provided clinical benefit both in noise and with localization.

Benitez (2021) conducted a retrospective case review study to determine the effect of CI in patients with SSD of different age groups.[88] Twenty-three post-lingually deaf children (ages 6-12 years) and 21 adult patients with single-side deafness were included. The authors reported the results as follows: In children the most common etiology was idiopathic sensory-neural hearing loss. Children showed positive results in the Auditory Lateralization Test. In the Speech Test, word recognition in noise improved from 2% preoperatively to 61.1% at a mean follow-up of 1 year (S0 condition) in children [test with signal in CI side 60% and signal normal hearing side (plugged) 31%]. For adults, the most common etiology was idiopathic sudden sensorineural hearing loss (SNHL). Positive results in the Auditory Lateralization Test were found. With respect to the Speech Test in quiet conditions: Word recognition in noise improved from 5.7% preoperatively to 71.8% at a mean follow-up of 1 year [test with signal in CI side 68% and signal normal hearing side (plugged) 41%]. No adverse events were reported during the study period. No differences were found between children and adults in all tests in this study. The authors conclude that Cochlear implantation in post-lingually deaf adults and children with SSD can achieve a speech perception outcome comparable with CI in conventional candidates. They also note that careful patient selection and counseling regarding potential benefits are important to optimize outcomes.

Rauch (2021) published the results of a retrospective study to investigate the audiological improvement, subjective benefit (parents/caregivers and children), identify long-term non-users outcome and identify critical age of cochlear implantation in congenital SSD.[89] Children (n=11) with congenital SSD were implanted with a CI. The authors report that nine children use their CI (> 8 h/day) and two became nonusers. In children aged below 3 years and 2 months at surgery, there was a substantial long-term increase in speech discrimination and subjective benefit. Children over 4 years and 4 months at CI surgery improved partially in audiological/subjective measurements. Among children above 5 years, the SSQ score did not improve despite further slight improvement in speech discrimination long-term. The authors conclude a critical age for CI surgery below 3 years in children with congenital SSD for successful hearing rehabilitation.

Poncet-Wallet (2020) conducted a multicentered prospective, non-randomized intervention study to investigate the audiological and tinnitus outcomes of cochlear implantation (CI) in adults with single-sided deafness (SSD) and tinnitus.[90] Twenty-six patients (from six clinics) with SSD and incapacitating tinnitus (Tinnitus Handicap Inventory [THI] >58) underwent cochlear implantation. The first month of white noise stimulation triggered a significant improvement in THI scores (72±9 to 55±20, $p<0.05$). After 1 year of standard CI stimulation, 23 patients (92%) reported a significant improvement in tinnitus. This improvement started 1 to 2 months after CI and exceeded 40% improvement for 14 patients (54%). Average speech-in-

noise perception after 1 year significantly improved for the 23 patients who completed these measures. The authors conclude that CI is efficacious to reduce the handicap of patient with SSD and incapacitating tinnitus, leading to a decrease in reported tinnitus and partial restoration of binaural hearing abilities.

Dillon (2020) conducted a prospective clinical trial evaluating 20 subjects with asymmetric hearing loss (AHL), defined as a hearing loss of ≥ 70 dB HL in the ear to be implanted and between 35 and 55 dB HL in the contralateral ear.[91] Patients were required to fail initial treatment with traditional or bone-conduction hearing aids. Subjects underwent cochlear implantation with the MED-EL Synchrony Standard electrode array. Significant subjective benefit was reported by patients within one month of implantation. At the 12-month interval, spatial hearing localization was significantly improved ($p<0.001$). Masked sentence recognition was found to improve at the 12-month interval in the SoNcontra configuration ($p<0.001$), but there was no significant difference in the SoNo or SoNci spatial configurations. Subjects demonstrated a significant improvement in CNC word recognition between one and six months ($p=0.002$) and 6 and 12 months ($p=0.010$). Findings were compared with previously published data for patients in the unilateral hearing loss cohort of this study.[92] Significant main effects of cohort were found for localization performance and spatial configuration in masked sentence recognition, indicating that the magnitude of benefit for these outcomes was reduced for subjects with AHL.[91] In 2019, Dillon published a clinical update reporting on the prevalence of low-frequency hearing preservation with the use of standard long electrode arrays (MED-EL Corporation) in a subset of 25 patients (12 with unilateral hearing loss) from earlier cohorts.[93] Unaided hearing thresholds at 125 Hz were compared between the preoperative and initial activation intervals in 24 participants to assess the change in low-frequency hearing. At activation, a significant elevation in the unaided hearing thresholds at 125 Hz was noted ($p<0.001$), with the majority of subjects (n=16) demonstrating no response to stimulus. The remaining nine participants maintained an unaided low-frequency hearing threshold of ≤ 95 dB, and 5/9 participants met the fitting criterion of ≤ 80 dB for electric-acoustic stimulation (EAS) at initial activation. An additional three participants demonstrated improvement in unaided low-frequency hearing thresholds at latter monitoring intervals. It is uncertain whether identifying patients with preservation of low-frequency hearing can help predict individuals that may benefit from EAS vs standard cochlear implants.

Galvin III (2019) reported data from on FDA-approved study of cochlear implantation in 10 patients with SSD.[94] Patients were implanted with the MED-EL Concerto Flex 28 device. Speech perception in quiet and noise, localization, and tinnitus severity were measured prior to implantation at one, three, and six months postactivation. Performance was assessed with both ears (binaural), with the implanted ear alone, and the normal hearing alone. No patient had previous experience with a contralateral routing of signal (CROS) or bone conduction device (BCD) system. Mean improvement for consonant-nucleus-consonant (CNC) word recognition vs baseline was 66.8%, 76.0%, and 84.0% at one, three, and six months postactivation, respectively. The normal hearing ear performed significantly better compared to the implanted ear for all outcome measures at all intervals ($p<0.05$). Audiological performance of the implanted ear at one, three, and six months postactivation was significantly better compared to baseline ($p<0.05$), with no significant difference across postactivation intervals ($p>0.05$). The change in root mean square error (RMSE) in localization with binaural listening postactivation reduced by 6.7, 7.6, and 11.5 degrees at one, three, and six months postactivation. Binaural performance was significantly improved compared to the normal hearing ear alone at all postactivation time intervals ($p<0.05$). Tinnitus visual analog scale (VAS) scores significantly decreased with the implant on at all postactivation time intervals

(p<0.05). Significant improvements on SSQ scores were reported for the Speech (p=0.003), Spatial (p<0.001), and Quality (p=0.034) subtests. Global scores were not reported. Adverse events were reported in 5/10 participants, including facial nerve stimulation, periorbital edema, mild postoperative balance disturbance, postauricular pain, and unresolved taste disturbance. The study is limited by small sample size.

Peter (2019) published the results of a Swiss multicenter study assessing cochlear implantation for use in adult patients in post-lingual single-sided deafness, defined as a hearing loss of 70 dB hearing level (HL) in the mean thresholds of 0.5, 1, 2, and 4 kHz in the affected ear, and 25 dB HL or better in the frequencies from 125 to 2 kHz and 35 dB HL or better from 4 to 8 kHz in the normally hearing contralateral ear.[95] A total of 10 patients were evaluated. Two years post-implantation, 90% of patients used their implant regularly for an average of more than 11 hours per day. Twelve months postactivation, speech from the front and noise at the healthy ear achieved a 2.7 dB improvement (p=0.0029). Speech to the implanted ear and noise from the front achieved a 1.5 dB improvement (p=0.018). The mean sound localization error of all participants was improved by 10.2 degrees (p=0.030) at 12 months postactivation. One participant experienced a loss in low-frequency residual hearing from surgery, resulting in poorer localization performance after surgery with an increased error of 11.3 degrees. Tinnitus severity decreased significantly 12 months postactivation from 41.2 points (SD 26.5) preoperatively to 23.0 points (SD 17.5; p=0.004) on the Tinnitus Handicap Inventory (THI). Quality of life measures showed a significant improvement on the global subscale of the WHO Quality of Life questionnaire (p=0.007). The Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ) indicated a significant improvement from 4.2 to 6 (p=0.004) in speech comprehension and from 3 to 5.3 (p=0.009) in spatial hearing. No significant difference was noted in the subscale qualities of hearing (6.2 to 6.9; p=0.13). The scores of the patients on the three subscales were significantly lower than for the normal hearing control group, with an average speech comprehension score of 8.7 (p=0.001), an average spatial hearing of 8.6 (p<0.001), and an average qualities of hearing score of 9.1 (p=0.005). Adverse events were not reported.

In July 2019, the FDA approved to expand the indication for the MED-EL Cochlear Implant System to include individuals aged five years and older with single-sided deafness (SSD) or asymmetric hearing loss (AHL). Approval was based on supporting evidence from a comprehensive literature review and a clinical feasibility study conducted at one site. In this prospective, non-blinded, repeated measures study, 40 subjects were implanted with the MED-EL CONCERT or SYNCHRONY Cochlear Implant System. Twenty patients each were enrolled into the SSD and AHL groups. All 20 patients completed testing in the SSD group. One patient withdrew from the AHL group and one patient had not yet completed follow-up at the time of data analysis. Patients were required to have previous experience of at least one month in duration with a conventional hearing aid, bone conduction device, or CROS device. Exclusion criteria included Meniere's disease with intractable vertigo, tinnitus as the primary concern for cochlear implantation, and severe or catastrophic score on the THI. Aided word recognition in the ear to be implanted was required to be 60% or less as measured with a 50-word CNC word list. Speech perception and localization were evaluated at baseline and at 1, 3, 6, 9, and 12 months post-operatively utilizing CNC word recognition and AzBio sentence tests. For patients in the AHL group, sound field testing was completed with a hearing aid in the contralateral ear. Quality of life measures included the SSQ, THI, and Abbreviated Profile of Hearing Aid Benefit (APHAB) scales. Primary effectiveness measures were comparisons of speech perception and localization performance between the bilateral, preoperative, unaided/best-aided condition and the bilateral, 12-month post-operative cochlear implant (CI) +

normal hearing (NH) or hearing aid (HA) condition. Nine device or procedure related adverse events were reported. Most frequently reported adverse events included vertigo/dizziness/imbalance (22.5%) and unrelated infection (7.5%). The data is limited by small sample size and including only adult subjects only and the effectiveness endpoints were not prespecified. Given these limitations, the clinical data collected from the UNC study are not sufficient on their own to support the generalization of the clinical outcomes to the proposed, intended adult and pediatric populations, and support the requested SSD/AHL indication expansion.

The FDA decision was further supported by a literature search yielding six publications comprising a total of 58 adults with SSD (n=50 of which implanted with MED-EL devices) and a total of 52 adults with AHL (n=37 of which implanted with MED-EL devices).[97] The candidacy criterion of ages five and older was based on a literature search yielding five publications comprising a total of 26 children with SSD (n=5 of which implanted with a MED-EL device) and a total of nine children with AHL. While the overall benefits of CI in children with SSD and AHL included improved performance in speech perception in quiet and noise, sound localization, and subjective measures of quality of life – these results are limited to primarily case series with small sample sizes, heterogeneous in methodology and outcome assessment, and at high risk of bias in self-reported measures. The FDA has required MED-EL to conduct a post-marketing study to continue to assess the safety and efficacy of the implant in a new enrollment cohort of adults and children.

Buss (2018) published the results of an FDA clinical trial that investigated the potential benefit of cochlear implant (CI) for use in adult patients with moderate-to-profound unilateral sensorineural hearing loss and normal to near-normal hearing on the other side.[92] The study population was 20 CI recipients with one normal or near-normal ear (NH) and the other met criterion for implantation (CI). All subjects received a MED-EL standard electrode array, with a full insertion based on surgeon report. They were fitted with an OPUS 2 speech processor. This group was compared to 20 normal hearing persons (control group) that were age-matched. Outcome measures included: sound localization on the horizontal plane; word recognition in quiet with the CI alone, and masked sentence recognition when the masker was presented to the front or the side of normal or near-normal hearing. The follow-up period was 12-months. While the majority of CI recipients had at least one threshold ≤ 80dB prior to implantation, only three subjects had these thresholds after surgery. For CI recipients, scores on consonant-nucleus-consonant (CNC) words in quiet in the impaired ear rose an average of 4% (0 to 24%) at the postoperative test to a mean of 55% correct (10 to 84%) with the CI alone at the 12-month test interval.

Arndt (2017) published a single center cohort study to provide evidence of successful treatment of SSD and asymmetric hearing loss with a CI compared to the untreated, monaural hearing condition and the therapy options of brain computer interface (BCI) and contralateral routing of signals (Bi)CROS devices.[98] A total of 85 patients (45 with SSD and 40 patients with asymmetric hearing loss) were treated with a CI. Monaural speech comprehension in noise and localization ability were examined with (Bi)CROS-Hearing Aid and BCI devices (on a test rod) both preoperatively and at 12 months after CI switch-on. At the same intervals, subjective evaluation of hearing ability was conducted using the Speech, Spatial and Qualities of Hearing Scale (SSQ). The authors report that binaural rehabilitation with CI was successful. Also, patients with long-term acquired deafness (>10 years) demonstrated a benefit from CI comparable to that observed in patients with shorter-term deafness.

A 2016 study from Sladen reported on a retrospective review of prospectively-collected data of short-term (six-month) follow-up for 23 adults and children with single-sided deafness from a variety of mechanisms who received a cochlear implant.[99] In the implanted ear, CNC word recognition improved significantly from pre-implantation to three months post-activation (P=0.001). However, for AzBio sentence understanding in noise (+5 dB signal-to-noise [SNR]), there was no significant improvement from pre-implantation to six months post-activation.

Also in 2016, Rahne reported on a retrospective review of four children and 17 adults with single-sided deafness treated with cochlear implants and followed for 12 months.[100] Sound localization with aided hearing improved from pre-implantation to aided hearing for all individuals. The Speech recognition threshold in noise (signal-to-noise) ratio improved from -1.95 dB (CI off, SD: 2.7 dB) to -4.0 dB after three months (SD 1.3 dB, P<0.05), with continued improvements through six months.

In 2016, Mertens reported a case series including 23 individuals who received cochlear implants for single-sided deafness with tinnitus.[101] Eligible patients had either single-sided deafness or asymmetric hearing loss and ipsilateral tinnitus. Subjects had a mean eight years of experience with their cochlear implant (range, 3 to 10 years). Patients demonstrated improvements in VAS from baseline (mean score, 8) to one month (mean score: 4; p<0.01 vs baseline) and three months (mean score: 3; p<0.01 vs baseline) after the first fitting. Tinnitus scores improved from baseline to three months post fitting (55 vs 31, p<0.05) and were stable for the remainder of follow-up.

In 2015, Ramos Macias reported results of a prospective multicenter study with repeated measures related to tinnitus, hearing, and quality of life, among 16 individuals with unilateral hearing loss and severe tinnitus who underwent cochlear implantation.[102] All patients had a severe tinnitus handicap (THI score ≥ 58%). Eight (62%) of the 13 patients who completed the six-month follow-up visit reported a lower tinnitus handicap on the THI score. Perceived loudness/annoyingness of the tinnitus was evaluated with a 10-point VAS. When the CI was on, tinnitus loudness decreased from 8.4 preoperatively to 2.6 at the six-month follow-up; 11 of 13 patients reported a change in score of three or more.

In 2015, Arndt reported outcomes for 20 children who underwent cochlear implantation for single-sided deafness, which represented a portion of their center's cohort of 32 pediatric patients with single-sided deafness who qualified for cochlear implants.[103] Repeated-measure analyses of hearing data sets were available for 13 implanted children, excluding five who had undergone surgery too recently to be evaluated and two children who were too young to be evaluated for binaural hearing benefit. There was variability in the change in localization ability across the tested children. Self- (or child-) reported hearing benefit was measured with the Speech, Spatial and Qualities of Hearing Scale (SSQ). Significant improvements were reported on the child and parent evaluations for the scale's three subcategories: speech hearing, spatial hearing, hearing quality, and total hearing.

In 2013, Hansen reported results of a prospective study of cochlear implantation for severe-to-profound single-sided sensorineural hearing loss in 29 patients, 10 of whom had single-sided deafness due to Meniere's disease.[104] Performance was compared pre- to post-implant within each subject; outcomes were measured at three-, six-, and 12-months postoperatively. Patients showed significant improvements in CNC word and AzBio sentence scores showed improvement in the implanted ear pre-and post-implant. For the 19 patients with pre- and post-

operative data available, the average improvement on CNC word score was 28% (range: -26% to 64%). The average AzBio score improvement was 40% (range: -57% to 92%).

Tavora-Vieira (2013) reported results of a prospective case series that included nine post-lingually deaf subjects with unilateral hearing loss, with or without tinnitus in the ipsilateral ear, with functional hearing in the contralateral ear, who underwent cochlear implantation.[105] Speech perception was improved for all subjects in the “cochlear implant on” state compared with the “cochlear implant off” state, and subjects with tinnitus generally reported improvement.

Section Summary

The available evidence for the use of cochlear implants in improving outcomes for patients with single sided deafness or unilateral hearing loss, with or without tinnitus includes SRs, open label RCTs with small sample sizes, two feasibility studies, prospective and retrospective studies, and two guidelines (one for adults and one for children). The FDA recently approved two devices for cochlear implantation for UHL or SSD. Two feasibility studies with single-sided deafness or asymmetric hearing loss demonstrated improvements in sound perception, sound localization, and subjective measures of quality of life compared to baseline conditions. Although data is limited to small sample sizes and heterogeneity of methodology and outcome measures, the use of cochlear implant in SSD or UHL may improve outcomes such as speech recognition in noise, sound source localization, tinnitus, and perceived quality of life in some patients.

Cochlear Restoration

The optimal timing of cochlear implantation in children is of particular interest given the strong associations between hearing and language development. While there is current research investigating the ability to restore hearing by stimulating cochlear hair cell regrowth, cochlear implantation damages the cochlea and eliminates the possibility of cochlear restoration. However, the potential to restore cochlear function is not foreseeable in the near future; therefore, if implantation of cochlear implants is felt to be most beneficial at a younger age when the nervous system is “plastic”, this potential development seems too far in the future to benefit young children who are current candidates for a cochlear implant.

HYBRID COCHLEAR IMPLANTATION

Systematic Review

Santa Maria (2014) conducted a systematic review and meta-analysis of hearing outcomes after various types of hearing-preservation cochlear implantation, including implantation hybrid devices, cochlear implantation with surgical techniques designed to preserve hearing, and the use of post-operative systemic steroids.[106] The study included 24 studies, but only two studies focused specifically on a hybrid cochlear implant system, and no specific benefit from a hybrid system was reported.

Nonrandomized Studies

The pivotal trial for the Med-EL EAS system was a prospective, multi-center, non-randomized, non-blinded, repeated measures clinical study of 73 subjects at 14 U.S. sites, implanted with either SONATA FLEX24 or a PULSAR FLEX24.[4] Final outcomes were reported in 2018 by Pillsbury.[107] Sixty-seven of 73 subjects (92%) completed outcome measures at 3, 6, and 12 months postactivation. A 30 dB or less low-frequency pure-tone average shift was experience

by 79% and 97% were able to use the acoustic unit at 12 months postactivation. In the EAS condition, 94% of subjects performed similarly or demonstrated improvement (85%) compared to preoperative performance on City University of New York sentences in noise at 12 months. Ninety-seven percent of subject performed similarly or improved (85%) on CNC words in quiet. Improvements in speech perception scores were statistically significant ($p<0.001$). The Abbreviated Profiled of Hearing Aid Benefit (APHAB) was administered preoperatively and at 12 months postactivation; 60 subjects completed the APHAB assessment at each time point. The mean score on the APHAB Global Scale improved by 30.2%, demonstrating a significant reduction in perceived disability ($p<0.001$). Thirty-five device-related adverse events were reported for 29 of 73 subjects (39.7%). The most frequently observed adverse event was profound/total loss of residual hearing, which occurred in 8 of 73 subjects (11.0%).

The pivotal trial for the Nucleus® Hybrid™ L24 Cochlear Implant System, published by Roland in 2016, was a prospective, multi-center, one-arm, non-randomized, non-blinded, repeated-measures clinical study of 50 subjects at 10 U.S. sites.[108] Performance was compared pre- to post-implant within each subject; outcomes were measured at three-, six-, and 12-months postoperatively. Post-operatively, patients' hearing was evaluated in three states: Hybrid (simultaneous electric and acoustic stimulation in the implanted ear via the Hybrid L24 including the acoustic component), Bimodal (electric stimulation only using the Hybrid L24 minus the acoustic component with contralateral acoustic stimulation), and Combined (electric and acoustic stimulation via the Hybrid L24 and contralateral acoustic stimulation). Results from the Bimodal and Combined conditions were grouped into an "Everyday Listening" category, which was not prospectively defined by the manufacturer. All 50 subjects enrolled underwent device implantation and activation. One subject had the device explanted and replaced with a standard cochlear implant between the three- and six- month follow up visit due to profound loss of low frequency hearing; an additional subject was explanted before the 12-month follow up visit and two additional subjects were explanted after 12 months. For the two primary effectiveness endpoints, CNC word-recognition score and AzBio sentence-in-noise score, a measure of sentence understanding in noisy environments, there were significant within-subject improvements from baseline to six-month follow up. The mean improvement in CNC word score was 35.7% (95% confidence interval [CI] 27.8% to 43.6%); for AzBio score, the mean improvement was 32.0% (95% CI 23.6% to 40.4%) For safety outcomes, 71 adverse events were reported, most commonly profound/total loss of hearing (occurring in 44% of subjects) with at least one adverse event occurring in 34 subjects (68%).

Five-year outcomes for the pivotal trial were reported by Roland in 2018.[109] Thirty-two out of 50 subjects (64%) enrolled in the postapproval study. Out of the 18 subjects who did not participate, six had been explanted and reimplanted with a long electrode array, two discontinued for unrelated medical reasons, two withdrew for other reasons, four declined to continue follow-up evaluations, and four chose not to participate in the postapproval study. At five years postactivation, 94% of subjects had measurable hearing and 72% continued to use electric-acoustic stimulation with functional hearing in the implanted ear, and 6% had a total loss. Changes from pre-operate hearing to six months were statistically significant ($p<0.001$), but changes six months through five years postactivation were not statistically different ($p>0.05$). Acoustic component amplification was utilized by 84% and 81% of patients at 12 and three years postactivation, respectively. Mean CNC word recognition in quiet scores were significantly improved over the preoperative condition at each postactivation interval ($p<0.001$). However, mean scores did not significantly differ after 12 months postactivation. At five years postactivation, 94% performed the same or better in unilateral CNC word scores, whereas 6% demonstrated a decline in performance. For bilateral CNC word scores, 97% performed the

same or better, whereas one subject showed a decline in performance. The Speech, Spatial, and Qualities of Hearing Questionnaire (SSQ) was implemented to measure subjective implant satisfaction and benefit. Scores significantly improved and remained stable through all postactivation intervals ($p<0.001$).

In 2016, Gantz published outcomes from a multicenter, longitudinal study evaluating outcomes with the Nucleus Hybrid S8 featuring a shorter cochlear array.[110] Eighty-seven subjects received an implant. At 12 months postactivation, five subjects had total hearing loss, whereas functional hearing was maintained by 80%. CNC word scores demonstrated 82.5% of subjects had experience a significant improvement in the hybrid condition. Improvement in speech understanding in noise were demonstrated in 55% of subjects. Fourteen patients requested implant explantation due to various reasons of dissatisfaction with the device. These patients were re-implanted with a standard-length Nucleus Freedom cochlear implant. CNC scores prior to loss of residual hearing were missing for six subjects. CNC scores following re-implantation were missing for two additional subjects. Similar or better CNC scores following re-implantation were observed in five of the six remaining subjects.

In 2015, Friedmann conducted a retrospective review that included 22 subjects implanted with a cochlear implant with either a standard electrode (n=12) or the Nucleus Hybrid L24 electrode (n=10).[111] At one year post-implant, 30% patients with the Hybrid-L and 58% patients with the standard electrode lost residual acoustic hearing resulting in a profound hearing loss in the implanted ear. The authors reported that while hearing preservation rates with the hybrid electrode tended to be better, among recipients who lost residual hearing, speech perception was better in those with the longer standard electrode.

Lenarz (2013) reported results of a prospective multi-center European study evaluating the Nucleus Hybrid™ L24 system.[112] The study enrolled 66 adults with bilateral severe-to-profound high frequency hearing loss. At one year post-operatively, 65% of subjects had significant gains in speech recognition in quiet and 73% had significant gains in noisy environments. Compared with the cochlear implant hearing alone, residual hearing significantly increased speech recognition scores.

Gifford (2013) compared hearing outcomes pre- and post-implantation for 44 adult cochlear implant recipients with preserved low-frequency hearing in two test conditions: cochlear implant plus low-frequency hearing in the contralateral plus low-frequency hearing in the contralateral ear (bimodal condition) and cochlear implant plus low-frequency hearing in both ears (best-aided condition).[113] The authors reported that there were small but statistically significant differences in improvements in adaptive sentence recognition and speech recognition in a noisy “restaurant” environment, suggesting that the presence of residual hearing is beneficial.

A small number of studies in a small number of patients suggest that a hybrid cochlear implant system is associated with improvements in hearing of speech in quiet and noise. However, there are currently no available studies that compare the use of a standard hearing aid with a hybrid cochlear implant, which would be an appropriate comparison to determine if a hybrid device improves outcomes for patients who currently have hearing loss, but might not be candidate for a cochlear implant. In addition, there is only limited data to suggest that the preservation of residual hearing associated with a hybrid device is associated with improved outcomes compared with a standard cochlear implant.

Section Summary

Prospective and retrospective studies using a single-arm, within-subjects comparison pre- and postintervention have suggested that a hybrid cochlear implant system is associated with improvements in hearing of speech in quiet and noise. For patients who have high-frequency hearing loss but preserved low-frequency hearing, the available evidence has suggested that a hybrid cochlear implant improves speech recognition better than a hearing aid alone. Some studies have suggested that a shorter cochlear implant insertion depth may be associated with preserved residual low-frequency hearing, although there is uncertainty about the potential need for reoperation following hybrid cochlear implantation if there is a loss of residual hearing. Studies reporting on long-term outcomes and results of re-implantation are lacking.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY- HEAD AND NECK SURGERY

In 2020, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) published a revised position statement on cochlear implants. The Academy "considers unilateral and bilateral cochlear implantation as appropriate treatment for adults and children over 9 months of age with severe to profound hearing loss who have failed a trial with appropriately fit hearing aids."[114]

In 2020, the AAO-HNS published a position statement on pediatric cochlear implants.[115] The Academy states that "there is ample evidence that early cochlear implantation of children with sensorineural hearing loss (SNHL) for whom hearing aids provide inadequate access to sound is advantageous." The statement goes on to say that "Children with bilateral severe to profound SNHL (4-frequency PTA > 80 dB HL or 2-frequency PTA > 85) will not receive adequate benefit from amplification and are candidates for bilateral cochlear implantation. Children with this degree of SNHL, including infants between 6 and 12 months, should receive cochlear implants as soon as practicable."

AMERICAN ACADEMY OF AUDIOLOGY

In July 2019, the American Academy of Audiology published clinical practice guidelines on cochlear implants.[116] These guidelines include recommendations regarding cochlear implant evaluation. They recommend determining unaided air conduction and bone conduction thresholds using developmentally appropriate assessment measures. They additionally recommend determining auditory speech perception using appropriately fit amplification using developmentally appropriate assessment measures. Other recommendations are included regarding non-audiologic evaluation prior to implantation, and surgical and post-surgical roles for the audiologist.

AMERICAN COCHLEAR IMPLANT ALLIANCE TASK FORCE

In 2022 the American Cochlear Implant Alliance Task Force published two guidelines for clinical assessment and management of cochlear implantation for SSD. One for adults [117] and a separate guideline for children.[118] The guidelines for adults with SSD has16 recommendations for preoperative evaluation and post-activation assessment and management of adults with SSD, including:

1. It is recommended that individuals with sudden and/or rapid progression of SSD undergo standard medical workup and monitoring to determine if the hearing spontaneously improves or is recoverable with treatment, and that cochlear implantation should not occur earlier than 3 to 6 months after the sudden hearing loss to allow ample time for potential recovery of hearing. The potential exception to this is cases exhibiting evidence of progressive ossification (e.g., meningitis, after vestibular schwannoma resection, otic capsule fracture) where early implantation may be advantageous.

2. Consideration of the potential for significant bilateral hearing loss is warranted, as well as the benefits of early implantation of the impaired hearing ear for long-term performance benefit.

The guidelines for children with SSD include 13 recommendations for preoperative evaluation and post-activation assessment and management of adults with SSD, including:1. Cochlear implantation to address SSD in an ear with cochlear nerve deficiency is contraindicated. Accurate diagnosis of nerve deficiency is important because it is present in almost half of children with SSD. Therefore, high resolution 3D MRI of the internal auditory canals is recommended rather than computer tomography alone.

2. Cochlear implantation should be considered a priority for children at risk of hearing loss progression in the better hearing ear. Children with SSD due to bacterial meningitis should be implanted promptly.

3. Younger age at implantation is expected to be advantageous in children with SSD. Children with longer lengths of deafness may experience fewer benefits and should be counseled as such. The impact of age and length of deafness is not yet fully understood in this population.

4.A CI evaluation is recommended for children with a unilateral three frequency pure tone average (3FPTA) of >60 dB HL and/or an aided SII < 0.65 because these children are unlikely to receive adequate benefit from traditional amplification.

SUMMARY

There is enough research to show that cochlear implants improve health outcomes, specifically, speech reception (especially in noise) and sound localization, for some patients who have severe to profound bilateral sensorineural hearing loss. Therefore, cochlear implants may be considered medically necessary in specific patients with bilateral hearing loss who meet the policy criteria.

The current research on cochlear implantation in patients diagnosed with enlarged vestibular aqueducts (EVA) has limitations. Despite these limitations, there is enough research to show that cochlear implants improve health outcomes, specifically, speech recognition, for patients with EVA. In addition, early placement of cochlear implants avoids atrophy and preserves hearing patients with EVA with moderate hearing loss. Therefore, cochlear implants may be considered medically necessary in patients with EVA when policy criteria are met.

The current research on hybrid cochlear implant/hearing aid systems has limitations. Despite these limitations, there is enough research to show that hybrid cochlear implant/hearing aid

systems improve health outcomes, specifically, speech recognition, for patients aged 18 years or older who have high frequency sensorineural hearing loss with preserved low frequency hearing. Therefore, hybrid cochlear implant/hearing aid systems may be considered medically necessary in specific patients with high frequency sensorineural hearing loss with preserved low frequency hearing who meet the policy criteria.

There are currently no cochlear implants that have approval from the U.S. Food and Drug Administration (FDA) for use in patients who are younger than 9 months of age. There is not enough research to show that cochlear implants improve health outcomes in patients younger than 9 months of age and it is unclear that the benefits of early cochlear implantation outweigh the risk of surgery and anesthesia in these very young patients. In addition, there are no clinical practice guidelines from U.S. professional societies that recommend cochlear implantation in these very young patients. Therefore, cochlear implantation in patients younger than 9 months of age is considered not medically necessary.

The current research on cochlear implantation in patients diagnosed with unilateral hearing loss (UHL) including single sided deafness (SSD) or Asymmetric Hearing Loss (AHL) has limitations. Despite these limitations, there is enough research to show that cochlear implants improve health outcomes for patients with UHL. Therefore, cochlear implants may be considered medically necessary in patients with UHL when policy criteria are met.

Bilateral or unilateral cochlear implants and hybrid cochlear implant/hearing aid systems do not improve health outcomes in all people with hearing loss, bilateral or single sided. Therefore, cochlear implants and hybrid cochlear implant/hearing aid systems, bilateral or unilateral, are considered not medically necessary when the policy criteria are not met.

Implant replacement, including replacement parts or upgrades to existing cochlear implants and/or components may be considered medically necessary only in those patients whose response to the existing device is inadequate to the point of interfering with activities of daily living, including school or work. Replacement of an existing cochlear implant device is considered not medically necessary when the policy criteria are not met.

REFERENCES

1. U.S. Food and Drug Administration (FDA). Approval Letter: Nucleus Hybrid L24 Cochlear Implant System --P130016. 2014. [cited 3/11/2024]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130016a.pdf.
2. U.S. Food and Drug Administration (FDA). Approval Letter: Nucleus Hybrid L24 Cochlear Implant System - P970051/S205. 2022. [cited 3/11/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf/P970051S205A.pdf.
3. Food and Drug Administration (FDA) premarket approval application (PMA) letter for the MED-EL EAS. [cited 3/11/2024]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf/p000025s084a.pdf.
4. FDA Summary of Safety and Effectiveness Data for Med-EL EAS System. [cited 3/11/2024]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf/p000025s084b.pdf.

5. U.S. Food and Drug Administration (FDA). Approval Letter: MED-EL Cochlear - P000025/S104. 2019. [cited 3/11/2024]. 'Available from:' www.accessdata.fda.gov/cdrh_docs/pdf/P000025S104A.pdf.
6. 1995 NIH Consensus Conference: Cochlear Implants in Adults and Children. NIH Consens Statement Online 1995 May 15-17;13(2):1-30. [cited 3/11/2024]. 'Available from:' http://consensus.nih.gov/1995/1995CochlearImplants100html.htm.
7. (NIDCD) NNIoDaoCD. Enlarged Vestibular Aqueducts and Childhood Hearing Loss. [cited 3/11/2024]. 'Available from:' https://www.nidcd.nih.gov/health/enlarged-vestibular-aqueducts-and-childhood-hearing-loss.
8. Alahmadi A, Abdelsamad Y, Salamah M, et al. Cochlear implantation in adults and pediatrics with enlarged vestibular aqueduct: a systematic review on the surgical findings and patients' performance. *Eur Arch Otorhinolaryngol.* 2022;279(12):5497-509. PMID: 35771280
9. Pan L, Lin H, Li X, et al. Systematic review and meta-analysis of cochlear implantation in deaf patients with large vestibular aqueduct deformity. *Ann Palliat Med.* 2021;10(12):12598-606. PMID: 35016448
10. Xu Q, Zhai S, Han D, et al. [Meta-analysis of the efficacy of cochlear implantation in deaf patients with inner ear malformation]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery.* 2014;29(8):743-7. PMID: 26248452
11. Pakdaman MN, Herrmann BS, Curtin HD, et al. Cochlear implantation in children with anomalous cochleovestibular anatomy: a systematic review. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2012;146:180-90. PMID: 22140206
12. Vassoler TM, Bergonse Gda F, Meira Junior S, et al. Cochlear implant and large vestibular aqueduct syndrome in children. *Brazilian journal of otorhinolaryngology.* 2008;74(2):260-4. PMID: 18568206
13. Temple RH, Ramsden RT, Axon PR, et al. The large vestibular aqueduct syndrome: the role of cochlear implantation in its management. *Clinical otolaryngology and allied sciences.* 1999;24(4):301-6. PMID: 10472464
14. Pritchett C, Zwolan T, Huq F, et al. Variations in the cochlear implant experience in children with enlarged vestibular aqueduct. *The Laryngoscope.* 2015;125(9):2169-74. PMID: 25647353
15. Powell HR, Birman CS. Large vestibular aqueduct syndrome: Impedance changes over time with different cochlear implant electrode arrays. *Cochlear Implants Int.* 2015;16(6):326-30. PMID: 26098963
16. Loundon N, Rouillon I, Munier N, et al. Cochlear implantation in children with internal ear malformations. *Otol Neurotol.* 2005;26:668-73. PMID: 16015165
17. Lee KH, Lee J, Isaacson B, et al. Cochlear implantation in children with enlarged vestibular aqueduct. *The Laryngoscope.* 2010;120(8):1675-81. PMID: 20641086
18. Fahy CP, Carney AS, Nikolopoulos TP, et al. Cochlear implantation in children with large vestibular aqueduct syndrome and a review of the syndrome. *Int J Pediatr Otorhinolaryngol.* 2001;59:207-15. PMID: 11397503
19. Buchman CA, Copeland BJ, Yu KK, et al. Cochlear implantation in children with congenital inner ear malformations. *The Laryngoscope.* 2004;114(2):309-16. PMID: 14755210
20. Manzoor NF, Wick CC, Wahba M, et al. Bilateral Sequential Cochlear Implantation in Patients With Enlarged Vestibular Aqueduct (EVA) Syndrome. *Otol Neurotol.* 2016;37:e96-103. PMID: 26756161

21. Harker LA, Vanderheiden S, Veazey D, et al. Multichannel cochlear implantation in children with large vestibular aqueduct syndrome. *The Annals of otology, rhinology & laryngology Supplement.* 1999;177:39-43. PMID: 10214800
22. Bent JP, 3rd, Chute P, Parisier SC. Cochlear implantation in children with enlarged vestibular aqueducts. *The Laryngoscope.* 1999;109(7 Pt 1):1019-22. PMID: 10401833
23. Ko HC, Liu TC, Lee LA, et al. Timing of surgical intervention with cochlear implant in patients with large vestibular aqueduct syndrome. *PLoS One.* 2013;8:e81568. PMID: 24282608
24. Au G, Gibson W. Cochlear implantation in children with large vestibular aqueduct syndrome. *The American journal of otology.* 1999;20(2):183-6. PMID: 10100520
25. Bichey BG, Hoversland JM, Wynne MK, et al. Changes in quality of life and the cost-utility associated with cochlear implantation in patients with large vestibular aqueduct syndrome. *Otol Neurotol.* 2002;23(3):323-7. PMID: 11981389
26. Sbeih F, Bouzaher MH, Appachi S, et al. Safety of Cochlear Implantation in Children 12 Months or Younger: Systematic Review and Meta-analysis. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2022:1945998211067741. PMID: 34982600
27. Forli F, Arslan E, Bellelli S, et al. Systematic review of the literature on the clinical effectiveness of the cochlear implant procedure in paediatric patients. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* 2011;31(5):281-98. PMID: 22287820
28. Vlastarakos PV, Proikas K, Papacharalampous G, et al. Cochlear implantation under the first year of age--the outcomes. A critical systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol.* 2010;74(2):119-26. PMID: 19896223
29. Food and Drug Administration. Summary of Safety and Effectiveness Data. Cochlear Americas Nucleus 24 Cochlear Implant System (P970051/S172). 2020. [cited 3/11/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf/P970051S172B.pdf.
30. Kalejaiye A, Ansari G, Ortega G, et al. Low surgical complication rates in cochlear implantation for young children less than 1 year of age. *The Laryngoscope.* 2017;127(3):720-24. PMID: 27411677
31. Guerzoni L, Murri A, Fabrizi E, et al. Social conversational skills development in early implanted children. *The Laryngoscope.* 2016;126(9):2098-105. PMID: 26649815
32. Colletti L, Mandala M, Zoccante L, et al. Infants versus older children fitted with cochlear implants: performance over 10 years. *Int J Pediatr Otorhinolaryngol.* 2011;75(4):504-9. PMID: 21277638
33. Colletti L. Long-term follow-up of infants (4-11 months) fitted with cochlear implants. *Acta Otolaryngol.* 2009;129(4):361-6. PMID: 19153846
34. Ching TY, Dillon H, Day J, et al. Early language outcomes of children with cochlear implants: interim findings of the NAL study on longitudinal outcomes of children with hearing impairment. *Cochlear Implants Int.* 2009;10 Suppl 1:28-32. PMID: 19067433
35. Johr M, Ho A, Wagner CS, et al. Ear surgery in infants under one year of age: its risks and implications for cochlear implant surgery. *Otol Neurotol.* 2008;29(3):310-3. PMID: 18364573
36. Bilateral Cochlear Implantation: A Health Technology Assessment. *Ontario health technology assessment series.* 2018;18(6):1-139. PMID: 30443278
37. McRackan TR, Bauschard M, Hatch JL, et al. Meta-analysis of quality-of-life improvement after cochlear implantation and associations with speech recognition abilities. *The Laryngoscope.* 2018;128(4):982-90. PMID: 28731538

38. McRackan TR, Bauschard M, Hatch JL, et al. Meta-analysis of Cochlear Implantation Outcomes Evaluated With General Health-related Patient-reported Outcome Measures. *Otol Neurotol.* 2018;39(1):29-36. PMID: 29227446
39. Gaylor JM, Raman G, Chung M, et al. Cochlear implantation in adults: a systematic review and meta-analysis. *JAMA otolaryngology-- head & neck surgery.* 2013;139(3):265-72. PMID: 23429927
40. Berrettini S, Baggiani A, Bruschini L, et al. Systematic review of the literature on the clinical effectiveness of the cochlear implant procedure in adult patients. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* 2011;31(5):299-310. PMID: 22287821
41. Raman G LJ, Chung M., et al. . Effectiveness of Cochlear Implants in Adults with Sensorineural Hearing Loss. AHRQ Technology Assessment Report. June 17, 2011. [cited 3/11/2024]. 'Available from:' http://www.cms.gov/determinationprocess/downloads/id80TA.pdf.
42. Vanstrum EB, Castellanos CX, Ziltzer RS, et al. Cochlear implantation in Waardenburg syndrome: Systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol.* 2023;175:111738. PMID: 37847940
43. Bo D, Huang Y, Wang B, et al. Auditory and Speech Outcomes of Cochlear Implantation in Children With Auditory Neuropathy Spectrum Disorder: A Systematic Review and Meta-Analysis. *The Annals of otology, rhinology, and laryngology.* 2023;132(4):371-80. PMID: 35499129
44. Fernandes NF, Morettin M, Yamaguti EH, et al. Performance of hearing skills in children with auditory neuropathy spectrum disorder using cochlear implant: a systematic review. *Brazilian journal of otorhinolaryngology.* 2015;81(1):85-96. PMID: 25458263
45. Lammers MJ, van der Heijden GJ, Pourier VE, et al. Bilateral cochlear implantation in children: a systematic review and best-evidence synthesis. *The Laryngoscope.* 2014;124(7):1694-9. PMID: 24390811
46. Eze N, Ofo E, Jiang D, et al. Systematic review of cochlear implantation in children with developmental disability. *Otol Neurotol.* 2013;34(8):1385-93. PMID: 24005167
47. Humphriss R, Hall A, Maddocks J, et al. Does cochlear implantation improve speech recognition in children with auditory neuropathy spectrum disorder? A systematic review. *International journal of audiology.* 2013;52(7):442-54. PMID: 23705807
48. Smulders YE, van Zon A, Stegeman I, et al. Comparison of Bilateral and Unilateral Cochlear Implantation in Adults: A Randomized Clinical Trial. *JAMA otolaryngology--head & neck surgery.* 2016;142:249-56. PMID: 26796630
49. van Zon A, Smulders YE, Stegeman I, et al. Stable benefits of bilateral over unilateral cochlear implantation after two years: A randomized controlled trial. *The Laryngoscope.* 2017;127(5):1161-68. PMID: 27667732
50. Ching TY, Incerti P, Hill M. Binaural benefits for adults who use hearing aids and cochlear implants in opposite ears. *Ear Hear.* 2004;25(1):9-21. PMID: 14770014
51. Ching TY, Incerti P, Hill M, et al. An overview of binaural advantages for children and adults who use binaural/bimodal hearing devices. *Audiol Neurootol.* 2006;11 Suppl 1:6-11. PMID: 17063004
52. Holt RF, Kirk KI, Eisenberg LS, et al. Spoken word recognition development in children with residual hearing using cochlear implants and hearing AIDS in opposite ears. *Ear Hear.* 2005;26(4 Suppl):82S-91S. PMID: 16082270
53. Litovsky RY, Johnstone PM, Godar S, et al. Bilateral cochlear implants in children: localization acuity measured with minimum audible angle. *Ear Hear.* 2006;27(1):43-59. PMID: 16446564

54. Litovsky R, Parkinson A, Arcaroli J, et al. Simultaneous bilateral cochlear implantation in adults: a multicenter clinical study. *Ear Hear.* 2006;27(6):714-31. PMID: 17086081
55. Ricketts TA, Grantham DW, Ashmead DH, et al. Speech recognition for unilateral and bilateral cochlear implant modes in the presence of uncorrelated noise sources. *Ear Hear.* 2006;27(6):763-73. PMID: 17086085
56. Ramsden R, Greenham P, O'Driscoll M, et al. Evaluation of bilaterally implanted adult subjects with the nucleus 24 cochlear implant system. *Otol Neurotol.* 2005;26(5):988-98. PMID: 16151348
57. Kuhn-Inacker H, Shehata-Dieler W, Muller J, et al. Bilateral cochlear implants: a way to optimize auditory perception abilities in deaf children? *Int J Pediatr Otorhinolaryngol.* 2004;68(10):1257-66. PMID: 15364496
58. Blamey PJ, Maat B, Baskent D, et al. A Retrospective Multicenter Study Comparing Speech Perception Outcomes for Bilateral Implantation and Bimodal Rehabilitation. *Ear Hear.* 2015;36(4):408-16. PMID: 25695925
59. Choi JS, Betz J, Li L, et al. Association of Using Hearing Aids or Cochlear Implants With Changes in Depressive Symptoms in Older Adults. *JAMA otolaryngology-- head & neck surgery.* 2016;142(7):652-7. PMID: 27258813
60. Escorihuela Garcia V, Pitarch Ribas MI, Llopez Carratala I, et al. Comparative study between unilateral and bilateral cochlear implantation in children of 1 and 2 years of age. *Acta otorrinolaringologica espanola.* 2016;67(3):148-55. PMID: 26632253
61. Killan CF, Royle N, Totten CL, et al. The effect of early auditory experience on the spatial listening skills of children with bilateral cochlear implants. *Int J Pediatr Otorhinolaryngol.* 2015;79(12):2159-65. PMID: 26520909
62. Friedmann DR, Green J, Fang Y, et al. Sequential bilateral cochlear implantation in the adolescent population. *The Laryngoscope.* 2015;125(8):1952-8. PMID: 25946482
63. Sarant J, Harris D, Bennet L, et al. Bilateral versus unilateral cochlear implants in children: a study of spoken language outcomes. *Ear Hear.* 2014;35(4):396-409. PMID: 24557003
64. Kontorinis G, Lloyd SK, Henderson L, et al. Cochlear implantation in children with auditory neuropathy spectrum disorders. *Cochlear Implants Int.* 2014;15 Suppl 1:S51-4. PMID: 24869444
65. Broomfield SJ, Murphy J, Emmett S, et al. Results of a prospective surgical audit of bilateral paediatric cochlear implantation in the UK. *Cochlear Implants Int.* 2013;14 Suppl 4:S19-21. PMID: 24533758
66. Illg A, Giourgas A, Kral A, et al. Speech comprehension in children and adolescents after sequential bilateral cochlear implantation with long interimplant interval. *Otol Neurotol.* 2013;34(4):682-9. PMID: 23640090
67. Sharma A, Dorman MF. Central auditory development in children with cochlear implants: clinical implications. *Adv Otorhinolaryngol.* 2006;64:66-88. PMID: 16891837
68. Sharma A, Dorman MF, Kral A. The influence of a sensitive period on central auditory development in children with unilateral and bilateral cochlear implants. *Hear Res.* 2005;203(1-2):134-43. PMID: 15855038
69. Baron S, Blanchard M, Parodi M, et al. Sequential bilateral cochlear implants in children and adolescents: Outcomes and prognostic factors. *European annals of otorhinolaryngology, head and neck diseases.* 2019;136(2):69-73. PMID: 30314876
70. Idriss SA, Reynard P, Marx M, et al. Short- and Long-Term Effect of Cochlear Implantation on Disabling Tinnitus in Single-Sided Deafness Patients: A Systematic Review. *J Clin Med.* 2022;11(19). PMID: 36233532

71. Oh SJ, Mavrommatis MA, Fan CJ, et al. Cochlear Implantation in Adults With Single-Sided Deafness: A Systematic Review and Meta-analysis. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2022:1945998221083283. PMID: 35230924
72. Donato M, Santos R, Correia F, et al. Single-sided deafness: Bone conduction devices or cochlear implantation? A systematic review with meta-analysis. *Acta Otorrinolaringol Esp (Engl Ed).* 2021;72(2):101-08. PMID: 33160618
73. Assouly KKS, van Heteren JAA, Stokroos RJ, et al. Cochlear implantation for patients with tinnitus - A systematic review. *Prog Brain Res.* 2021;260:27-50. PMID: 33637223
74. Benchetrit L, Ronner EA, Anne S, et al. Cochlear Implantation in Children With Single-Sided Deafness: A Systematic Review and Meta-analysis. *JAMA otolaryngology-- head & neck surgery.* 2021;147(1):58-69. PMID: 33151295
75. Implantable Devices for Single-Sided Deafness and Conductive or Mixed Hearing Loss: A Health Technology Assessment. *Ontario health technology assessment series.* 2020;20(1):1-165. PMID: 32194878
76. Levy DA, Lee JA, Nguyen SA, et al. Cochlear Implantation for Treatment of Tinnitus in Single-sided Deafness: A Systematic Review and Meta-analysis. *Otol Neurotol.* 2020;41(8):e1004-e12. PMID: 32558752
77. Peter N, Liyanage N, Pfiffner F, et al. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2019;161(4):576-88. PMID: 31060475
78. Cabral Junior F, Pinna MH, Alves RD, et al. Cochlear Implantation and Single-sided Deafness: A Systematic Review of the Literature. *Int Arch Otorhinolaryngol.* 2016;20(1):69-75. PMID: 26722349
79. Peters JP, Ramakers GG, Smit AL, et al. Cochlear implantation in children with unilateral hearing loss: A systematic review. *The Laryngoscope.* 2016;126(3):713-21. PMID: 26343240
80. van Zon A, Peters JP, Stegeman I, et al. Cochlear implantation for patients with single-sided deafness or asymmetrical hearing loss: a systematic review of the evidence. *Otol Neurotol.* 2015;36(2):209-19. PMID: 25502451
81. Vlastarakos PV, Nazos K, Tavoulari EF, et al. Cochlear implantation for single-sided deafness: the outcomes. An evidence-based approach. *Eur Arch Otorhinolaryngol.* 2014;271(8):2119-26. PMID: 24096818
82. Blasco MA, Redleaf MI. Cochlear implantation in unilateral sudden deafness improves tinnitus and speech comprehension: meta-analysis and systematic review. *Otol Neurotol.* 2014;35(8):1426-32. PMID: 24786540
83. Marx M, Mosnier I, Venail F, et al. Cochlear Implantation and Other Treatments in Single-Sided Deafness and Asymmetric Hearing Loss: Results of a National Multicenter Study Including a Randomized Controlled Trial. *Audiol Neurootol.* 2021;26(6):414-24. PMID: 33789270
84. Peters JPM, van Heteren JAA, Wendrich AW, et al. Short-term outcomes of cochlear implantation for single-sided deafness compared to bone conduction devices and contralateral routing of sound hearing aids-Results of a Randomised controlled trial (CINGLE-trial). *PLoS One.* 2021;16(10):e0257447. PMID: 34644322
85. Arras T, Boudewyns A, Swinnen F, et al. Longitudinal auditory data of children with prelingual single-sided deafness managed with early cochlear implantation. *Sci Rep.* 2022;12(1):9376. PMID: 35672363

86. Brown KD, Dillon MT, Park LR. Benefits of Cochlear Implantation in Childhood Unilateral Hearing Loss (CUHL Trial). *The Laryngoscope.* 2022;132 Suppl 6(Suppl 6):S1-s18. PMID: 34542181
87. Administration USFaD. Summary of Safety and Effectiveness Data: Nucleus Cochlear Implant System: PMA970051/s205B 2022. [cited 03/11/2024]. 'Available from:' www.accessdata.fda.gov/cdrh_docs/pdf/P970051S205B.pdf.
88. Falcón Benítez N, Falcón González JC, Ramos Macías Á, et al. Cochlear Implants in Single-Sided Deafness. Comparison Between Children and Adult Populations With Post-lingually Acquired Severe to Profound Hearing Loss. *Front Neurol.* 2021;12:760831. PMID: 34803893
89. Rauch AK, Arndt S, Aschendorff A, et al. Long-term results of cochlear implantation in children with congenital single-sided deafness. *Eur Arch Otorhinolaryngol.* 2021;278(9):3245-55. PMID: 33079248
90. Poncet-Wallet C, Mamelle E, Godey B, et al. Prospective Multicentric Follow-up Study of Cochlear Implantation in Adults With Single-Sided Deafness: Tinnitus and Audiological Outcomes. *Otol Neurotol.* 2020;41(4):458-66. PMID: 32176124
91. Dillon MT, Buss E, Rooth MA, et al. Cochlear Implantation in Cases of Asymmetric Hearing Loss: Subjective Benefit, Word Recognition, and Spatial Hearing. *Trends in hearing.* 2020;24:2331216520945524. PMID: 32808881
92. Buss E, Dillon MT, Rooth MA, et al. Effects of Cochlear Implantation on Binaural Hearing in Adults With Unilateral Hearing Loss. *Trends in hearing.* 2018;22:2331216518771173. PMID: 29732951
93. Dillon MT, Buss E, O'Connell BP, et al. Low-Frequency Hearing Preservation With Long Electrode Arrays: Inclusion of Unaided Hearing Threshold Assessment in the Postoperative Test Battery. *American journal of audiology.* 2020;29(1):1-5. PMID: 31835906
94. Galvin JJ, 3rd, Fu QJ, Wilkinson EP, et al. Benefits of Cochlear Implantation for Single-Sided Deafness: Data From the House Clinic-University of Southern California-University of California, Los Angeles Clinical Trial. *Ear Hear.* 2019;40(4):766-81. PMID: 30358655
95. Peter N, Kleinjung T, Probst R, et al. Cochlear implants in single-sided deafness - clinical results of a Swiss multicentre study. *Swiss medical weekly.* 2019;149:w20171. PMID: 31880806
96. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): MED-EL Cochlear Implant System (P000025/S104). 2019. [cited 3/11/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf/P000025S104B.pdf.
97. Food and Drug Administration. Post-Approval Studies (PAS): MED-EL New Enrollment SSD/AHL Study. 2020. [cited 3/11/2024]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=647845&c_id=5585.
98. Arndt S, Laszig R, Aschendorff A, et al. Cochlear implant treatment of patients with single-sided deafness or asymmetric hearing loss. *Hno.* 2017;65(Suppl 2):98-108. PMID: 28188428
99. Sladen DP, Frisch CD, Carlson ML, et al. Cochlear implantation for single-sided deafness: A multicenter study. *The Laryngoscope.* 2017;127(1):223-28. PMID: 27346874
100. Rahne T, Plontke SK. Functional Result After Cochlear Implantation in Children and Adults With Single-sided Deafness. *Otol Neurotol.* 2016;37(9):e332-40. PMID: 27631656

101. Mertens G, De Bodt M, Van de Heyning P. Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years. *Hear Res.* 2016;331:1-6. PMID: 26433053
102. Ramos Macias A, Falcon Gonzalez JC, Manrique M, et al. Cochlear implants as a treatment option for unilateral hearing loss, severe tinnitus and hyperacusis. *Audiol Neurootol.* 2015;20 Suppl 1:60-6. PMID: 25997672
103. Arndt S, Prosse S, Laszig R, et al. Cochlear implantation in children with single-sided deafness: does aetiology and duration of deafness matter? *Audiol Neurootol.* 2015;20 Suppl 1:21-30. PMID: 25999052
104. Hansen MR, Gantz BJ, Dunn C. Outcomes after cochlear implantation for patients with single-sided deafness, including those with recalcitrant Meniere's disease. *Otol Neurotol.* 2013;34:1681-7. PMID: 24232066
105. Tavora-Vieira D, Marino R, Krishnaswamy J, et al. Cochlear implantation for unilateral deafness with and without tinnitus: a case series. *The Laryngoscope.* 2013;123(5):1251-5. PMID: 23553411
106. Santa Maria PL, Gluth MB, Yuan Y, et al. Hearing preservation surgery for cochlear implantation: a meta-analysis. *Otol Neurotol.* 2014;35(10):e256-69. PMID: 25233333
107. Pillsbury HC, 3rd, Dillon MT, Buchman CA, et al. Multicenter US Clinical Trial With an Electric-Acoustic Stimulation (EAS) System in Adults: Final Outcomes. *Otol Neurotol.* 2018;39(3):299-305. PMID: 29342054
108. Roland JT, Jr., Gantz BJ, Waltzman SB, et al. United States multicenter clinical trial of the cochlear nucleus hybrid implant system. *The Laryngoscope.* 2016;126(1):175-81. PMID: 26152811
109. Roland JT, Jr., Gantz BJ, Waltzman SB, et al. Long-term outcomes of cochlear implantation in patients with high-frequency hearing loss. *The Laryngoscope.* 2018;128(8):1939-45. PMID: 29330858
110. Gantz BJ, Dunn C, Oleson J, et al. Multicenter clinical trial of the Nucleus Hybrid S8 cochlear implant: Final outcomes. *The Laryngoscope.* 2016;126(4):962-73. PMID: 26756395
111. Friedmann DR, Peng R, Fang Y, et al. Effects of loss of residual hearing on speech performance with the CI422 and the Hybrid-L electrode. *Cochlear Implants Int.* 2015;16(5):277-84. PMID: 25912363
112. Lenarz T, James C, Cuda D, et al. European multi-centre study of the Nucleus Hybrid L24 cochlear implant. *International journal of audiology.* 2013;52(12):838-48. PMID: 23992489
113. Gifford RH, Dorman MF, Skarzynski H, et al. Cochlear implantation with hearing preservation yields significant benefit for speech recognition in complex listening environments. *Ear Hear.* 2013;34(4):413-25. PMID: 23446225
114. American Academy of Otolaryngology-Head and Neck Surgery. AAO-HNS Position Statement - Cochlear Implants. [cited 3/11/2024]. 'Available from:' http://www.entnet.org/content/position-statement-cochlear-implants.
115. American Academy of Otolaryngology-Head and Neck Surgery. AAO-HNS Position Statement - Pediatric Cochlear Implantation Candidacy. [cited 3/11/2024]. 'Available from:' https://www.entnet.org/resource/position-statement-pediatric-cochlear-implantation-candidacy/.
116. American Academy of Audiology. Clinical Practice Guideline: Cochlear Implants. [cited 3/11/2024]. 'Available from:' https://www.audiology.org/wp-content/uploads/2021/05/CochlearImplantPracticeGuidelines.pdf.

117. Dillon MT, Kocharyan A, Daher GS, et al. American Cochlear Implant Alliance Task Force Guidelines for Clinical Assessment and Management of Adult Cochlear Implantation for Single-Sided Deafness. *Ear Hear.* 2022;43(6):1605-19. PMID: 35994570
118. Park LR, Griffin AM, Sladen DP, et al. American Cochlear Implant Alliance Task Force Guidelines for Clinical Assessment and Management of Cochlear Implantation in Children With Single-Sided Deafness. *Ear Hear.* 2022;43(2):255-67. PMID: 35213890

CODES

Codes	Number	Description
CPT	69930	Cochlear device implantation, with or without mastoidectomy
	92601	Diagnostic analysis of cochlear implant, patient younger than 7 years of age; with programming
	92602	;subsequent reprogramming
	92603	Diagnostic analysis of cochlear implant, age 7 years or older; with programming
	92604	;subsequent reprogramming
HCPCS	L8614	Cochlear device, includes all internal and external components
	L8615	Headset/headpiece for use with cochlear implant device, replacement
	L8616	Microphone for use with cochlear implant device, replacement
	L8617	Transmitting coil for use with cochlear implant device, replacement
	L8618	Transmitter cable for use with cochlear implant device or auditory osseointegrated device, replacement
	L8619	Cochlear implant external speech processor and controller, integrated system, replacement
	L8621	Zinc air battery for use with cochlear implant device and auditory osseointegrated sound processors, replacement, each
	L8622	Alkaline battery for use with cochlear implant device, any size, replacement, each
	L8623	Lithium ion battery for use with cochlear implant device speech processor
	L8624	Lithium ion battery for use with cochlear implant or auditory osseointegrated device speech processor, ear level, replacement, each
	L8625	External recharging system for battery for use with cochlear implant or auditory osseointegrated device, replacement only, each
	L8627	Cochlear implant, external speech processor, component, replacement
	L8628	Cochlear implant, external controller component, replacement
	L8629	Transmitting coil and cable, integrated, for use with cochlear implant device, replacement

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 12

Cosmetic and Reconstructive Procedures

Effective: April 1, 2024

Next Review: May 2024
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Cosmetic procedures are performed to alter or reshape normal body structures in order to improve appearance.

Reconstructive surgery is primarily performed to improve or correct a functional impairment.

NOTE: This policy is not intended to address treatment of gender dysphoria which is addressed in the Gender Affirming Interventions for Gender Dysphoria medical policy, Medicine, Policy No. 153, which may be applicable.

MEDICAL POLICY CRITERIA

Notes:

- Many member contracts have very specific language regarding covered reconstructive services and excluded cosmetic procedures. Specific member contract language has precedence over medical policy, and requests for coverage of potentially cosmetic services should be reviewed by applicable member contract language.
- Specific services may be addressed in separate medical policies. Please see cross references below.

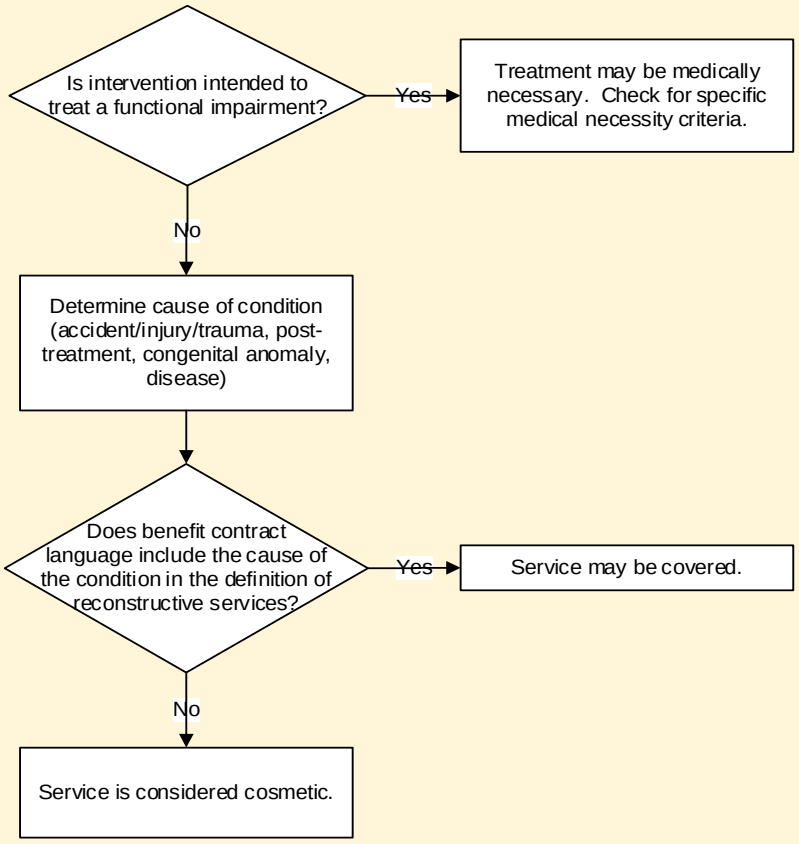
I. The following criteria may be applied when member contract language is not specific:

A. If the intervention is intended to treat a functional impairment and if no other contract exclusions apply, it may be considered **medically necessary**.

B. If the intervention is not intended to treat a functional impairment, the cause of the condition must be determined, for example, accident/injury/trauma, post-treatment, congenital anomaly, disease. If the cause is included in the definition of reconstructive services in the benefits contract language, then the treatment may be covered.

C. If the intervention is not intended to treat a functional impairment, the cause of the condition must be determined, for example, accident/injury/trauma, post-treatment, congenital anomaly, disease. If the cause is *not* included in the definition of reconstructive services in the benefits contract language, then the treatment is considered **cosmetic**.

The following flow chart may be used as a guide to interpreting benefits language.



CROSS REFERENCES

1. Gender Affirming Interventions for Gender Dysphoria, Medicine, Policy No. 153
2. Endometrial Ablation, Surgery, Policy No. 01
3. Panniculectomy, Surgery, Policy No. 12.01
4. Pectus Excavatum, Surgery, Policy No. 12.02
5. Ventral Hernia Repair, Surgery, Policy No. 12.03
6. Dermabrasion or Microdermabrasion, Surgery, Policy No. 12.04
7. Blepharoplasty and Brow Ptosis Repair, Surgery, Policy No. 12.05

8. Mastectomy as a Treatment of Gynecomastia Cosmetic Services, Surgery, Policy No. 12.06
9. Rhinoplasty, Surgery, Policy No. 12.28
10. Laser Treatment for Port Wine Stains, Surgery, Policy No. 12.34
11. Chemical Peels, Surgery, Policy No. 12.50
12. Reconstructive Breast Surgery/Management of Breast Implants, Surgery, Policy No. 40
13. Reduction Mammaplasty, Surgery, Policy No. 60
14. Varicose Vein Treatment, Surgery, Policy No. 104
15. Orthognathic Surgery, Surgery, Policy No. 137
16. Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells, Surgery, Policy No. 182

REFERENCES

None

CODES

NOTE: CPT codes 17106-17108 are used for the destruction of vascular proliferative lesions only. If the treatment does not destroy the lesion, or if a lesion is not considered a "vascular proliferative lesion" (e.g., hypervascular, hypertrophic, or keloid scars), then the treatment should not be reported using these codes. Unlisted code 17999 *(Unlisted procedure, skin, mucous membrane and subcutaneous tissue)* should be reported instead.

Codes	Number	Description
CPT	11920	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq cm or less
	11921	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm
	11922	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; each additional 20.0 sq cm, or part thereof
	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate
	15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	15775	Punch graft for hair transplant; 1 to 15 punch grafts
	15776	Punch graft for hair transplant; more than 15 punch grafts
	15819	Cervicoplasty
	15824	Rhytidectomy; forehead
	15825	Rhytidectomy; neck with platysmal tightening (platysmal flap, P-flap)
	15826	Rhytidectomy; glabellar frown lines
	15828	Rhytidectomy; cheek, chin and neck
	15829	Rhytidectomy; superficial musculoaponeurotic system (SMAS) flap

15832	Excision, excessive skin and subcutaneous tissue (includes lipectomy); thigh
15833	Excision, excessive skin and subcutaneous tissue (includes lipectomy); leg
15834	Excision, excessive skin and subcutaneous tissue (includes lipectomy); hip
15835	Excision, excessive skin and subcutaneous tissue (includes lipectomy); buttock
15836	Excision, excessive skin and subcutaneous tissue (includes lipectomy); arm
15837	Excision, excessive skin and subcutaneous tissue (includes lipectomy); forearm or hand
15839	Excision, excessive skin and subcutaneous tissue (includes lipectomy); other area
15876	Suction assisted lipectomy; head and neck
15877	Suction assisted lipectomy; trunk
15878	Suction assisted lipectomy; upper extremity
15879	Suction assisted lipectomy; lower extremity
17106	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); less than 10 sq cm
17107	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); 10.0 to 50.0 sq cm
17108	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); over 50.0 sq cm
17380	Electrolysis epilation, each 30 minutes
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
19355	Correction of inverted nipples
21137	Reduction forehead; contouring only
21138	Reduction forehead; contouring and application of contouring material or bone graft (includes obtaining autograft)
21139	Reduction forehead; contouring and setback of anterior frontal sinus wall
21230	Graft; rib cartilage, autogenous, to face, chin, nose or ear (includes obtaining graft)
21244	Reconstruction of mandible, extraoral, with transosteal bone plate (eg, mandibular staple bone plate)
21245	Reconstruction of mandible, or maxilla, subperiosteal implant; partial
21246	Reconstruction of mandible, or maxilla, subperiosteal implant; complete
21248	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); partial
21249	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); complete
21270	Malar augmentation, prosthetic material
21280	Medial canthopexy
21282	Lateral canthopexy
21295	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); extraoral approach
21296	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); intraoral approach
26590	Repair macrodactylia, each digit
31830	Revision of tracheostomy scar
41510	Suture of tongue to lip for micrognathia (Douglas type procedure)
49250	Umbilectomy, omphalectomy, excision of umbilicus
54360	Plastic operation on penis to correct angulation
67950	Canthoplasty
67999	Unlisted procedure, eyelids
69090	Ear piercing
69300	Otoplasty, protruding ear, with or without size reduction

HCPCS	G0429	Dermal filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 12.01

Panniculectomy

Effective: July 1, 2023

Next Review: May 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Panniculectomy refers to the removal of excess skin and subcutaneous tissue typically from the abdominal area.

MEDICAL POLICY CRITERIA

Note: Member contract language takes precedent over medical policy. Member contracts for covered services vary and may exclude weight loss surgery and all associated, services, supplies, and/or complications.

I. Panniculectomy may be considered **medically necessary** when all of the following Criteria (A.-D.) are met:

   A. Submission of photographs documenting significant pannus which hangs below the level of the pubis; and

   B. The pannus causes a chronic and persistent skin condition (e.g., intertriginous dermatitis, panniculitis, cellulitis or skin ulcerations) that is refractory to at least 3 months of medical treatment and associated with at least one episode of cellulitis requiring systemic antibiotics (oral and/or intravenous). In addition to good

hygiene practices, treatment should also include topical antifungals, topical and/or systemic corticosteroids; and

C. The pannus causes functional physical impairment documented to interfere with activities of daily living (see Policy Guidelines); and

D. Clinical documentation of stable weight for at least six months or at least 18 months after bariatric surgery.

II. Panniculectomy which does not meet the above Criteria I. is considered **cosmetic.**

III. Abdominoplasty with or without panniculectomy is considered **cosmetic**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Activities of Daily Living (ADLs) Definition: Instrumental ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- The specific functional physical impairment caused by the pannus
- Front and lateral view photographs demonstrating redundant/excessive skin and the size of the pannus
- Clinical documentation about the nature and extent of the chronic and persistent skin condition that is refractory to at least three months of medical treatment [at least one episode of cellulitis requiring systemic antibiotics (oral and/or intravenous) and good hygiene practices including topical antifungals, topical and/or systemic corticosteroids]
- Any bariatric surgery procedure performed within the past three years, including date of procedure
- Clinical documentation of stable weight for at least six months or at least 18 months after bariatric surgery

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12

BACKGROUND

This procedure is often performed after substantial weight loss as a result of bariatric surgery or diet. According to the American Society of Plastic Surgeons, “abdominoplasty, typically performed for cosmetic purposes, involves the removal of excess skin and fat from the pubis to the umbilicus or above, and may include fascial plication of the rectus muscle diastasis and a neoumbilicoplasty. Panniculectomy involves the removal of hanging excess skin/fat in a transverse or vertical wedge but does not include muscle plication, neoumbilicoplasty or flap elevation. ”[1] There is limited evidence and clinical practice guidelines which indicate when

panniculectomy may be appropriate due to functional impairment.[2, 3] Typically no functional impairment is associated with pannus development.

REFERENCES

1. American Society of Plastic Surgeons (ASPS): Recommended Insurance Coverage Criteria for Third-Party Payers; Panniculectomy January 2019, Re-approved March 2019 [cited 05/11/2023]. 'Available from:' https://www.plasticsurgery.org/documents/Health-Policy/Reimbursement/insurance-2019-panniculectomy.pdf.
2. American Society for Metabolic & Bariatric Surgery, American Association of Clinical Endocrinologists, and The Obesity Society: Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. [cited 05/11/2023]. 'Available from:' https://asmbs.org/resources/clinical-practice-guidelines-for-the-perioperative-nutritional-metabolic-and-nonsurgical-support-of-the-bariatric-surgery-patient.
3. Pestana IA, Campbell D, Fearmonti RM, et al. "Supersize" panniculectomy: indications, technique, and results. *Annals of plastic surgery.* 2014;73(4):416-21. PMID: 23722576

CODES

Codes	Number	Description
CPT	15830	Excision, excessive skin and subcutaneous tissue (includes lipectomy); abdomen, infraumbilical panniculectomy
	15838	Excision, excessive skin and subcutaneous tissue (includes lipectomy); submental fat pad
	15847	Excision, excessive skin and subcutaneous tissue (includes lipectomy), abdomen (eg, abdominoplasty) (includes umbilical transposition and fascial plication) (List separately in addition to code for primary procedure)
	17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
HCPCS	None	

Date of Origin: *August 2018*

Regence

Medical Policy Manual Surgery, Policy No. 12.02

Pectus Excavatum and Carinatum Treatment

Effective: April 1, 2024

Next Review: May 2024
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Pectus excavatum, commonly referred to as "funnel chest," is a chest wall malformation in which the sternum is depressed inward, causing midline narrowing of the thoracic cavity. In contrast, pectus carinatum describes a deformity in which there is protrusion of the anterior chest wall.

MEDICAL POLICY CRITERIA

I. Surgical repair of pectus excavatum may be considered **medically necessary** in children or adults when at least two of the following medical necessity criteria are met:

   A. Documented progression of the deformity with associated symptoms.

   B. Pulmonary function studies indicate components of restrictive airway disease.

   C. Haller index greater than 3.25 at end-inspiration. This Haller index is the ratio derived from a chest CT or magnetic resonance imaging (MRI) scan by dividing the transverse diameter by the anterior-posterior diameter.

   D. Cardiac evaluation (electrocardiogram [EKG], chest CT, and/or echocardiogram) demonstrates compression-caused mitral valve prolapse, abnormal rhythm, conduction abnormalities, or significant cardiac deformity.

II. Surgical repair of pectus excavatum that does not meet at least two of the criteria in I.A. – I. D. above is considered **not medically necessary**.

III. Surgical repair of pectus carinatum is considered **not medically necessary**.

IV. The use of orthotic braces for the treatment of pectus carinatum is considered **not medically necessary**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12

BACKGROUND

Although pectus excavatum may be visually prominent, in most cases the loss of volume is not significant and does not interfere with ventilation. Pectus excavatum is occasionally associated with upper or lower airway obstruction; however, when this condition is successfully treated or resolves spontaneously, the pectus deformity may lessen or disappear. Pectus excavatum may also be associated with segmental bronchomalacia, and in some patients, cardiac function may be adversely affected. In many children, the heart is shifted leftward, and in the rare patient, cardiac function may be adversely affected.

Surgical correction of pectus excavatum is not physiologically beneficial for the vast majority of patients; surgery is most often sought due to psychological and cosmetic concerns. However, for some patients with extreme deformity, operative interventions may be indicated for functional reasons.

Pectus carinatum may also be visually prominent but is not generally associated with any respiratory or cardiac functional deficits, and surgery and bracing are typically requested for psychological and cosmetic concerns.

SUMMARY

There is enough research to show that surgical repair of pectus excavatum may improve health outcomes for individuals with the severity and functional impairment outlined in the policy criteria. Therefore, surgical repair of pectus excavatum may be considered medically necessary to when policy criteria are met.

Surgical repair of pectus excavatum is not clinically needed when the severity and functional impairment outlined in the policy criteria are not demonstrated. Therefore, when policy criteria are not met, surgical repair of pectus excavatum is considered not medically necessary.

Surgical repair or bracing of pectus carinatum is not clinically needed, as the condition is not associated with functional impairment that requires surgical intervention. Therefore, surgical repair or bracing of pectus carinatum is considered not medically necessary.

REFERENCES

None

CODES

Codes	Number	Description
CPT	21740	Reconstructive repair of pectus excavatum or carinatum; open
	21742	Reconstructive repair of pectus excavatum or carinatum; minimally invasive approach (Nuss procedure), without thoracoscopy
		Reconstructive repair of pectus excavatum or carinatum; minimally invasive approach (Nuss procedure), with thoracoscopy
HCPCS	L1320	Thoracic, pectus carinatum orthosis, sternal compression, rigid circumferential frame with anterior and posterior rigid pads, custom fabricated
	L1499	Spinal orthosis, not otherwise specified

Date of Origin: *August 2018*

Regence

Medical Policy Manual Surgery, Policy No. 12.03

Ventral (Including Incisional) Hernia Repair

Effective: December 1, 2023

Next Review: May 2024
Last Review: July 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ventral hernias occur in the abdomen and develop when a portion of the lining of the peritoneum pushes through a weak area of the abdominal wall fascia. This results in a protrusion which can be filled with intra-abdominal fat or intestine. An incisional hernia is a protrusion of tissue that forms in a prior surgical incision in the abdomen.

MEDICAL POLICY CRITERIA

Notes:

- Umbilical hernias have a specific ICD-10 code (K42) and should not be coded as a ventral hernia.
- Epigastric, spigelian, and lumbar hernias do not have specific ICD-10 codes and are reported by the non-specific ventral hernia code K43.
- An incarcerated hernia is defined as: a hernia in which the intraperitoneal contents are trapped or twisted within the hernia sac.
- A ventral hernia at the site of a prior surgery is considered an incisional hernia.

I. Surgical repair of a ventral (including incisional) hernia may be considered **medically necessary** in symptomatic patients when there is documentation that one or more of the following Criteria is met:
   A. Hernia associated pain of documented severity to interfere with activities of daily living (see Policy Guidelines); or
   B. Bowel obstruction or strangulation; or
   C. Incarceration; or
   D. Thinning of the overlying skin; or
   E. Loss of abdominal domain (see Policy Guidelines).

II. Surgical repair using the component separation technique (CST) may be considered **medically necessary** for a large (defined as width greater than or equal to 10 cm) midline ventral (including incisional) hernia (see Policy Guidelines).

III. Surgical repair of a ventral (including incisional) hernia is considered **not medically necessary** when Criterion I. is not met.

IV. Surgical repair of an abdominal wall defect, including a ventral or incisional hernia, using the component separation technique (CST) is considered **not medically necessary** when Criterion II. is not met.

V. Surgical repair of an asymptomatic ventral (including incisional) hernia found incidentally during surgery is considered **not medically necessary**.

VI. Surgical repair of diastasis recti is considered **cosmetic**.

VII. Abdominoplasty and related procedures, including but not limited to fascial plication, surgical imbrication, and tightening of lax fascia, are considered **cosmetic**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

- Loss of abdominal domain is defined as 50% of the abdominal viscera reside outside the abdominal cavity.[1]
- The component separation technique (CST) is based on subcutaneous lateral dissection, fasciotomy lateral to the rectus abdominis muscle, and dissection on the plane between external and internal oblique muscles with medial advancement of the block that includes the rectus muscle and its fascia. This release allows for medial advancement of the fascia and closure of up to 20 cm-wide defects in the midline area. Extraperitoneal or retrorectus placement of mesh or preparation for placement of mesh is not considered CST.
- Activities of Daily Living (ADLs) definition: ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Documentation of the impact of hernia related pain on impaired activities of daily living (ADL, including the specific ADL) and how pain impacts performance
- Current symptomology and description of associated functional physical impairment if applicable
- Diagnostic testing results as applicable to request and associated policy criteria
- Photographs as applicable to request and associated policy criteria
- If the component separation technique is being performed, documentation of the location and size of the hernia in centimeters.

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
2. Correct Coding Guidelines, Reimbursement Policy, Administrative, Policy No. 129

BACKGROUND

Ventral hernias are usually acquired when pressure is applied to an area of the abdomen which is weakened. They can occur spontaneously, known as a primary hernia, or at the site of a previous surgical incision, known as an incisional hernia.

Abdominal wall hernias (Epigastric, Umbilical, Lumbar and Spigelian) are defined by their anatomical location. Patients who are obese, older, under-weight, pregnant, have ascites or other factors which increase intra-abdominal pressure may be predisposed to developing abdominal hernias. Most hernias are acquired; however, the occurrence of umbilical hernias in infants is considered a congenital defect which usually resolves before the age of two. Children with persistent symptoms may require surgical repair.

Diastasis recti is defined as increased distance between the right and left rectus abdominis muscles that is created by the stretching of the collagen sheath (the linea alba) connecting the two rectus abdominis muscles. Diastasis recti is not considered a hernia as there is no fascial defect.

In general, small, asymptomatic hernias do not require surgical repair. Adults with larger symptomatic hernias should be considered for ventral hernia repair. Over time, hernia symptoms may develop and include pain, bowel obstruction, incarceration, thinning of the overlying skin, strangulation, and displacement of abdominal contents into the hernia itself, known as loss of abdominal domain.

LOSS OF ABDOMINAL DOMAIN

Loss of abdominal domain is defined as 50% of the abdominal viscera reside outside the abdominal cavity.[1]

COMPONENT SEPARATION TECHNIQUE

The component separation technique (CST) is a surgical method that may be used to repair large, complicated ventral hernias using a rectus abdominis muscle advancement flap. A defect width greater than or equal to 10 cm is classified as a large hernia by the European

Hernia Society.[2] This surgical technique is based on subcutaneous lateral dissection, fasciotomy lateral to the rectus abdominis muscle, and dissection on the plane between external and internal oblique muscles with medial advancement of the block that includes the rectus muscle and its fascia. This release allows for medial advancement of the fascia and closure of up to 20 cm-wide defects in the midline area. Mesh reinforcement is often used in recurrent repairs where the abdominal defect is too large and there is a large amount of tension on the CST repair. CST is not typically used as an initial surgical approach for small primary ventral hernia repairs.

SUMMARY

There is enough evidence to show that the surgical repair of a ventral hernia improves health outcomes for symptomatic patients meeting criteria. Therefore, surgical repair of a ventral hernia may be considered medically necessary in symptomatic patients when policy criteria are met.

The component separation technique is a method that may be used to repair large (greater than 10 centimeters) midline ventral hernias. Therefore, surgical repair of large (greater than or equal to 10 centimeters in width) midline ventral or incisional hernias using the component separation technique may be considered medically necessary. Surgical repair of an abdominal wall defect, including but not limited to ventral or incisional hernias that are less than 10 centimeters in width using the component separation technique is considered not medically necessary.

There is not sufficient evidence that surgical repair of asymptomatic ventral (including incisional) hernias improves health outcomes. Therefore, surgical repair of asymptomatic ventral (including incisional) hernias is considered not medically necessary. Surgical repair of diastasis recti, abdominoplasty, and related procedures, including but not limited to fascial plication, surgical imbrication, and tightening of lax fascia, are considered cosmetic.

REFERENCES

1. Mancini GaL, Hien. *Loss of Abdominal Domain: Definition and Treatment Strategies*, 2016, pp. 361-370.
2. Muysoms FE, Miserez M, Berrevoet F, et al. Classification of primary and incisional abdominal wall hernias. *Hernia : the journal of hernias and abdominal wall surgery.* 2009;13(4):407-14. PMID: 19495920

CODES

NOTE:

- Laparoscopic (including robotic) or open ventral (including incisional) hernia repair may be reported with CPT codes listed below depending on the size of defect and the indication.
- The separation component (CST) is reported with CPT code 15734 when performed open. When performed by laparoscopic technique, it is reported by unlisted CPT code 49659 with reference to CPT code 15734.

Codes	Number	Description
CPT	15734	Muscle, myocutaneous, or fasciocutaneous flap; trunk
	~~49560~~	~~Repair initial incisional or ventral hernia; reducible~~ (Deleted 01/01/2023)
	~~49565~~	~~Repair recurrent incisional or ventral hernia; reducible~~ (Deleted 01/01/2023)
	49591	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, reducible
	49593	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, reducible
	49595	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, reducible
	49613	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, reducible
	49615	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, reducible
	49617	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, reducible
	49621	Repair of parastomal hernia, any approach (ie, open, laparoscopic, robotic), initial or recurrent, including implantation of mesh or other prosthesis, when performed; reducible
	~~49652~~	~~Laparoscopy, surgical, repair, ventral, umbilical, spigelian or epigastric hernia (includes mesh insertion, when performed); reducible~~ (Deleted 01/01/2023)
	~~49654~~	~~Laparoscopy, surgical, repair, incisional hernia (includes mesh insertion, when performed); reducible~~ (Deleted 01/01/2023)
	~~49656~~	~~Laparoscopy, surgical, repair, recurrent incisional hernia (includes mesh insertion, when performed); reducible~~ (Deleted 01/01/2023)
	49659	Unlisted laparoscopy procedure, hernioplasty, herniorrhaphy, herniotomy
HCPCS	None	

Date of Origin: *May 2010*

Regence

Medical Policy Manual Surgery, Policy No. 12.05

Blepharoplasty, Repair of Blepharoptosis, and Brow Ptosis Repair

Effective: July 1, 2023

Next Review: May 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Blepharoplasty is a surgical procedure performed on the upper and/or lower eyelids to remove or repair excess tissue that obstructs the field of vision. Blepharoptosis repair involves repair of drooping of the eyelid and can include shortening or advancement of the elevator muscle of the eyelid. These procedures may also be performed for cosmetic purposes in the absence of visual field obstruction.

MEDICAL POLICY CRITERIA

Note: Blepharoplasty CPT codes and policy criteria do not apply to eyelid retraction.

I. One surgical session for either unilateral or bilateral blepharoplasty, repair of blepharoptosis, and/or brow ptosis repair may be considered **medically necessary** when one or more of the following Criteria is met.

   A. Blepharoplasty and repair of blepharoptosis may be considered **medically necessary** when one or more of the following Criteria (1. or 2.) is met:

1. Trichiasis, ectropion or entropion for an affected upper or lower lid when documented by lateral and full-face photographs clearly showing the affected lid(s); or
2. Anophthalmia when there is clinical documentation that the upper eyelid position interferes with the fit of a prosthesis in the socket.

B. Unilateral or bilateral upper lid blepharoplasty or repair of blepharoptosis may be considered **medically necessary** for reconstructive purposes when all of the following Criteria (1.- 4.) are met:
1. Documentation of clinically decreased vision with functional impairment due to visual field loss; and
2. Prior to manual elevation of redundant upper eyelid skin (taping), the superior visual field, in at least one eye is less than or equal to 20 degrees. Examinations may be either automated or hand drawn, but need to clearly document multiple (including central axis) specific visual points not seen; and
3. With taping of the eyelids, in at least one eye, superior visual fields improve by at least 12 degrees; and
4. Photographs taken in the pupillary plane with a primary gaze (looking straight ahead) that demonstrate pupillary obstruction in at least one eye.

C. Brow ptosis repair including open and endoscopic procedures may be considered medically necessary for reconstructive purposes when both of the following Criteria (1. and 2.) are met:
1. At least one eye meets either Criterion I.A. or I.B. above; and
2. Frontal and lateral facial photographs demonstrate the eyebrow is below the supraorbital rim.

II. Surgical session(s) in excess of one, for unilateral or bilateral blepharoplasty, repair of blepharoptosis, and/or brow ptosis repair is considered **not medically necessary**.

III. Unilateral or bilateral upper lid blepharoplasty, repair of blepharoptosis, and brow ptosis repair is considered **not medically necessary** in either of the following scenarios:
A. Criterion I. above is not met; or
B. There is documentation of unstable related disease process, such as myasthenia gravis or a thyroid condition.

IV. Blepharoplasty of the lower lids for excessive skin is considered **not medically necessary.**

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

Trichiasis, ectropion or entropion

- Any congenital or anatomical issue causing issues with vision
- Lateral and full-face photographs

Anophthalmia

- Clinical documentation that the upper eyelid position interferes with the fit of a prosthesis in the socket

Blepharoplasty for all other reasons

- Any disease process that can affect vision (e.g. myasthenia gravis or thyroid condition) or documentation to support absence of such disease process
- Clinical documentation of functional impairment due to vision loss
- Clinical documentation of visual field testing and examinations including 0-20 degrees as well as above 20 degrees, documenting:
    - Points of vision seen and not seen (optimal), or points not seen as long as clearly identified and including points on the central axis., and
    - Proof that taping improves vision enough to meet criteria guidelines
- Clear direct frontal and lateral photographs in the pupillary plane with gaze in the primary position (looking straight ahead) that are consistent with the above visual fields and examinations
- Clinical documentation that surgical repair will be completed in one session (surgery)
- Clinical documentation to support the procedure is for the upper lid only

Brow Ptosis

- Photographs demonstrate the eyebrow is below the supraorbital rim

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12

BACKGROUND

Functional visual impairment occurs when excess upper eyelid tissue overhangs the upper eyelid margin and results in significant superior visual field obstruction. Visual field studies (VFs) are used to determine the degree of obstruction. VFs should be measured both with and without elevation of the excess tissue to determine the extent of visual field defect at rest and the amount of improvement that may be obtained from blepharoplasty. VFs with points of vision seen and not seen is optimal; however, the plan will accept VFs with only points not seen as long as clearly identified and must include points on the central axis.

Cahill (2011) published a report by the American Academy of Ophthalmology, on functional indications for upper eyelid ptosis and blepharoplasty surgery.[1] Thirteen studies were included. The authors stated that there are certain indicators that predict surgery outcomes, including margin reflex distance of 1 (MRD(1)) of 2mm or less and superior visual field loss of at least 12 degrees or 24%.

REFERENCES

1. Cahill KV, Bradley EA, Meyer DR, et al. Functional indications for upper eyelid ptosis

and blepharoplasty surgery: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2011;118(12):2510-7. PMID: 22019388

CODES

Codes	Number	Description
CPT	15820	Blepharoplasty, lower eyelid;
	15821	Blepharoplasty, lower eyelid; with extensive herniated fat pad
	15822	Blepharoplasty, upper eyelid;
	15823	Blepharoplasty, upper eyelid; with excessive skin weighting down lid
	67900	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)
	67901	Repair of blepharoptosis; frontalis muscle technique with suture or other material (eg, banked fascia)
	67902	Repair of blepharoptosis; frontalis muscle technique with autologous fascial sling (includes obtaining fascia)
	67903	Repair of blepharoptosis; (tarso) levator resection or advancement, internal approach
	67904	Repair of blepharoptosis; (tarso) levator resection or advancement, external approach
	67906	Repair of blepharoptosis; superior rectus technique with fascial sling (includes obtaining fascia)
	67908	Repair of blepharoptosis; conjunctivo-tarso-Muller's muscle-levator resection (eg, Fasanella-Servat type)
	67909	Reduction of overcorrection of ptosis
	67999	Unlisted procedure, eyelids
	67911	Correction of lid retraction
	67916	Repair of ectropion; excision tarsal wedge
	67917	Repair of ectropion; extensive (eg, tarsal strip operations)
	67923	Repair of entropion; excision tarsal wedge
	67924	Repair of entropion; extensive (eg, tarsal strip or capsulopalpebral fascia repairs operation)
	67950	Canthoplasty (reconstruction of canthus)
HCPCS	None	

Date of Origin: *August 2018*

Regence

Medical Policy Manual Surgery, Policy No. 12.28

Rhinoplasty

Effective: September 1, 2023

Next Review: May 2024
Last Review: July 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Rhinoplasty surgery reshapes the nose and is usually considered cosmetic. Reconstructive rhinoplasty may be performed to improve nasal respiratory function and/or to correct anatomic abnormalities caused by birth defects, disease or trauma.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contracts may have specific language defining congenital and developmental anomalies. Member contract language takes precedence over medical policy.
    - A congenital anomaly is defined as an anomaly that is present at birth (e.g., cleft palate).
    - Developmental anomalies are conditions that develop some time after birth.

I. Initial or revision rhinoplasty may be considered **medically necessary** for reconstruction of a nasal deformity in only **one or more** of the following circumstances:

A. Secondary to a congenital anomaly, including but not limited to facial cleft; or

B. After tumor resection; or

C. After trauma which causes significant functional impairment, including but not limited to displaced nasal bone fracture severe enough to cause symptomatic nasal airway obstruction; or

D. Symptomatic nasal airway obstruction (i.e., difficulty breathing related to nasal passage obstruction) when all of the following Criteria (1. – 3.) are met:

1. There is significant bony obstruction of one or both nares documented by an advanced imaging modality such as computed tomography (CT) or magnetic resonance imaging (MRI); and
2. Septoplasty, vestibular stenosis, alar collapse, and/or turbinectomy surgeries are not expected to resolve the bony deformity; and
3. Nasal airway obstruction is poorly responsive to a documented six-week trial of conservative medical management (e.g., topical/nasal corticosteroids, antihistamines).

II. Excision and/or shaving of rhinophyma maybe considered **medically necessary** when there is documented evidence (i.e., imaging studies and/or anterior - posterior, lateral and inferior photographs) demonstrating functional airway obstruction).

III. Initial or revision rhinoplasty is considered a **cosmetic** procedure unless Criterion I. is met.

IV. Excision and/or shaving of rhinophyma is considered a **cosmetic** procedure unless Criterion II. is met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Condition causing the need for rhinoplasty
- If not caused by congenital anomaly, including but not limited to facial cleft or tumor:
  - Computed tomography (CT), magnetic resonance imaging (MRI) or other advanced imaging documenting significant obstruction of one or both nares
  - Conservative medical management provided, timeline and outcomes
  - Any surgeries performed, with outcomes or documentation of why septoplasty, vestibular stenosis, alar collapse, and/or turbinectomy surgeries alone are not expected to resolve the nasal deformity.
- Documentation of airway obstruction for rhinophyma treatment (i.e., imaging studies and/or photographs with a minimum of one each: anterior - posterior, lateral and inferior views).

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
2. Absorbable Nasal Implant for Treatment of Nasal Valve Collapse, Surgery, Policy No. 209
3. Cryoablation for Chronic Rhinitis, Surgery, Policy No. 224

REFERENCES

None

CODES

Codes	Number	Description
CPT	30120	Excision or surgical planing of skin of nose for rhinophyma
	30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip
	30410	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip
	30420	Rhinoplasty, primary; including major septal repair
	30430	Rhinoplasty secondary; minor revision (small amount of nasal tip work)
	30435	Rhinoplasty secondary; intermediate revision (bony work with osteotomies)
	30450	Rhinoplasty secondary; major revision (nasal tip work and osteotomies)
	30460	Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip only
	30462	Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip, septum, osteotomies
HCPCS	None	

Date of Origin: *August 2018*

Regence

Medical Policy Manual Surgery, Policy No. 12.34

Laser Treatment for Port Wine Stains

Effective: July 1, 2023

Next Review: May 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Port wine stain (PWS) is a capillary malformation that begins as a pale pink flat area (macular lesion) in childhood and grows as the patient ages.

MEDICAL POLICY CRITERIA

I. Laser treatment may be considered **medically necessary** for port wine stains.

II. Destruction of cutaneous vascular lesions for removal of telangiectasias (spider veins) is considered **cosmetic**.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could our impact review and decision outcome:

Medical records related to history and physical/chart notes documenting presence of port wine stain.

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12

BACKGROUND

Common areas for port wine stains (PWS) to appear are on the face over the areas of the first and second trigeminal nerves and the eyes or mouth. It is common to see a PWS overlying an arteriovenous, arterial or venous malformation. The abnormal blood vessels within the PWS become progressively more dilated in size, which results in the lesion becoming dark purple and elevated in some instances. Nodules and hypertrophy may develop in the soft tissue underlying the PWS. Nodules may continue to grow and can bleed easily if traumatized. PWS persists into adult life and is associated with systemic abnormalities such as glaucoma.

Treatment of a PWS in its macular stage will prevent the development of the hypertrophic component of the lesion. Laser treatment of a PWS diminishes the existing blood vessels making them smaller, fewer in number, and less likely to progress in size.

REFERENCES

None

CODES

Codes	Number	Description
CPT	17106	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); less than 10 sq cm
	17107	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); 10.0 to 50.0 sq cm
	17108	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); over 50.0 sq cm
HCPCS	None	

Date of Origin: *August 2018*

Regence

Medical Policy Manual Surgery, Policy No. 12.50

Chemical Peels

Effective: September 1, 2023

Next Review: May 2024
Last Review: July 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A chemical peel refers to a controlled removal of varying layers of the epidermis and superficial dermis with the use of a 'wounding' agent, such as phenol or trichloroacetic acid (TCA).

MEDICAL POLICY CRITERIA

EPIDERMAL CHEMICAL PEELS

I. Epidermal chemical peels with 50 - 70% alpha hydroxy acids may be considered **medically necessary** as a treatment of active acne that has failed to respond to a trial of topical and/or oral antibiotic acne therapy.

II. Epidermal chemical peels with 50 - 70% alpha hydroxy acids are considered **not medically necessary** as a first-line treatment of active acne.

III. Epidermal chemical peels that do not meet Criterion I. or II. above, including but not limited to the treatment of photoaged skin, wrinkles, or acne scarring, are considered **cosmetic**.

DERMAL CHEMICAL PEELS

I. Dermal chemical peels may be considered **medically necessary** to treat numerous (>10) actinic keratoses or other premalignant skin lesions, when treatment of the

individual lesions becomes impractical.

II. Dermal chemical peels are considered **not medically necessary** to treat less than 10 actinic keratoses or other premalignant skin lesions.

III. Dermal chemical peels that do not meet Criterion I. or II. above, including but not limited to treatment of end-stage acne scarring, are considered **cosmetic**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12

BACKGROUND

The most common indication for chemical peeling is as a treatment of photoaged skin, correcting pigmentation abnormalities, solar elastosis, and wrinkles. However, chemical peeling has also been used as a treatment for various stages of acne and multiple actinic keratoses when treatment of individual lesions is not feasible.

An epidermal peel may be used to remove fine, subtle lines, soften the appearance of enlarged pores, improve the skin texture and lighten hyper-pigmentary disorders. Multiple epidermal peels (also referred to as chemical exfoliation) may also be used in patients with active acne.

Dermal peels may be used to treat deep wrinkling, actinic damage, or actinic keratoses. Acne scarring has also been treated with dermal peels.

REFERENCES

None

CODES

Codes	Number	Description
CPT	15788	Chemical peel, facial; epidermal
	15789	Chemical peel; facial; dermal
	15792	Chemical peel; nonfacial; epidermal
	15793	Chemical peel; nonfacial; dermal
	17360	Chemical exfoliation for acne (eg, acne paste, acid)
HCPCS	None	

Date of Origin: *August 2018*

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Surgery, Policy No. 40

Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants

Effective: September 1, 2022

Next Review: August 2022
Last Review: April 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Policy provides breast reconstruction and implant management criteria based on Public Law 105-277, the Women's Health and Cancer Rights Act of 1998.

MEDICAL POLICY CRITERIA

Notes:

- Contractual limitations and exclusions may apply to both reconstructive and cosmetic procedures, to illnesses and conditions initially occurring prior to coverage, and to complications of non-covered procedures.
- For the purposes of this policy, mastectomy is defined as complete or partial, including lumpectomy.
- Some codes listed may have specific criteria to be met in other medical policies (e.g., reduction mammaplasty), or may not be considered medically necessary for any indication. See Cross References to confirm the correct policy is applied.
- This policy does not address procedures related to gender affirming interventions for gender dysphoria. See Cross References for the correct policy to be applied.

I. Reconstructive breast surgery of a diseased or injured breast may be considered **medically necessary** when either of the following criteria is met and the treating physician recommends it:

   A. After prophylactic or therapeutic mastectomy

   B. After accidental injury or trauma to the breast resulting in significant malformation

II. Reconstructive breast surgery of an unaffected breast to achieve symmetry with the contralateral breast may be considered **medically necessary** when reconstruction of the contralateral diseased or injured breast was medically necessary as defined in Criterion I. above and it is recommended by the treating physician.

III. Breast implant explantation and/or replacement may be considered **medically necessary** when the implant(s) was/were placed during reconstructive breast surgery that was medically necessary as defined in Criterion I. Explantation of implant(s) requires documentation of the original indication for implantation.

IV. Breast revision surgery, including breast implant explantation and/or replacement, following a cosmetic primary breast procedure is considered **cosmetic** when one or more of Criteria I., II., or III. is not met.

V. Mastopexy is considered **cosmetic** when medical necessity Criteria I., II., or III. are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Gender Affirming Interventions for Gender Dysphoria, Medicine, Policy No. 153
2. Endometrial Ablation, Surgery, Policy No. 01
3. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
4. Reduction Mammaplasty, Surgery, Policy No. 60
5. Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast, Surgery, Policy No. 182

BACKGROUND

Reconstructive breast surgery is defined as those surgical procedures which are intended to restore the normal appearance of the breast after surgery, accidental injury, or trauma. The most common indication for reconstructive breast surgery is mastectomy. In contrast, cosmetic breast surgery is defined as surgery intended to alter or enhance the appearance of a breast which does not have a significantly altered appearance due to surgery, accidental injury, or trauma. Reduction mammoplasty and surgery to alter the appearance of a congenital breast abnormality are examples of breast surgeries which may be cosmetic. (See Surgery Policy No. 60, Reduction Mammoplasty and Surgery Policy No. 12, Cosmetic and Reconstructive Surgery).The most common type of reconstructive breast surgery is insertion of a silicone gel-filled or saline-filled breast implant, either inserted immediately at the time of mastectomy -or sometime afterward in conjunction with the previous use of a tissue expander. Significant local complications of breast implants, such as contracture, may require removal of the implant. Other types of reconstruction include nipple/areola reconstruction, nipple tattooing, and/or the use of autologous tissue, such as a transverse rectus abdominis myocutaneous flap (TRAM procedure) or a latissimus dorsi flap. In addition, mastopexy, reduction mammoplasty, or

implant on the contralateral breast may be performed in order to achieve symmetry with the reconstructed breast.

POSITION STATEMENT

This policy is written to assist in interpreting Public Law 105-277, the Women's Health and Cancer Rights Act of 1998[1] which requires all health insurance carriers that cover mastectomies to also cover the following in a manner determined in consultation with the attending physician and patient:

- All stages of reconstruction of the breast on which the mastectomy was performed
- Surgery and reconstruction of the contralateral breast to produce a symmetrical appearance
- Prostheses
- Treatment of physical complications of mastectomy, including lymphedema

SUMMARY

Reconstructive breast surgery of a diseased or injured breast may be considered medically necessary after prophylactic or therapeutic mastectomy or after accidental injury or trauma to the breast resulting in significant malformation when the treating physician recommends it.

Reconstructive breast surgery of an unaffected breast to achieve symmetry with the contralateral breast may be considered medically necessary when reconstruction of the contralateral diseased or injured breast was medically necessary as defined in policy criteria and it is recommended by the treating physician.

Breast implant explantation and/or replacement may be considered medically necessary when the implant(s) was/were placed during reconstructive breast surgery that was medically necessary as defined in policy criteria.

Breast revision surgery, including breast implant explantation and/or replacement, following a cosmetic primary breast procedure is considered cosmetic when medical necessity criteria are not met.

Mastopexy is considered cosmetic when medical necessity criteria are not met.

REFERENCES

1. Your Rights After A Mastectomy...Women's Health & Cancer Rights Act of 1998. [cited 10/26/2021]. Available from: https://www.dol.gov/sites/default/files/ebsa/about-ebsa/our-activities/resource-center/publications/your-rights-after-a-mastectomy.pdf.

CODES

NOTE:

- Codes 15769, 15771, and 15772 should be reported for autologous fat grafting for reconstructive breast surgery as code 20926 was deleted 1/1/2020.
- CPT codes 11950, 11951, 11952, and 11954 [subcutaneous injection of filling material (eg, collagen)], 19366 (breast flap graft other technique), 19380 (revision of reconstructed breast), and 19499 (unlisted code) are not reported for breast fat grafting.
- For autologous fat grafting ***with additional*** adipose-derived stem cells (aka, stem cell enrichment), see Cross References to confirm correct criteria is applied.

Codes	Number	Description
CPT	11920	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq. cm or less
	11921	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm
	11970	Replacement of tissue expander with permanent implant
	11971	Removal of tissue expander(s) without insertion of implant
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	19316	Mastopexy
	19318	Breast reduction
	19325	Breast augmentation with implant
	19328	Removal of intact breast implant
	19330	Removal of ruptured implant, including implant contents (eg, saline, silicone gel)
	19340	Insertion of breast implant on same day of mastectomy, (ie, immediate)
	19342	Insertion or replacement of breast implant on separate day from mastectomy
	19350	Nipple/areola reconstruction
	19355	Correction of inverted nipples
	19357	Tissue expander placement in breast reconstruction, including subsequent expansion(s)
	19361	Breast reconstruction; with latissimus dorsi flap
	19364	Breast reconstruction; with free flap (eg, fTRAM, DIEP, SIEA, GAP flap)
	~~19366~~	~~Breast reconstruction with other technique~~ (Deleted 01/01/2021)
	19367	Breast reconstruction; with single-pedicle transverse rectus abdominis myocutaneous (TRAM) flap
	19368	; requiring separate microvascular anastomosis (supercharging)
	19369	Breast reconstruction; with bipedicled transverse rectus abdominis myocutaneous (TRAM) flap
	19370	Revision of peri-implant capsule, breast, including capsulotomy, capsulorrhaphy, and/or partial capsulectomy
	19371	Peri-implant capsulotomy, breast, complete, including removal of all intracapsular contents
	19380	Revision of reconstructed breast (eg, significant removal of tissue, re-advancement and/or re-inset of flaps in autologous reconstruction or significant capsular revision combined with soft tissue excision in implant-based reconstruction)
		Preparation of moulage for custom breast implant

Codes	Number	Description
	19499	Unlisted procedure, breast
	L8039	Breast prosthesis, not otherwise specified
	L8600	Implantable breast prosthesis, silicone or equal
	S2066	Breast reconstruction with gluteal artery perforator (GAP) flap, including harvesting of the flap, microvascular transfer, closure of donor site and shaping the flap into a breast, unilateral
	S2067	Breast reconstruction of a single breast with "stacked" deep inferior epigastric perforator (DIEP) flap(s) and/or gluteal artery perforator (GAP) flap(s), including harvesting of the flap(s), microvascular transfer, closure of donor site(s) and shaping the flap into a breast, unilateral
	S2068	Breast reconstruction with deep inferior epigastric perforator (DIEP) flap or superficial inferior epigastric artery (SIEA) flap, including harvesting of the flap, microvascular transfer, closure of donor site and shaping the flap into a breast, unilateral

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 45

Spinal Cord and Dorsal Root Ganglion Stimulation

Effective: January 1, 2024

Next Review: April 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Standard and high-frequency spinal cord stimulation, as well as dorsal root ganglion stimulation, delivers electrical stimulation to the spinal cord using implanted electrodes to block pain sensation. Dorsal root ganglion stimulation is different from spinal cord stimulation in terms of the placement of the electrodes.

MEDICAL POLICY CRITERIA

Notes:

- Spinal cord stimulation should be initiated with a *trial period* of spinal cord stimulation with a *temporarily implanted* lead and may be followed by *permanent implantation*. This policy addresses these services as one combined episode beginning with the temporary placement.
- Please see the Regulatory Status section for a list of standard (non-high frequency), high-frequency, and dorsal root ganglion devices.

I. Spinal cord stimulation (standard or high frequency) may be considered **medically necessary** for severe and chronic refractory neuropathic pain of the trunk or limbs, *other than* critical limb ischemia, when one of the following Criteria is met:

A. Other treatment modalities (pharmacological, surgical, psychological, or physical, if applicable) have been tried and failed; or

B. Other treatment modalities are judged to be unsuitable or contraindicated.

II. Revision(s) to an existing spinal cord stimulator may be considered **medically necessary** after the device has been placed.

III. The replacement of all or part of an existing spinal cord stimulator and/or generator is considered **medically necessary** when the existing spinal cord stimulator and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

IV. Replacement of all or part of an existing spinal cord stimulator and/or generator is considered **not medically necessary** when Criterion III. is not met.

V. Spinal cord stimulation is considered **not medically necessary** for severe and chronic refractory neuropathic pain of the trunk or limbs when Criterion I. is not met.

VI. Spinal cord stimulation is considered **investigational** for all other indications, including but not limited to treatment of the following: critical limb ischemia, cancer-related pain, central deafferentation pain (related to CNS damage from a stroke or spinal cord injury), headache including chronic cluster headaches, nociceptive pain (resulting from irritation, not damage to the nerves), postherpetic neuralgia, and visceral pain.

VII. Dorsal root ganglion stimulation may be considered **medically necessary** for severe and chronic refractory pain of the trunk or limbs due to type I or type II complex regional pain syndrome, including reflex sympathetic dystrophy or causalgia, when one of the following Criteria is met:

A. Other treatment modalities (pharmacological, surgical, psychological, or physical, if applicable) have been tried and failed; or

B. Other treatment modalities are judged to be unsuitable or contraindicated.

VIII. Revision(s) to an existing dorsal root ganglion stimulator may be considered **medically necessary** after the device has been placed.

IX. The replacement of all or part of an existing dorsal root ganglion stimulator and/or generator is considered **medically necessary** when the existing dorsal root ganglion stimulator and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

X. Replacement of all or part of an existing dorsal root ganglion stimulator and/or generator is considered **not medically necessary** when Criterion IX. is not met.

XI. Dorsal root ganglion stimulation is considered **not medically necessary** for severe and chronic refractory pain of the trunk or limbs due to type I or type II complex regional pain syndrome, including reflex sympathetic dystrophy or causalgia, when Criterion VII. is not met.

XII. Dorsal root ganglion stimulation is considered **investigational** for all other indications, including but not limited to treatment of the following: critical limb ischemia, cancer-related pain, central deafferentation pain (related to CNS damage from a stroke or spinal cord injury), headache including chronic cluster headaches, nociceptive pain (resulting from irritation, not damage to the nerves), postherpetic neuralgia, and visceral pain.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Documentation of other treatment modalities (pharmacological, psychological, surgical, or physical if applicable) tried and failed or judged to be unsuitable or contraindicated

CROSS REFERENCES

1. Deep Brain Stimulation, Surgery, Policy No. 84
2. Occipital Nerve Stimulation, Surgery, Policy No. 174
3. Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin, Surgery, Policy No. 205

BACKGROUND

Spinal cord stimulation (SCS; also called dorsal column stimulation) involves the use of low-level epidural electrical stimulation of the spinal cord dorsal columns. The neurophysiology of pain relief after SCS is uncertain but may be related to either activation of an inhibitory system or to blockage of facilitative circuits. SCS has been used in a wide variety of chronic refractory pain conditions, including pain associated with cancer, failed back pain syndromes, arachnoiditis, and complex regional pain syndrome (i.e., chronic reflex sympathetic dystrophy). There has also been interest in SCS as a treatment of critical limb ischemia, primarily in patients who are poor candidates for revascularization and in patients with refractory chest pain.

SCS devices consist of several components: (1) the lead that delivers the electrical stimulation to the spinal cord; (2) an extension wire that conducts the electrical stimulation from the power source to the lead; and (3) a power source that generates the electrical stimulation. The lead may incorporate from 4 to 8 electrodes, with 8 electrodes more commonly used for complex pain patterns. There are two basic types of power source. One type, the power source (battery), can be surgically implanted. The other, a radiofrequency receiver, is implanted, and the power source is worn externally with an antenna over the receiver. Totally implantable systems are most commonly used.

The patient's pain distribution pattern dictates at what level in the spinal cord the stimulation lead is placed. The pain pattern may influence the type of device used; for example, a lead with 8 electrodes may be selected for those with complex pain patterns or bilateral pain. Implantation of the spinal cord stimulator is typically a 2-step process. Initially, the electrode is temporarily implanted in the epidural space, allowing a trial period of stimulation. Once treatment effectiveness is confirmed (defined as at least 50% reduction in pain), the electrodes and radio-receiver/transducer are permanently implanted. Successful SCS may require extensive programming of the neurostimulators to identify the optimal electrode combinations and stimulation channels.

Traditional SCS devices use electrical stimulation with a frequency on the order of 100 to 1000 Hz. In 2015, an SCS device, using a higher frequency of electrical stimulation (10,000 Hz) than

predicate devices was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The high-frequency stimulation is proposed to be associated with fewer paresthesias, which are a recognized effect of SCS. In addition, in 2016, FDA approved a clinician programmer "app" that allows an SCS device to provide stimulation in "bursts" rather than at a constant rate. Burst stimulation is proposed to provide pain relief with fewer paresthesias. The burst stimulation device works in conjunction with standard SCS devices. With the newly approved app, stimulation is provided in five 500-Hz burst spikes at a rate of 40 Hz, with a pulse width of 1 ms.

Another variation on SCS stimulation is the wireless injectable stimulator. These miniaturized neurostimulators are transforaminally placed at the dorsal root ganglion (DRG) and are used to treat pain. DRG are located between spinal nerves and the spinal cord on the posterior root and are believed to play an important role in neuropathic pain perception. Two systems have received approval or clearance from FDA.

REGULATORY STATUS

A large number of neurostimulator devices, some used for spinal cord stimulation (SCS), have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process. Examples of fully implantable SCS devices approved through the PMA process include the Cordis programmable neurostimulator (Cordis Corp., Downers Grove, IL), approved in 1981, the Itrel□ (Medtronic, Minneapolis, MN), approved in 1984, the Genesis and Eon devices (St Jude Medical) in 2001 and the Precision Spinal Cord Stimulator (Advanced Bionics, Switzerland), approved in 2004. FDA product code: LGW.

In May 2015, the Nevro Senza™ Spinal Cord Stimulator (Nevro Corp., Menlo Park, CA), a totally implantable neurostimulator device, was approved by FDA for the following indications: chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome (FBSS), intractable low back pain, and leg pain. This device uses a higher frequency of electrical stimulation (10 kHz) than standard devices.

Two wireless injectable neurostimulators have been approved or cleared by FDA. In February 2016, FDA approved the Axium Neurostimulator System (Spinal Modulation, Menlo Park, CA) through the PMA process. The device is indicated as an aid the management of moderate-to-severe intractable pain of the lower limbs in adults with complex regional pain syndrome types 1 and II. In August 2016, the Freedom Spinal Cord Stimulator (Stimwave Technologies, Fort Lauderdale, FL) was cleared by FDA through the 510(k) process for treating chronic, intractable pain of the trunk and/or lower limbs.

In October 2016, FDA approved BurstDR stimulation (St Jude Medical, Plano, TX), a clinician programmer application that provides intermittent "burst" stimulation for patients with certain St Jude SCS devices.

EVIDENCE SUMMARY

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, randomized controlled trials (RCTs) are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the

placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

In the evaluation of the risks for implantable devices, observational studies can provide data on the likelihood of potential complications. The following complications for spinal cord stimulation (SCS) have been reported:[1]

- Lead migration, connection failure, generator failure, and/or lead breakage
- Superficial and deep infection with or without abscess
- Hematoma
- Nerve injury

The following evidence summary focuses on the investigational indications noted in criteria III, as listed above.

CANCER-RELATED PAIN

In 2015, Peng published an update to their 2013 systematic review, to evaluate the effectiveness of SCS for cancer-related pain compared with standard care using conventional analgesic medication.[2, 3] The literature search yielded 430 initial articles; however, just 18 were deemed relevant to include in the review. No RCTs were identified that evaluated the efficacy of SCS in adult patients with cancer-related pain. No new publications were identified, since the four case series[4-7] using a before-after design, with a total of 92 patients, included in the original review. In the absence of randomized controlled studies, the efficacy of SCS for treating cancer-related pain cannot be determined.

CHRONIC REFRACTORY ANGINA

Two populations of patients have been studied: 1) patients who were not considered candidates for a revascularization procedure due to comorbidities or other factors, where SCS was compared to continued medical management; or 2) patients who would be considered candidates for a revascularization procedure for the purpose of symptom relief only, where SCS was compared to coronary artery bypass grafting. Aggregating results across these different patient populations may yield misleading conclusions about treatment effect or patient selection criteria as these patient populations may not be interchangeable (both sets of patients may not be eligible for both procedures). Therefore, the trials included in this review for each of these distinct patient populations are discussed separately below.[8-13]

Systematic Reviews

In 2016, Pan identified 12 RCTs that evaluated SCS in patients with refractory angina pectoris.[14] Most studies had small sample sizes (ie <50 patients) and together there were a total of 476 patients. Reviewers did not report the control interventions reported in the RCTs. Pooled analyses favored the SCS group in most cases for exercise time after intervention, pain level (VAS score) and angina frequency, but there was not a significant difference between intervention and control groups on physical limitation and angina stability.

A 2015 systematic review by Tsigaridas included nine RCTs evaluating SCS for refractory angina, seven of which compared SCS to low or no stimulation and two of which compared SCS to alternative medical or surgical therapy for angina.[15] Similar to the Taylor et al. review described below, the authors found that most RCTs were small and variable in quality based

on assessment with the modified Jadad score. The authors reported: “two of the RCTs were of high quality; two were of low quality and the remaining ones were of intermediate quality.” Most trials which compared SCS to low or no stimulation, found improvements in outcomes with SCS; however, given limitations in the evidence base, the authors concluded that larger multicenter RCTs are needed to assess the efficacy of SCS for angina.

In 2009 Taylor published a systematic review of five randomized controlled trials comparing active SCS with placebo (four studies) or no treatment (one study).[16] The studies included for analysis were judged to be of moderate or poor quality (based on a lack of reported treatment randomization and/or treatment blinding among cited limitations). Follow-up ranged from 48 hours to two-months and study size ranged from 22 to 30 patients. Primary outcomes identified by the review included impact on health-related quality of life, functional class and exercise capacity. Of these outcomes, active treatment was significantly associated with improvement in exercise capacity and health-related quality of life. No other differences between groups were identified. However, these results are limited by the moderate to poor quality of the reviewed studies which, because of their small sample sizes and limited follow-up duration, do not answer questions about the long-term durability of this type of treatment. In addition, the lack of distinction between placebo- and natural history- controlled groups does not allow for isolation of any treatment benefit of SCS over and beyond that conferred by placebo alone.

In 2008, a systematic review of the literature based on the Swedish Council on Technology Assessment in Health Care report on SCS in severe angina pectoris was published.[17] Seven controlled studies (five randomized), two follow-up reports, and a preliminary report, as well as two nonrandomized studies determined to be of medium-to-high quality were included in the review.

- The largest RCT[11-13] included 104 subjects and compared SCS and coronary artery bypass graft (CABG) in patients accepted for CABG and who were considered to have only symptomatic indication (i.e., no prognostic benefit) for CABG, according to the American College of Cardiology/American Heart Association guidelines, to run an increased risk of surgical complications, and to be unsuitable for percutaneous transluminal coronary angioplasty. Between-group differences on nitrate consumption, anginal attack frequency, and self-estimated treatment effect were not statistically significant at the 6-month follow-up. At the 5-year follow-up, significantly fewer patients in the CABG group were taking long-acting nitrates, and between-group differences on quality of life and mortality were not significant.
- A 2006 report by McNab compared SCS and percutaneous myocardial laser revascularization (PMR) in a study with 68 subjects.[10] Thirty subjects in each group completed a 12-month follow-up, and differences on mean total exercise time and mean time to angina were not significant. Eleven participants in the SCS group and 10 in the PMR group had no angina during exercise.
- The remaining RCTs included in the systematic review included 25 or fewer subjects.

Randomized Controlled Trials

Patient populations had failed back surgery syndrome, diabetic neuropathy, and complex regional pain syndrome. The comparators were primarily conventional medical management, although one RCT compared spinal cord stimulation with reoperation for failed back surgery syndrome, and another compared spinal cord stimulation with physical therapy. All RCTs reported results at 6 months. The most common primary outcome reported was a responder

outcome of 50% reduction in pain; Kemler (2000) reported absolute change in visual analog scale pain score.[18] Consistent with clinical practice, RCTs included a trial period of spinal cord stimulation, usually a few days to a week. Patients not reporting improvement in pain during the trial period did not continue receiving spinal cord stimulation during the remainder of follow-up. In most RCTs, these patients were included in the intention-to-treat analyses either as failures to respond or using imputation techniques. All RCTs with the responder primary outcomes reported clinically and statistically significant differences in the primary outcomes at 6 months, favoring spinal cord stimulation (spinal cord stimulation range, 39%-63% vs. comparator range, 5%-12%). Outcomes measuring the reduction in analgesic use were consistently numerically larger for spinal cord stimulation but not statistically significant in all studies. Four of the 5 studies did not report differences in functional, quality of life, or utility outcomes. Device-related complications ranged from 17% to 32%, with the most common being infection and discomfort or pain due to positioning or migration of electrodes or leads. However, two studies reported dural puncture headaches and Slangen (2014) reported a dural puncture headache ending in death.[19] Two studies reported longer-term results for both treatment groups. In each, results continued to favor spinal cord stimulation at 2 years, but for 1 with 5 years of follow-up, results were not statistically significant at 5 years.

In another small pilot RCT, conducted by Eldabe in 2016 to address uncertainties related to recruitment, outcome measures, and care standardization for a larger trial comparing SCS to usual care for refractory angina, enrollment was planned for 45 patients, but the trial failed to meet its enrollment target.[20] Among the 29 patients randomized to SCS (n=15) or usual care (n=14), there were no significant differences in primary or secondary outcomes between groups, but the trial was underpowered.

In 2012 Zipes published the results from a multi-center, single-blind RCT (n=68) which compared high SCS (two-hours of stimulation four times per day) versus sham SCS (one-minute of stimulation once per day) among patients with angina who were not candidates for revascularization.[21] The study was terminated (at 6 months) due to slow enrollment and per the Data Safety Monitoring Board recommendation that the study be terminated for futility based on an interim data analysis. The 68 subjects who underwent SCS implantation were randomized to either high stimulation (n=32) or low stimulation (control group; n=36). The low-stimulation control was designed so that patients would feel paresthesia, but the effect of stimulation would be subtherapeutic. Major adverse cardiac events (MACE) and rate of angina attacks were the primary outcomes of interest, along with total exercise time and exercise time to onset of angina. At 6 months an intention-to-treat analysis was conducted; data was available only for 58 of the 68 subjects (85%) No differences were found between groups in any of the outcomes, prompting the researchers to conclude the SCS was not more effective than placebo. However, long-term differences between groups are still not known as the study was terminated early. In addition, the small sample size may have been underpowered for assessing clinically meaningful differences.

In 2011 Lanza reported on a small RCT in which 25 patients were randomly assigned to 1 of 3 treatment groups: SCS with standard levels of stimulation (n=10), SCS with low-level stimulation (75% to 80% of the sensory threshold) (n=7), or SCS with very low intensity stimulation (n=8).[22] Thus, patients in groups 2 and 3 were unable to feel sensation during stimulation. After a protocol adjustment at 1 month, patients in the very low intensity group were re-randomized to one of the other groups after which there were 13 patients in the standard stimulation group and 12 patients in the low-level stimulation group. At the 3-month follow-up (2 months after re-randomization), there were statistically significant between-group

differences in 1 of 12 outcome variables. There were a median of 22 angina episodes in the standard stimulation group and 10 in the low-level stimulation group (p=0.002), indicating evidence for a significantly higher rate of angina episodes with standard SCS treatment. Non-significant variables included use of nitroglycerin, quality of life (VAS), Canadian Cardiovascular Society angina class, exercise-induced angina, and five sub-scales of the Seattle angina questionnaire. The small sample size and short-term follow-up does not permit conclusions about the long-term safety and effectiveness of SCS in these patients.

Section Summary

Numerous small RCTs have evaluated SCS as a treatment for refractory angina. While some studies have reported benefit, most have not. In two of the larger, more recent RCTs that enrolled more than 100 patients reported no benefit on the primary outcomes. Overall, this evidence is mixed and is not sufficient to allow conclusions on whether health outcomes are improved.

CRITICAL LIMB ISCHEMIA

Critical limb ischemia (CLI) is described as pain at rest or the presence of ischemic limb lesions. If the patient is not a suitable candidate for limb revascularization (typically due to insufficient distal run-off), it is estimated that amputation will be required in 60-80% of these patients within a year. Spinal cord stimulation has been investigated in this small subset of patients as a technique to relieve pain and decrease the incidence of amputation.

Systematic Reviews

In 2015, Aub Dabrh conducted a systematic review of non-revascularization-based treatments, including SCS, for patients with critical limb ischemia also included five RCTs.[23] In pooled analysis, the authors found that SCS was associated with reduced risk of amputation (odds ratio [OR], 0.53; 95% CI, 0.36 to 0.79). However, the reviewers concluded that there was “relatively low quality of the evidence mainly due to imprecision (ie, small sample size and wide CIs) and the risk of bias.”

A 2013 update of a systematic review from the Cochrane group on use of SCS in non-reconstructible chronic critical leg ischemia (NR-CCLI) included 10 articles of six studies with a total of 444 patients.[24] None of the studies were blinded due to the nature of the treatment. One of the studies was non-randomized and one included only patients with ischemic ulcers. Treatment groups received SCS along with the same standard nonsurgical treatment as the control groups. At 12, 18 and 24 months follow-up individual studies showed a trend toward a better limb salvage that did not reach statistical significance. However, when results were pooled, a small but significant decrease in amputations was found for the SCS group at 12 months follow-up (pooled risk difference (RD): -0.11, 95% confidence interval: -0.20 to -0.02). The 11% difference in the rate of limb salvage means that 9 patients would need to be treated to prevent one additional amputation (number needed to treat [NNT]: 9, 95% CI: 5 to 50). Upon excluding results from the non-randomized trial from the analysis, the treatment difference for the group treated with SCS was no longer significant (pooled RD: -0.09, 95% confidence interval: -0.19 to 0.01). When results from the study with patients in Fontaine stage IV (the most severe stage of critical limb ischemia) were excluded, the direction of treatment benefit switched (from negative to positive, RD: 0.13, 95% CI 0.02 to 0.23), indicating evidence for increased risk of amputation following treatment with SCS.

Outcomes for pain relief and ulcer healing could not be pooled and the researchers reported mixed findings. Quality of life was unchanged in both control and treatment groups. The overall risk of complications or additional SCS treatment was 17%. Nevertheless, the report concluded that "There is evidence that SCS is better than conservative treatment alone to achieve amputation risk reduction, pain relief and improvement of the clinical situation" in patients with chronic critical leg ischemia. This seemingly incongruous conclusion may be explained by the authors' conclusion that, "The benefits of SCS against the possible harm of relatively mild complications and costs must be considered." A potential conflict of interest was noted for the principal investigator, who was part of the non-randomized study included in the analysis. Published comments by Klomp and Steyerberg strongly criticized the inclusion of this non-randomized trial, along the exclusion of data from a randomized study from the pooled analysis, stating:[25]

The same meta-analysis, performed with a different amputation data input of five randomized studies [instead of 4 RCTs and a non-randomized study], generated a risk difference of -0.07 (95% CI: -0.17 to +0.03) instead of -0.13 (95% CI: -0.22 to -0.04). The main conclusion, that spinal cord stimulation is better than conservative treatment alone in achieving a reduction in amputation risk, is not justified. If SCS is beneficial, the magnitude of the effect is very small.

In 2009, Klomp and colleagues published a meta-analysis of the same five RCTs identified in the 2013 Cochrane review.[26] The authors did not find a statistically significant difference in the rate of amputation in the treatment and control groups. There was a relative risk of amputation of 0.79 and a risk difference of -0.07 (p=0.15). They found insufficient evidence that SCS is more efficacious than best medical treatment alone. They also conducted additional analyses of data from their 1999 RCT to identify factors associated with a better or worse prognosis. They found that patients with ischemic skin lesions had a higher risk of amputation compared to patients with other risk factors. There were no significant interactions between this or any other prognostic factor. The analyses did not identify any subgroup of patients who might benefit from SCS.

In 2009, Simpson systematic review described above also reviewed studies on SCS for treatment of inoperable critical limb ischemia.[27] Four RCTs met inclusion criteria; comparators were conventional medical management (CMM)[28-31], oral analgesics[32], or prostaglandin E1 injection[33]. The authors concluded that evidence for a treatment difference was found in reduction of analgesics up to six months, but not at 18 months. However, no between-group differences were found in pain relief, limb survival, health-related quality of life, or any other outcomes.

Randomized Controlled Trials

There have been no new randomized trials published since those included in the systematic reviews summarized above.

Conclusion

A number of small RCTs of SCS versus usual care have been completed on patients with critical limb ischemia. In pooled analyses of these RCTs, SCS did not result in a significantly lower rate of amputation, although one systematic review and meta-analysis did report a significant difference. This evidence is not sufficient to conclude that SCS improves outcomes for patients with critical limb ischemia.

HEART FAILURE

Randomized Controlled Trials

In 2016, Zipes reported the results of the DEFEAT-HF trial, a prospective, multicenter, single-blind RCT trial comparing SCS with active stimulation to sham control in patients with New York Heart Association functional class III heart failure with a left ventricular ejection fraction of 35% or less.[34] Sixty-six patients were implanted with an SCS and randomized in a 3:2 manner to SCS ON (n=42) or SCS OFF (sham; n=24). For the study's primary end point (change in left ventricular end systolic volume index from baseline to six months), there was no significant difference between groups (p=0.30). Other end points related to heart failure hospitalization and heart failure-related QOL scores and symptoms did not differ significantly between groups. After completion of the six month randomization period, all subjects received active SCS stimulation. From baseline to 12 months of follow-up, there were no significant echocardiographic treatment effects in the overall patient population in echocardiographic parameters (p=0.36). The study was originally powered based on a planned enrollment of 195 implanted patients, but enrollment was stopped early due to enrollment futility. The nonsignificant difference between groups may have been the result of underpowering. However, the absence of any treatment effects or between-group differences are further suggestive of a lack of efficacy of SCS for heart failure.

Findings of a small pilot crossover RCT evaluating SCS for heart failure were published in 2014 by Torre-Amione.[35] Eligibility included symptomatic heart failure despite optimal medical therapy, left ventricular ejection fraction less than 30%, hospitalization or need for intravenous inotropic support in the past year, and inability to walk more than 450 meters on a six-minute walk test. All patients had an implanted heart device. Nine patients underwent SCS implantation. The efficacy of SCS therapy was assessed by changes in patient symptoms, LV function, and BNP level. In all cases, ICD sensing, detection, and therapy delivery were unaffected by SCS. Symptoms were improved in the majority of patients with SCS, while markers of cardiac structure and function were, in aggregate, unchanged. Two patients had minor implant-related events and no reported implant-related HF exacerbations or hospitalizations. These small, preliminary pilot studies were intended to report first-in-human feasibility and safety to support further study. RCTs with large sample sizes and long-term follow-up are needed to draw conclusions on the safety and effectiveness of the therapy for this indication.

Nonrandomized Studies

In 2015 Tse performed a small, nonrandomized, prospective, multicenter pilot trial in male patients with New York Heart Association (NYHA) class III HF, left ventricular ejection fraction (LVEF) 20%-35%, and implanted defibrillator device who were prescribed stable optimal medical therapy.[36] Seventeen patients underwent implantation of a SCS device (cases) and four patients who did not fulfill the study criteria served as nontreated controls. At six-month follow up, no deaths or device-device interactions were reported. Composite score improved by 4.2 ± 1.3 in all cases, and 11 cases (73%) showed improvement in ≥4 of 6 efficacy parameters, including NYHA class ($p = 0.002$); peak maximum oxygen consumption ($p = 0.013$); LVEF ($p<0.001$); and LV end-systolic volume ($p = 0.002$). No improvements were observed in the four controls.

DORSAL ROOT GANGLION STIMULATION

Systematic Review

Stelter (2021) published a systematic review of 28 reports consisting of 354 patients evaluating the evaluating the efficacy of dorsal root ganglion stimulation for non-complex regional pain syndromes.[37] The authors reported that the majority of patients demonstrated at least a 50% mean pain reduction at their last follow-up time following treatment. Additional outcomes assessed including physical function, quality of life, and pain medication use also showed significant improvements.

Deer (2020) published a systematic literature review of three studies of dorsal root ganglion neurostimulation for the treatment of pain.[38] This review concluded that dorsal root ganglion neurostimulation has level II evidence (moderate) for treating chronic focal neuropathic pain and complex regional pain syndrome based on 1 high-quality pivotal RCT (ACCURATE) and 2 lower quality studies.

Huygen (2020) reported a pooled analysis of prospective studies of dorsal root ganglion stimulation for the treatment of chronic pain.[39] One RCT was included (ACCURATE) which is described in the following section and 6 prospective, single-arm, observational studies were included. The analysis included 217 patients with a permanent implant at 12-month follow-up. Analysis of pooled data showed an overall weighted mean pain score of 3.4, with 63% of patients reporting ≥50% pain relief. Effectiveness sub-analyses in CRPS-I, causalgia, and back pain resulted in a mean reduction in pain intensity of 4.9, 4.6, and 3.9 points, respectively. The pooled analysis showed a pain score for primary affected region ranging from 1.7 (groin) to 3.0 (buttocks) and responder rates of 80% for foot and groin, 75% for leg, and 70% for back. A substantial improvement in all PROs was observed at 12 months.

Vuka (2019) conducted a systematic review of the use of dorsal root ganglion stimulation for various pain syndromes (for example, complex regional pain syndrome, diabetic and non-diabetic peripheral neuropathy).[40] The literature search, conducted through September 2018, identified 29 studies for inclusion, 1 RCT, (ACCURATE trial; discussed below) and the remaining were case series or case reports. The median sample size was 6 (range 1 to 152). Most of the studies reported positive results with dorsal root ganglion stimulation. No meta-analyses could be conducted.

A systematic review, published in 2013 by Pope, evaluated therapeutics for chronic pain that target the dorsal root ganglion.[41] This review focused on ganglionectomy, and radiofrequency treatment of the dorsal root ganglion, with discussion of electrical stimulation of the DRG as an emerging therapy. Three studies of electrical DRG stimulation were included in the review, two case reports and one nonrandomized feasibility trial. The Deer feasibility trial (described below) prospectively followed 10 patients with chronic, intractable neuropathic pain, over four weeks.[42] Eight of the nine patients who completed the trial experienced a clinically meaningful (>30%) reduction in pain, as measured using a visual analog scale, with an average pain reduction of 70%. Seven of the nine reduced their utilization of pain medication. There were no adverse events reported. The two case studies included in the review described successful treatment of cervicogenic headache, post-herpetic neuralgia, and discogenic pain.

Randomized Controlled Trials

One RCT, the ACCURATE study, compared wireless injectable neurostimulators and standard SCS.[43] The trial, published by Deer in 2016, was a multicenter unblinded noninferiority trial. Eligibility criteria included chronic (≥6 months) intractable (failed ≥2 drugs from different

classes) neuropathic pain of the lower limbs associated with a diagnosis of CRPS or causalgia and no previous neurostimulation. Patients were randomized to receive DRG stimulation with the Axium device or standard SCS. They first underwent a temporary trial of stimulation lasting 3 to 30 days, depending on the protocol at each site. Patients who had 50% or greater reduction in lower limb pain after the temporary trial were eligible for permanent stimulation. Those who failed temporary stimulation exited the trial but were included in the analysis as treatment failures. Implanted patients were followed for 12 months, with assessments at 3, 6, 9, and 12 months postimplant.

A total of 152 patients were randomized and 115 (n=61 DRG, n=54 SCS) had a successful temporary trial and continued to permanent implantation. Twelve-month data were available for 105 patients (55 patients in the DRG group, 50 in the SCS group). The primary outcome was a composite measure of treatment success. Success was defined as: (1) 50% or greater reduction in VAS score from baseline to the end of the trial phase; (2) VAS at 3 months that was 50% or greater lower than baseline; and (3) no stimulation-related neurologic deficits experienced during the study. The noninferiority margin was set at 10%; the trial was designed such that, if the noninferiority end point was met, a superiority analysis was also performed. Treatment success at 3 month was achieved by 55 (81.2%) of 69 patients in the DRG arm and 39 (55.7%) of 70 in the SCS arm. The noninferiority margin was met, and DRG was found to be statistically superior to SCS ($p<0.001$). At the 12-month follow-up, the primary end point was achieved by 49 (74.2%) of 66 in the DRG group and 35 (53%) of 66 in the SCS group and, again, DRG was considered noninferior to SCS and also superior ($p<0.001$). In terms of paresthesias, at 3 months and 12, SCS patients were significantly more likely to report paresthesias in nonpainful areas than DRG patients. At 3 months, 84.7% of DRG patients and 65% of SCS patients reported paresthesias only in their painful areas; at 12 months, these percentages were 94.5% and 61.2%, respectively. Twenty-one serious adverse events occurred in 19 patients (8 in the DRG group, 11 in the SCS group; difference between groups, p=NS). A limitation of the study was that it was unblinded and industry-sponsored, which could potentially bias outcome assessment and reporting.

Mekhail (2019) conducted a sub-analysis on the patients receiving DRG neurostimulation in the ACCURATE study, to evaluate the occurrence and risk factors for paresthesia.[44] Among the 61 patients with DRG implants, the rates of paresthesia at 1 month, 3 months, 6 months, 9 months, and 12 months were 84%, 84%, 66%, 62%, and 62%, respectively. The patients who were parasthesia-free reported similar or better outcomes for pain and quality of life. Risk factors for parasthesia occurrence included higher stimulation amplitudes and frequencies, number of implanted leads, and younger age.

Nonrandomized Studies

Several case series have been published.[45-47] The largest of them are summarized below. Liem (2015) reported on the outcomes of an industry-sponsored multicenter, prospective trial of DRG stimulation at six months[48] and one year.[45] The trial consisted of a run-in period in which 51 participants received DRG stimulation via leads connected to an external stimulator, followed by surgical placement of a fully-implanted neurostimulator in 32 of the 39 patients that achieved 50% or greater pain relief during the run-in period. More than half of the patients with fully implanted DNG stimulators reported at least 50% relief in pain, as measured by visual analog scale. Average pain ratings were 58% lower than baseline at six months and 56% lower at 12 months post-implantation. Patients also reported improved quality of life and mood by questionnaire (EQ-5D-3L and POMS). Over 12 months, there were 86 adverse events

reported in 29 patients, including temporary motor stimulation (12 events), CSF leak (seven events) and infection (seven events). Approximately half of these events were judged by the investigators to be related to the device. Seven subjects had their devices removed and were withdrawn from the study.

A subgroup analysis of the Liem study examined positional effects on paresthesia during DRG stimulation in the 32 patients with implanted neurostimulators.[49] Paresthesia and pain relief achieved with spinal cord stimulation can change as patients change position from upright to prone or supine, causing uncomfortable sensations. This study found no statistically significant difference in paresthesia intensity by body position. In order to truly determine the efficacy and safety of DRG stimulation well designed comparative studies with long-term follow-up must be performed to compare it to standard spinal cord stimulation.

Schu reported on an industry-sponsored multicenter European case series of 29 patients treated with DRG stimulation for chronic neuropathic groin pain.[46] Of the 29 patients who underwent a 30-day trial period, 25 (86.2%) underwent implantation with the Axium DRG device. Final lead placement between T12 and L4 was determined based on patient feedback during paraesthesia mapping. Data analysis was based on the results of 23 patients with a mean follow-up of 27.8 weeks. The average pain reduction was 71.4 ± 5.6%, and 82.6% (19/23) of patients experienced a > 50% reduction in their pain at the latest follow-up. Adverse events were not reported. The authors stated that paraesthesia was largely unaffected by positional changes. Limitations of this study include small sample size, lack of comparative data, and potential bias inherent in pain as a subjective outcome measure.

In 2013 Deer conducted an industry-sponsored case series to evaluate the efficacy and safety of the Axium DRG system in ten patients with chronic intractable pain of the trunk and/ or limbs.[42] The study was conducted across four centers for a period of four weeks. The study protocol and lead implantation procedures were similar to those reported by Liem above; however, only results of trial DRGS over a period of three to seven days were reported. On average, there was a 70% reduction in pain following stimulation ($p = 0.0007$). Eight of the nine patients experienced a clinically meaningful (>30%) reduction in pain, and seven of the nine reduced their pain medication utilization. The study did not consider longer term effects with a permanently implanted device. Seventeen adverse events occurred of which 14 were considered to be device-related; none were thought to be serious.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS (ASIPP)[50]

In 2013, the ASIPP updated their evidence-based guidelines for interventional techniques in the management of chronic spinal pain. The guidelines included the statement that there is fair evidence in support of SCS in managing patient with failed back surgery syndrome.

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION AND THE AMERICAN HEART ASSOCIATION (ACCF/AHA)

Guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published in 2007 with focused updates in 2011[51] and 2012[52]) for the management of patients with unstable angina/non ST-Elevation myocardial infarction state:

> "Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain

despite the implementation of Class I measures may be considered for patients with syndrome X. (Level of Evidence: B)."[53] However, the level of evidence indicates that the "treatment usefulness/ efficacy [is] less well established" and that this recommendation may be based on a single randomized controlled trial or one or more non-randomized studies.

The 2012 updated joint ACCF/AHA guidelines recommend that SCS may be considered for relief of refractory angina in patients with stable ischemia heart disease (Level of evidence: C, defined as very limited populations evaluated and/or only consensus opinion of experts, cases studies, or standard of care).[54] The guidelines conclude:

"Studies of spinal cord stimulation suggest that this technique might have some use as a method to relieve angina in patients with symptoms that are refractory to standard medical therapy and revascularization. There is a paucity of data on the mechanisms and long-term risks and benefits of this therapeutic approach, however."

NEUROPATHIC PAIN SPECIAL INTEREST GROUP OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN[55]

In 2013, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG) published consensus recommendations on management of neuropathic pain. The recommendations supporting the use of SCS for failed back surgery syndrome and for complex regional pain syndrome we rated as weak (quality of evidence moderate to low; strength of recommendation weak to inconclusive). The recommendation for SCS for postherpetic neuralgia was also rated as weak (quality of evidence low; strength of recommendation inconclusive).

INTERNATIONAL NEUROMODULATION SOCIETY[56]

The International Neuromodulation Society convened a Neuromodulation Appropriateness Consensus Committee (NACC) to develop best practices for the use of DRG stimulation for the treatment of chronic pain syndromes. The NACC was comprised of experts in anesthesiology, neurosurgery, and pain medicine. The NACC performed a systematic literature search through June 2017 and identified 29 publications providing evidence for the consensus recommendations. The evidence was graded using the modified Pain Physician criteria and the USPSTF criteria. The NACC report gave a strong recommendation that DRG stimulation is recommended for CRPS type I or type II.

AMERICAN SOCIETY OF PAIN AND NEUROSCIENCE

The American Society of Pain and Neuroscience issued a comprehensive guideline in 2021 on the management of cancer-related pain.[57] The guideline found that spinal cord stimulation may be considered for 1) treatment of refractory cancer pain (Level II-3-C evidence: multiple series compared over time, with or without intervention, and surprising results in noncontrolled experience; treatment is neither recommendable nor inadvisable), and 2) on a case-by-case basis for "pain that is related to cancer treatment such as chemotherapy-induced peripheral neuropathy" (level III-C evidence: clinical experiences-based opinions, descriptive studies, clinical observations, or reports of expert committee; treatment is neither recommendable nor inadvisable).

ASPN also published consensus guidelines on interventional therapies for knee pain in 2022.[58]The guidelines state that "Chronic pain that is refractory to acute treatment is managed

by progressing to spinal cord stimulator, dorsal root ganglion stimulator, or botulinum toxin (Botox) injection." They also include the statement that "DRG [Dorsal Root Ganglion Stimulation] is a safe and effective treatment option for chronic post-surgical and focal neuropathic pain of the knee (ie, complex regional pain syndrome [CRPS]); Level I, Grade A, Consensus Strong."

Consensus guidelines on interventional therapies for back pain were also published in 2022 and made the following recommendations for SCS: following lumbar surgery (Level I-A, Grade A), treatment of non-surgical low back pain (Level I-C, Grade B), and treatment of lumbar spinal stenosis (Level I-C, Grade C).[59]

SUMMARY

SPINAL CORD STIMULATORS

There is enough research to show that spinal cord stimulation (SCS) including high frequency SCS for the treatment of chronic trunk or limb pain, when all other treatment modalities have failed to adequately reduce symptoms may improve health outcomes. In addition, practice guidelines recommend SCS for select patients. Therefore, SCS including temporary and the potential permanent implantation may be considered medically necessary for treatment of chronic refractory pain of the trunk or limbs when policy criteria are met.

In certain situations, a spinal cord stimulator may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing spinal cord stimulator may be considered medically necessary after the device has been placed.

In certain situations, a spinal cord stimulator may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient’s medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a spinal cord stimulator may be considered medically necessary when device replacement Criteria are met.

When a stimulator is in its warranty period or can be repaired or adapted adequately to meet the patient’s medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a spinal cord stimulator is considered not medically necessary when device replacement Criteria are not met.

When criteria are not met, spinal cord stimulation for severe and chronic refractory neuropathic pain of the trunk or limbs is not clinically appropriate and is therefore considered not medically necessary.

There is not enough research to show that spinal cord stimulation (SCS), including standard or high frequency, in the treatment of conditions not related to severe and chronic refractory pain of the trunk or limbs improves health outcomes or is more effective than standard of care. Therefore, the use of SCS, including standard or high frequency is investigational for the treatment of all other conditions not related to severe and chronic refractory pain of the trunk or limbs.

DORSAL ROOT GANGLION STIMULATORS

There is enough research to show that dorsal root ganglion (DRG) stimulation for the treatment of chronic trunk or limb pain, when all other treatment modalities have failed to adequately reduce symptoms may improve health outcomes. In addition, practice guidelines recommend DRG stimulation for select patients. Therefore, DRG stimulation may be considered medically necessary for treatment of chronic refractory pain of the trunk or limbs when policy criteria are met.

In certain situations, a dorsal root ganglion stimulator may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing spinal cord stimulator may be considered medically necessary after the device has been placed.

In certain situations, a dorsal root ganglion stimulator may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a spinal cord stimulator may be considered medically necessary when device replacement Criteria are met.

When a stimulator is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a dorsal root ganglion stimulator is considered not medically necessary when device replacement Criteria are not met.

When criteria are not met, dorsal root ganglion stimulation for severe and chronic refractory pain of the trunk or limbs due to type I or type II complex regional pain syndrome, including reflex sympathetic dystrophy or causalgia, is not clinically appropriate and is therefore considered not medically necessary.

For all other indications, there is not enough research to show that dorsal root ganglion (DRG) stimulation is safer and/or more effective than standard of care when policy criteria are not met. Therefore, the use of dorsal root ganglion stimulation is considered investigational when policy criteria are not met.

REFERENCES

1. Mekhail NA, Mathews M, Nageeb F, et al. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. *Pain Pract.* 2011;11(2):148-53. PMID: 21371254
2. Lihua P, Su M, Zejun Z, et al. Spinal cord stimulation for cancer-related pain in adults. *The Cochrane database of systematic reviews.* 2013;2:CD009389. PMID: 23450600
3. Peng L, Min S, Zejun Z, et al. Spinal cord stimulation for cancer-related pain in adults. *The Cochrane database of systematic reviews.* 2015;6:CD009389. PMID: 26121600
4. Yakovlev AE, Resch BE. Spinal cord stimulation for cancer-related low back pain. *Am J Hosp Palliat Care.* 2012;29:93-7. PMID: 21669945
5. Yakovlev AE, Resch BE, Karasev SA. Treatment of cancer-related chest wall pain using spinal cord stimulation. *Am J Hosp Palliat Care.* 2010;27:552-6. PMID: 20555037
6. Shimoji K, Hokari T, Kano T, et al. Management of intractable pain with percutaneous epidural spinal cord stimulation: differences in pain-relieving effects among diseases and sites of pain. *Anesthesia and analgesia.* 1993;77(1):110-6. PMID: 8317715

7. Meglio M, Cioni B, Rossi GF. Spinal cord stimulation in management of chronic pain. A 9-year experience. *Journal of neurosurgery.* 1989;70(4):519-24. PMID: 2538588
8. de Jongste MJ, Hautvast RW, Hillege HL, et al. Efficacy of spinal cord stimulation as adjuvant therapy for intractable angina pectoris: a prospective, randomized clinical study. Working Group on Neurocardiology. *J Am Coll Cardiol.* 1994;23(7):1592-7. PMID: 8195519
9. Hautvast RW, DeJongste MJ, Staal MJ, et al. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. *Am Heart J.* 1998;136(6):1114-20. PMID: 9842028
10. McNab D, Khan SN, Sharples LD, et al. An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPiRiT trial. *Eur Heart J.* 2006;27(9):1048-53. PMID: 16554313
11. Mannheimer C, Eliasson T, Augustinsson LE, et al. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. *Circulation.* 1998;97(12):1157-63. PMID: 9537342
12. Ekre O, Eliasson T, Norrsell H, et al. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study. *Eur Heart J.* 2002;23(24):1938-45. PMID: 12473256
13. Norrsell H, Pilhall M, Eliasson T, et al. Effects of spinal cord stimulation and coronary artery bypass grafting on myocardial ischemia and heart rate variability: further results from the ESBY study. *Cardiology.* 2000;94(1):12-8. PMID: 11111139
14. Pan X, Bao H, Si Y, et al. Spinal Cord Stimulation for Refractory Angina Pectoris: A Systematic Review and Meta-analysis. *The Clinical journal of pain.* 2016. PMID: 27875377
15. Tsigaridas N, Naka K, Tsapogas P, et al. Spinal cord stimulation in refractory angina. A systematic review of randomized controlled trials. *Acta cardiologica.* 2015;70(2):233-43. PMID: 26148385
16. Taylor RS, De Vries J, Buchser E, et al. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *BMC Cardiovasc Disord.* 2009;9:13. PMID: 19320999
17. Borjesson M, Andrell P, Lundberg D, et al. Spinal cord stimulation in severe angina pectoris--a systematic review based on the Swedish Council on Technology assessment in health care report on long-standing pain. *Pain.* 2008;140:501-8. PMID: 19004553
18. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *The New England journal of medicine.* 2000;343(9):618-24. PMID: 10965008
19. Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes care.* 2014;37(11):3016-24. PMID: 25216508
20. Eldabe S, Thomson S, Duarte R, et al. The Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina (RASCAL Study): A Pilot Randomized Controlled Trial. *Neuromodulation : journal of the International Neuromodulation Society.* 2016;19(1):60-70. PMID: 26387883
21. Zipes DP, Svorkdal N, Berman D, et al. Spinal Cord Stimulation Therapy for Patients With Refractory Angina Who Are Not Candidates for Revascularization. *Neuromodulation : journal of the International Neuromodulation Society.* 2012. PMID: 22494013

22. Lanza GA, Grimaldi R, Greco S, et al. Spinal cord stimulation for the treatment of refractory angina pectoris: a multicenter randomized single-blind study (the SCS-ITA trial). *Pain.* 2011;152(1):45-52. PMID: 21084162
23. Abu Dabrh AM, Steffen MW, Asi N, et al. Nonrevascularization-based treatments in patients with severe or critical limb ischemia. *Journal of vascular surgery.* 2015;62(5):1330-9 e13. PMID: 26409842
24. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *The Cochrane database of systematic reviews.* 2013;2:CD004001. PMID: 23450547
25. Klomp HM, Steyerberg EW. Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischaemia (Br J Surg 2004; 91: 948-955). *The British journal of surgery.* 2005;92(1):120; author reply 20-1. PMID: 15635617
26. Klomp HM, Steyerberg EW, Habbema JD, et al. What is the evidence on efficacy of spinal cord stimulation in (subgroups of) patients with critical limb ischemia? *Ann Vasc Surg.* 2009;23(3):355-63. PMID: 19128928
27. Simpson EL, Duenas A, Holmes MW, et al. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess.* 2009;13(17):iii, ix-x, 1-154. PMID: 19331797
28. Klomp HM, Spincemaille GH, Steyerberg EW, et al. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. *Lancet.* 1999;353(9158):1040-4. PMID: 10199350
29. Klomp HM, Spincemaille GH, Steyerberg EW, et al. Design issues of a randomised controlled clinical trial on spinal cord stimulation in critical limb ischaemia. ESES Study Group. *Eur J Vasc Endovasc Surg.* 1995;10(4):478-85. PMID: 7489218
30. Spincemaille GH, Klomp HM, Steyerberg EW, et al. Technical data and complications of spinal cord stimulation: data from a randomized trial on critical limb ischemia. *Stereotact Funct Neurosurg.* 2000;74(2):63-72. PMID: 11251396
31. Spincemaille GH, Klomp HM, Steyerberg EW, et al. Pain and quality of life in patients with critical limb ischaemia: results of a randomized controlled multicentre study on the effect of spinal cord stimulation. ESES study group. *Eur J Pain.* 2000;4(2):173-84. PMID: 10957698
32. Jivegard LE, Augustinsson LE, Holm J, et al. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study. *Eur J Vasc Endovasc Surg.* 1995;9(4):421-5. PMID: 7633987
33. Claeys LG, Horsch S. Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation. *Int Angiol.* 1996;15(4):344-9. PMID: 9127776
34. Zipes DP, Neuzil P, Theres H, et al. Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure: The DEFEAT-HF Study. *JACC Heart failure.* 2016;4(2):129-36. PMID: 26682789
35. Torre-Amione G, Alo K, Estep JD, et al. Spinal cord stimulation is safe and feasible in patients with advanced heart failure: early clinical experience. *European journal of heart failure.* 2014;16(7):788-95. PMID: 24961194
36. Tse HF, Turner S, Sanders P, et al. Thoracic Spinal Cord Stimulation for HEArt Failure as a Restorative Treatment (SCS HEART Study): First-in-man Experience. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2014. PMID: 25500165
37. Stelter B, Karri J, Marathe A, et al. Dorsal Root Ganglion Stimulation for the Treatment of Non-Complex Regional Pain Syndrome Related Chronic Pain Syndromes: A

Systematic Review. *Neuromodulation : journal of the International Neuromodulation Society.* 2021. PMID: 33501749
38. Deer TR, Hunter CW, Mehta P, et al. A Systematic Literature Review of Dorsal Root Ganglion Neurostimulation for the Treatment of Pain. *Pain Med.* 2020;21(8):1581-89. PMID: 32803221
39. Huygen F, Kallewaard JW, Nijhuis H, et al. Effectiveness and Safety of Dorsal Root Ganglion Stimulation for the Treatment of Chronic Pain: A Pooled Analysis. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(2):213-21. PMID: 31730273
40. Vuka I, Marciuš T, Došenović S, et al. Neuromodulation with electrical field stimulation of dorsal root ganglion in various pain syndromes: a systematic review with focus on participant selection. *Journal of pain research.* 2019;12:803-30. PMID: 30881093
41. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Med.* 2013;14(10):1477-96. PMID: 23802747
42. Deer TR, Grigsby E, Weiner RL, et al. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation : journal of the International Neuromodulation Society.* 2013;16(1):67-71; discussion 71-2. PMID: 23240657
43. Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain.* 2017;158(4):669-81. PMID: 28030470
44. Mekhail N, Deer TR, Kramer J, et al. Paresthesia-Free Dorsal Root Ganglion Stimulation: An ACCURATE Study Sub-Analysis. *Neuromodulation : journal of the International Neuromodulation Society.* 2019. PMID: 30861286
45. Liem L, Russo M, Huygen FJ, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation : journal of the International Neuromodulation Society.* 2015;18(1):41-8; discussion 48-9. PMID: 25145467
46. Schu S, Gulve A, ElDabe S, et al. Spinal cord stimulation of the dorsal root ganglion for groin pain-a retrospective review. *Pain Pract.* 2015;15(4):293-9. PMID: 24690212
47. Weiner RL, Yeung A, Montes Garcia C, et al. Treatment of FBSS Low Back Pain with a Novel Percutaneous DRG Wireless Stimulator: Pilot and Feasibility Study. *Pain Med.* 2016;17(10):1911-16. PMID: 27125284
48. Liem L, Russo M, Huygen FJ, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation : journal of the International Neuromodulation Society.* 2013;16(5):471-82; discussion 82. PMID: 23668228
49. Kramer J, Liem L, Russo M, et al. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. *Neuromodulation : journal of the International Neuromodulation Society.* 2015;18(1):50-7; discussion 57. PMID: 25147020
50. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain physician.* 2013;16(2 Suppl):S49-283. PMID: 23615883
51. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;123:e426-579. PMID: 21444888

52. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013. PMID: 23630129
53. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol.* 2007;50(7):e1-e157. PMID: 17692738
54. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2012;60(24):e44-e164. PMID: 23182125
55. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain.* 2013;154(11):2249-61. PMID: 23748119
56. Deer TR, Pope JE, Lamer TJ, et al. The Neuromodulation Appropriateness Consensus Committee on Best Practices for Dorsal Root Ganglion Stimulation. *Neuromodulation : journal of the International Neuromodulation Society.* 2019;22(1):1-35. PMID: 30246899
57. Aman MM, Mahmoud A, Deer T, et al. The American Society of Pain and Neuroscience (ASPN) Best Practices and Guidelines for the Interventional Management of Cancer-Associated Pain. *Journal of pain research.* 2021;14:2139-64. PMID: 34295184
58. Hunter CW, Deer TR, Jones MR, et al. Consensus Guidelines on Interventional Therapies for Knee Pain (STEP Guidelines) from the American Society of Pain and Neuroscience. *Journal of pain research.* 2022;15:2683-745. PMID: 36132996
59. Sayed D, Grider J, Strand N, et al. The American Society of Pain and Neuroscience (ASPN) Evidence-Based Clinical Guideline of Interventional Treatments for Low Back Pain. *Journal of pain research.* 2022;15:3729-832. PMID: 36510616

CODES

NOTE: HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
		Insertion or replacement of percutaneous electrode array, spinal, with integrated
	0785T	Revision or removal of neurostimulator electrode array, spinal, with integrated neurostimulator
		Electronic analysis with simple programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact

Codes	Number	Description
		group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, spinal cord or sacral
	0789T	Electronic analysis with complex programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, spinal cord or sacral nerve, 4 or more parameters
	63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
	63662	Removal of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
	63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
		Insertion or replacement of spinal neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse
	63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver, with detachable connection to electrode array
		Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve,
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
		;with complex spinal cord, or peripheral (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
		Generator, neurostimulator (implantable), includes closed feedback loop leads
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month

Codes	Number	Description
	L8680	Implantable neurostimulator electrode, each
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 52

Ventricular Assist Devices and Total Artificial Hearts

Effective: March 1, 2024

Next Review: December 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ventricular assist devices and total artificial hearts provide mechanical circulation for patients with end-stage heart disease who are waiting for, or cannot survive, a heart transplant.

MEDICAL POLICY CRITERIA

Note: This policy does not address the use of percutaneous ventricular assist devices (pVADs) which may be considered medically necessary.

I. Implantable ventricular assist devices (i.e., LVADs, RVADs and BiVADs)

A. Implantable ventricular assist devices with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** for any of the following indications (1.-3.):

1. As a bridge to transplantation for patients who meet all of the following criteria:

a. Currently listed as a heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation; and

b. Not expected to survive until a donor heart can be obtained; or

2. For use in the post-cardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass; or
3. As destination therapy in patients meeting all of the following criteria (a.- e.):
    a. End-stage heart failure; and
    b. New York Heart Association (NYHA) Class III heart failure with dyspnea upon mild physical activity or NYHA Class IV (NYHA Class III = marked limitation of physical activity; less than ordinary activity leads to symptoms. NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest.); and
    c. Left ventricular ejection fraction 25% or less; and
    d. One of the following criteria is met:
        i. Inotrope-dependent; or
        ii. Cardiac index is less than 2.2 liters per minute per meter squared while not on inotropes; and
    e. One of the following criteria is met:
        i. On optimal medical management, including beta-blockers and/or ACE inhibitors if not contraindicated, for at least 45 of the last 60 days and are failing to respond; or
        ii. Advanced heart failure for at least 14 days and dependent on intra-aortic balloon pump for 7 days or more.

B. Ventricular assist devices and aortic counterpulsation devices are considered **investigational** in all other circumstances, including but not limited to the use of a non-FDA approved device.

II. Total Artificial Hearts

A. Total artificial hearts with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** as a bridge to heart transplantation in patients meeting all of the following criteria:
1. Have biventricular failure; and
2. Currently listed as heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation; and
3. Not considered a candidate for a univentricular or biventricular support device; and
4. Have no other reasonable medical or surgical treatment options; and
5. Not expected to survive until a donor heart can be obtained.

B. Total artificial hearts are considered **investigational** in all other circumstances, including but not limited to the following:
1. Use as destination therapy; or
2. Use of a total artificial heart that does not have FDA PMA, 510(k), or HDE clearance

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- For Implantable Ventricular Assist Devices:
    - Documentation as to whether this is a bridge to heart transplant, being used post-cardiotomy for patient who is unable to be weaned of cardiopulmonary bypass, or as destination therapy
    - For destination therapy:
        - Documentation of end-stage heart failure, documentation of ejection fraction, documentation of inotrope dependency or cardiac index score when not on inotropes, documentation of optimal medical management or documentation of advanced heart failure and dependency on an intra-aortic balloon pump, and current NYHA classification, including duration of NYHA classification, symptoms, and treatments tried.
- For Total Artificial Heart:
    - Documentation that this is a bridge to heart transplant and patient has biventricular failure; is listed as heart transplant candidate or undergoing evaluation to determine candidacy for heart transplant; is not considered a candidate for univentricular or biventricular support device; has no other reasonable medical or surgical treatment options; and is not expected to survive until a donor heart can be obtained

CROSS REFERENCES

1. Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults, Medicine, Policy No. 152
2. Surgical Ventricular Restoration, Surgery, Policy No. 149
3. Heart Transplant, Transplant, Policy No. 02
4. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

VENTRICULAR ASSIST DEVICES (VADS)

Biventricular, Right Ventricular, and Left Ventricular Devices

There are three kinds of ventricular assist devices: biventricular (BiVADs), right ventricular (RVADs), and left ventricular (LVADs). Surgically implanted ventricular assist devices (VADs) are attached to the native heart and vessels to provide temporary mechanical circulatory support by augmenting cardiac output. LVADs to support the left ventricle are the most commonly used VADs, but right ventricular and biventricular devices may also be used. LVADs are most commonly used as a bridge to transplantation for those patients who are not expected to survive without mechanical support until a heart becomes available. LVADs may also be used as a bridge to recovery in patients with reversible conditions affecting cardiac output (e.g., post-cardiotomy cardiogenic shock). More recently, given the success of LVADs for prolonged periods of time, there has been interest in using LVADs as permanent

"destination" therapy for patients with end-stage heart disease who are not candidates for human heart transplantation due to age or other comorbidities.

Aortic Counterpulsation Devices

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved.

TOTAL ARTIFICIAL HEARTS

The total artificial heart (TAHs) replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. TAHs may be implanted temporarily as a bridge to heart transplantation or permanently as destination therapy in those who are not candidates for transplantation.

The CardioWest™ Total Artificial Heart is a temporary TAH, which is used in the inpatient hospital setting as a bridge to heart transplantation. The CardioWest TAH is implanted after the native ventricles have been excised. The AbioCor® Implantable Replacement Heart is a permanent TAH currently available as destination therapy for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. The device has an internal battery that allows the recipient to be free from all external connections for up to one hour. The system also includes two external batteries that allow free movement for up to two hours. During sleep and while batteries are being recharged, the system can be plugged into an electrical outlet. In order to receive the AbioCor® artificial heart, in addition to meeting other criteria, patients must undergo a screening process to determine if their chest volume is large enough to hold the two-pound device which is too large for about 90% of women and many men.

REGULATORY STATUS

Device Name	Device Type	Manufacturer	FDA Approval	Indication
HeartMate II®	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
HeartMate 3™	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
Thoratec® IVAD	BiVAD	Thoratec Corp.	PMA + Supplement	Bridge to transplant and postcardiotomy
Centrimag®	RVAD	Thoratec Corp.	PMA	Postcardiotomy, bridge to decision
Novacor®	LVAD	World Heart, Inc.	PMA	Bridge to transplant
DeBakey VAD® Child	LVAD	MicroMed Technology, Inc.	HDE	Bridge to transplant in children 5-16 years of age
EXCOR® Pediatric System	BiVAD	Berlin Heart, Inc.	HDE	Bridge to transplant, pediatric (newborns to teens)

Device Name	Device Type	Manufacturer	FDA Approval	Indication
Jarvik 2000	LVAD	Jarvik Heart, Inc.	*IDE-Investigational*†	
AutoCat 2 WAVE® IABP System	IABP	Arrow Intl., Inc.	none	
Maquet CS300™ IABP	IABP	Maquet Cardiovascular, LLC	none	
SynCardia Temporary TAH (formerly called CardioWest™)	Temporary total artificial heart	SynCardia Systems, Inc.	510(k)	Bridge to transplant – for use inside the hospital
AbioCor® TAH	Implantable Replacement Heart System	AbioMed, Inc.	HDE	Destination therapy

†FDA Investigational Device Exemption (IDE) is not considered a full FDA approval. Devices with an IDE designation are considered investigational.

In August 2015, the U.S. Food and Drug Administration (FDA) published a safety communication about serious adverse events with implantable left ventricular assist devices.[1]

In August 2016, HeartWare® recalled its VAD Pumps due to a design flaw that was deemed by FDA as potentially causing serious injuries or death (class I recall). The devices affected were manufactured and distributed from March 2006 and May 2018. The device was discontinued in 2021 due to evidence demonstrating a higher frequency of neurological adverse events and mortality compared to other devices. FDA product codes: 204 and 017. Additional FDA class I and II recalls associated with the HeartWare VAD have been issued in since the HeartWare® was discontinued in 2021.[2]

A class I recall was issued for the HeartMate 3™ in April 2018 affecting all manufacturing dates. FDA product code: DSQ.

Although adverse events have been reported, the FDA recognizes “that LVADs are life-sustaining, life-saving devices for patients with advanced left ventricular heart failure. When used for the currently approved indications in appropriately selected patients, we believe the benefits of these LVADs continue to outweigh the risks”.

EVIDENCE SUMMARY

The principal outcome associated with treatment of refractory heart failure (HF) is to prolong survival, either temporarily as a bridge to decision, recovery, or heart transplantation, or permanently as a replacement for the damaged heart in patients who are not candidates for heart transplantation.

VENTRICULAR ASSIST DEVICES

BRIDGE TO TRANSPLANTATION, LEFT VENTRICULAR ASSIST DEVICES

Systematic Reviews

A systematic review (SR) published in 2011 supported the conclusions reached in the 1996 BCBSA TEC assessment.[3, 4] The 2011 review included 31 observational studies that compared outcomes of transplant in patients who did and did not have pre-transplant left ventricular assist devices (LVADs). Survival at one year was more likely in patients who had LVAD treatment, but this benefit was confined to patients who received an intra-corporeal device (relative risk [RR] 1.8, 95% confidence interval [CI] 1.53 to 2.13). For patients treated with an extracorporeal device, the likelihood of survival was not different from patients who were not treated with an LVAD (RR 1.08, 95% CI 0.95 to 1.22). There was no difference in the risk of rejection between patients who did and did not receive LVAD treatment.

Nonrandomized Studies

Adult PatientsAdditional reports not included in the 1996 TEC assessment or the 2011 SR are consistent with the above analysis.[5-7] It should be recognized that left ventricular assist devices cannot change the number of patients undergoing heart transplantation due to the fixed number of donor hearts. However, the LVAD will categorize its recipient as a high priority heart transplant candidate. Currently available LVADs consist of pulsatile devices that require both stiff power vent lines that perforate the skin and bulky implantable pump chambers. There is considerable research interest in developing non-pulsatile axial flow systems that have the potential for small size and low-noise levels.[8-13]

Pagani (2021) used Medicare claims data to analyze survival outcomes in patients who received different LVADs between January 2014 and December 2018, with followup through December 2019.[14] Of 4195 patients who received implants, there were 117 (14.3%) deaths among 821 Heartmate3™ patients, 375 (20.4%) deaths among 1840 Heartmate II® patients, and 375 (24.5%) deaths among 1534 patients with other VADs. The adjusted hazard ratio for mortality at 1-year (confirmed in a propensity score matched analysis) for the HeartMate 3 versus HeartMate II® was 0.64 (95% CI; 0.52 to 0.79, p<.0001) and for the HeartMate 3™ versus other-VADs was 0.51 (95% CI; 0.42 to 0.63, p<.0001).

Aissaoui (2018) published an observational study comparing 224 patients in Germany and France with end-stage heart failure who received VAD as first option (group I, n=83) or either heart transplantation or medical therapy as first option (group II, n=141).[15] The estimated two-year survival was 44% for group I and 70% for group II (p<0.001). The study was limited by the lack of randomization and possible patient selection bias.

Grimm (2016) compared outcomes for patients based on the duration of LVAD use, using data from the United Network for Organ Sharing database.[16] Of the 1,332 included patients, 130 (9.8%) were classified as short duration (< 90 days), 729 (54.7%) were classified as intermediate duration (90 to 365 days), and 473 (35.5%) were classified as long duration (>365 days). A greater proportion of patients in the intermediate and long duration groups were considered functionally independent prior to transplantation compared with the short duration patients. There was no difference in 30-day survival, six-month survival, or one-year survival between the groups. Also, despite worse renal function in the intermediate and long-term groups, there was no difference between groups in new-onset post-transplant renal failure.

Another report by Grimm (2016),which used the United Network for Organ Sharing database, suggested that patients bridged to transplant with an LVAD have better outcomes than those bridged with TAH or biventricular assist devices.[17] Cheng (2016) compared BiVAD to TAH outcomes in this database, and found similar wait-list survival between the groups.[18]

Deo (2014) reported no significant differences in outcomes for 37 patients bridged to transplant with a ventricular assisted device (VAD) and 70 patients who underwent a heart transplant directly.[19] In 2013, Slaughter reported combined outcomes for patients included in the HeartWare® bridge-to-transplant study.[20] The study included 322 patients with heart failure, eligible for heart transplant, who received the HeartWare® (140 patients from the original study; 190 patients in the continue-access protocol) who were monitored to outcome or had completed 180 days of follow-up at the time of this analysis. Survival at 60, 180, and 360 days was 97%, 91%, and 84%, respectively. The most common adverse events were respiratory dysfunction, arrhythmias, sepsis, and driveline exit-site infections. Patients generally had improvements in quality of life measures.

Aaronson (2012) reported results of a multicenter, prospective study of a newer generation LVAD, the HeartWare®, which is a smaller, continuous flow centrifugal device that is implanted in the pericardial space.[21] The study enrolled 140 patients who were awaiting heart transplantation who underwent HeartWare® implantation. A control group of 499 subjects was comprised of patients drawn from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, which collects data on patients who receive FDA-approved durable mechanical circulatory support devices. The study's primary outcome was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes were comparisons of survival between groups and functional, quality of life, and adverse event outcomes in the HeartWare® group. Success occurred in 90.7% of the HeartWare® group and 90.1% of controls ($p<0.001$, noninferiority with a 15% margin). Serious adverse events in the HeartWare® group included, most commonly, bleeding, infections, and perioperative right heart failure.

Evidence suggests that the HeartMate II® axial achieves similar or better results than the earlier pulsatile HeartMate I model. In six reports with samples ranging from 32 to 279 patients, most participants received the new device as a bridge to transplantation.[22-27] Survival rates at six months and one year were 67% to 87%, and 50% to 80%, respectively. These rates are similar to those reported from INTERMACS.[28] An additional report from INTERMACS comparing the HeartMate II® to other LVAD devices for patients who received them with a bridge to transplantation indication reported that 80% and 91% of HeartMate II® and other LVAD patients reached transplant, cardiac recovery, or ongoing LVAD support by six months.[29] One report, however, compared HeartMate I and HeartMate II® recipients at a single center, finding the same one year survival and similar rates of subsequent development of right heart failure.[24] Serious adverse events occurring after HeartMate II® implantation included bleeding episodes requiring reoperation, stroke, infection, and device failure. A European study that included 67 bridge to transplant patients and 31 destination therapy patients found similar one-year survival rates in the two groups: 63% and 69%, respectively. A report on HeartMate II® recipients at a single institution found that out of 250 LVAD patients between November 2011 and June 2016, 6% (16) required a device pump exchange during the study period, and all but one patient survived until hospital discharge.[30]

Pediatric Patients

Systematic Review

Palazzolo (2022) published a SR to analyze current landscape of pediatric mechanical circulatory assist (MCA) devices.[31] They included 27 devices including VADs, Fontan assist devices and TAHs. The authors conclude that there is still not sufficient pump technology that

meets the constraints of a pediatric population such as patient sizes, increased cardiovascular demand with growth and physiologic heterogeneity of congenital heart disease.

Publications on children using VADs as a bridge to transplantation have reported positive outcomes. For example, a retrospective study of all children listed for a heart transplant at a single center between 1993 and 2009 found that mortality dropped significantly after the availability of VADs.[32] Davies (2008) reported that pediatric patients requiring a pretransplantation VAD had similar long-term survival to those not receiving mechanical circulatory support.[33]

A retrospective registry study by Jeewa (2018) assessed long-term outcomes for pediatric VAD use as a bridge to transplantation in patients from the Berlin Heart investigational device exemption trial.[34] These patients (n=109) were compared with matched controls from the Pediatric Heart Transplant Study who did not require mechanical circulatory support (n=166). There was no significant difference between the groups for five-year survival (81% for VAD, 88% for non-VAD, p=0.09) or for rates of infection or rejection.

Bulic (2017) identified all U.S. children between 1 and 21 years of age at heart transplant between 2006 and 2015 for dilated cardiomyopathy who were supported with an LVAD or vasoactive infusions alone at the time of heart transplant from the Organ Procurement and Transplant Network registry (n=701).[35] Children receiving LVAD were older, on a higher level of hemodynamic support, more likely to be on dialysis and waited long to receive a donor heart than children receiving vasoactive infusions. Functional status as measured by the median Karnofsky Performance Scale at heart transplant was higher for children receiving LVAD compared with vasoactive infusion (6 vs 5, p<0.001) and children receiving LVAD were more likely to be discharged from the hospital at the time of transplant. The percent of children having stroke at the time of transplant was higher in those receiving LVAD (3% vs 1%, p=0.04).

Almond (2013) reported results from a prospective, multicenter registry to evaluate outcomes in children who received the Berlin Heart EXCOR® device as a bridge to transplant.[36] All patients were followed up from the time of EXCOR® implantation until transplantation, death, or recovery. The study included 204 children, 67% of whom received the device under compassionate use. Survival at 12 months on EXCOR® support was 75%, including 64% who survived to transplantation, 6% who recovered (device explanted and patient survived 30 days), and 5% alive with the device in place. In a follow-up study which evaluated 204 children from the same registry, Jordan reported relatively high rates of neurologic events in pediatric patients treated with the EXCOR® device (29% of patients), typically early in the course of device use.[37] A 2016 report on this group included 358 bridge-to-transplant EXCOR® patients, and found that short- and mid-term post-transplant survival in these patients was similar to that of patients who did not receive pre-transplant mechanical circulatory support.[38]

Wehman (2016) reported on post-transplant survival outcomes for pediatric patients who received a VAD, extracorporeal membrane oxygenation (ECMO), or no mechanical circulatory support, in the pre-transplant period.[39] The study included 2,777 pediatric patients who underwent heart transplant from 2005 to 2012, who were identified through the United Network for Organ Sharing Database, of whom 428 were bridged with VADs and 189 were bridged with ECMO. In unadjusted analysis, the actuarial five-year survival was highest in the direct-to-transplant group (77%), followed by the VAD group (49%) and then the ECMO group (35%). In a proportional hazards model to predict time to death, restricted to the first four months post-

transplant, ECMO bridging was significantly associated with higher risk of death (adjusted hazard ratio [HR] 2.77 vs direct-to-transplant, 95% CI 2.12 to 3.61, p<0.0001). However, a model to predict time to death excluding deaths in the first four months post-transplant, the bridging group was not significantly associated with risk of death.

Section Summary

In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of numerous nonrandomized studies comparing different LVADs devices among patients who have no other treatment options. In children, the evidence consists of several nonrandomized studies. These studies report that substantial numbers of patients survive the transplant in situations in which survival would not be otherwise expected. Despite the lack of high-quality studies, this evidence is sufficient to determine that outcomes are improved in patients who have no other options for survival.

VENTRICULAR ASSIST DEVICES AS BRIDGE TO RECOVERY

VADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle. Several additional studies have investigated the role of VADs in bridging patients to decision.

Systematic Reviews

Reid (2022) published an SR with meta analysis to evaluate the outcomes for patients undergoing right ventricular assist device (RVAD) implantation following left ventricular assist device (LVAD) implantation.[40] A total of 35 studies were included (3260 patients). The primary endpoint was mortality during the hospital stay and at follow-up. Mortality reported at short-term as well at long-term was 19.66% (CI 15.73-23.59%) and 33.90% (CI 8.84-59.96%) in LVAD respectively versus 45.35% (CI 35.31-55.4%) $p \leqslant 0.001$ and 48.23% (CI 16.01-80.45%) $p = 0.686$ in LVAD/RVAD group respectively. The authors conclude temporary RVAD implantation following LVAD is associated with decreased in-hospital, as well as short-term survival as compared to isolated LVAD implantation. The analysis is limited due to incomplete reporting, small sample sizes, and that the LVAD/RVAD cohorts are likely to be sicker and therefore have a higher mortality.

A scoping review with meta-analysis of selected studies was completed to examine the impact of 3rd generation LVADs on quality of life.[41] Eleven articles met the inclusion criteria. Three were randomized trials and eight were retrospective and registry studies. A meta-analysis was completed on four studies which included the EroQOL 5L tool at 6 months post LVAD implantation and reported a mean difference increase of 28.9 points (95% CI: 26.71 – 31.41). The authors conclude that the improved QOL support use of LVAD not only for prognosis but also for symptom control. The data are limited by lack of randomized studies and limited number of studies included in the meta-analysis.

Nonrandomized Studies

Support from VADs was originally indicated for the treatment of postcardiotomy cardiogenic shock in patients who could not be weaned from cardiopulmonary bypass. VAD use in this setting is temporary and brief, lasting between 1.4 and 5.7 days. The overall salvage rate for this indication is low, at approximately 25%; however, without VAD support, patients with refractory postcardiotomy cardiogenic shock would experience 100% mortality.[7, 42, 43]

Agrawal (2018) published a retrospective cohort study evaluating the 30-day readmissions of 2,510 patients undergoing LVAD implantation.[44] Of the patients who met the inclusion criteria, 788 (31%) were readmitted within 30 days after surviving initial index hospitalization. Cardiac causes accounted for 23.8% of readmissions, 13.4% due to heart failure, and 8.1% to arrhythmias. Infection (30.2%), bleeding (17.6%), and device-related causes (8.2%) comprised the 76.2% of non-cardiovascular causes for readmission. The study's limitations relate to the nature of nonclinical data collection and gaps in current subject knowledge.

A retrospective cohort study by Adesyiun (2017) assessed LVAD complications and overall effect on mortality to determine factors associated with development of early and long-term complications.[45] Utilizing logistic regression and Cox proportional hazards analyses at univariable and multivariable stages, the study found 24% of patients developed early complications and 18.5% developed both early and late complications. There was a significant association between death and early complications (p=0.017), while the additional presence of two or more complications produced a 2.7-fold increase in mortality odds (p=0.016). Mortality odds increased by 20% with each subsequent complication (p=0.004). The study was limited in that, during its long, 13-year team span, practice associated with LVAD maintained had changed but were not address by the study. Further limitations include the difficulty in determining the strictness to which a patient might have met the complication definitions, as well as the small sample size of the study.

Kawajiri (2017) evaluated the outcomes of patients with end-stage heart failure who had conventional surgery as opposed to transplant or mechanical support.[46] A total of 133 patients of this retrospective cohort study were identified with left ventricular ejection fraction (LVEF) less than 20% and VO2 max < 14 mL/min/m^2 and, after initial referral for advanced therapies, were instead offered a conventional procedure. Of the originally identified 133 patients, 68 were determined transplant eligible. Actuarial survival at 5 and 10 years was 72% and 39%, respectively, after 12% in-hospital mortality. Outcomes were acceptable for conventional cardiac surgery in highly selected patients with end-stage HF, and long-term survival was comparable with advanced surgical therapies. The study was limited by a small study population, its nonclinical nature, and the potential underestimation the VAD/transplant mortality by measuring survival dates starting from first surgery as opposed to date of decision.

Raju (2017) focused their retrospective cohort study on consecutive LVAD patients who received more than one year of total LVAD support time.[47] During the study period, 103 patients received LVADs, 37 received LVAD support for more than one year, and 18 received support for more than two years. Average support time was 786 days. Mortality and hospital readmissions were used to determine the efficacy of continuous-flow LVADs. During a median follow-up of two years, the one-year conditional survival was 74%. Readmission reasons were due to major infection (24%), major bleeding (19%), and device malfunction/thrombosis (13%), and totaled 112 completed readmission procedures, 60% of which were done in 13% (n=5) of patients. The study had the limitations of a descriptive retrospective analysis and small sample size, and quality of life (QOL) self-assessments would have provided necessary patient perspective.

Takayama (2014) reported outcomes for a retrospectively-defined cohort of 143 patients who received a CentriMag® VAD as a "bridge to decision" for refractory cardiogenic shock due to a variety of causes.[48] Patients were managed with a bridge-to-decision algorithm. Causes of cardiogenic shock included failure of medical management (n=71), postcardiotomy shock (n=37), graft failure post-heart transplantation (n=2), and right ventricular failure post-

implantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated left VAD in 8%. After a mean duration of support of 14 days (interquartile range 8 to 26 days), 30% of patients had myocardial recovery, 15% had device exchange to an implantable VAD, and 18% had a heart transplantation.

Acharya (2016) reported on patients who underwent VAD placement in the setting of acute myocardial infarction (AMI) who were enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, a prospective national registry of FDA-approved durable mechanical circulatory support devices.[49] Patients who had an AMI as the admitting diagnosis or a major myocardial infarction (MI) as a hospital complication that resulted in VAD implantation (n=502) were compared with patients who underwent VAD implantation for non-AMI indications (n=9,727). Patients in the AMI group were generally sicker at baseline, with higher rates of smoking, severe diabetes, and peripheral vascular disease, but had fewer cardiac surgeries and recent cardiovascular hospitalizations. Most AMI patients (53.8%) were implanted with a “bridge-to-candidacy” strategy. At one-month post VAD, 91.8% of the AMI group were alive with the device in place. At one-year post-VAD, 52% of the AMI group were alive with the device in place, 25.7% had received a transplant, 1.6% had their VAD explanted for recovery, and 20.7% died with the device in place. Another retrospective study of 15,138 patients in the INTERMACS registry found that the incidence of recovery was significantly higher in bridge-to-recovery patients than in non-bridge-to-recovery patients (11.2% vs 1.2%, p<0.0001).[50]

Topkara (2016) reported a similar analysis of 13,454 INTERMACS adults with implants between June 2006 and June 2015 without TAH, pulsatile-flow LVAD, or heart transplant.[51] Device explant rates for cardiac recovery were 0.9% at one-year, 1.9% at two-year, and 3.1% at three-year follow-up. An additional 9% of patients demonstrated partial cardiac recovery.

In a smaller single-center retrospective cohort study, Mohamedali (2015) reported outcomes for 48 patients treated with biventricular support with the CentriMag® device as a “bridge to decision”, 18 of whom had biventricular support with venoarterial (VA) extracorporeal membrane oxygenation (ECMO), while the remainder received just biventricular VAD support.[52] Overall, 23 patients were explanted, nine to recovery, 14 to a durable LVAD, with three additional patients explanted for withdrawal of care. However, given that the study included patients who received VA ECMO, it is difficult to assess the relative impact of VAD support alone.

Six studies using the Centrimag® RVAD included between 12 and 32 patients, the majority of whom received biventricular devices.[43, 53-57] Indications and numbers of patients in these five studies were: support for post-cardiotomy cardiogenic shock (bridge to recovery), bridge to long-term device implantation (n=9), treatment of right heart failure in patients who previously received LVADs, bridge to later decision when neurologic status is clarified, and acute donor graft failure. The mean time on mechanical circulatory support ranged from 9.4 days to 46.9 days. The 30-day mortality rates were between 17% and 63%. The proportion of patients discharged from the hospital was between 30% and 83%. Major complications included bleeding requiring reoperation, sepsis, and stroke. No device failures were observed in these studies.

In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum (2007) evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure.[58] After 30 days, patients

demonstrated significant improvements compared with pre-LVAD state in LVEF (17.1% vs 34.12%, p<0.001), left ventricular end-diastolic diameter (7.1 cm vs 5.1 cm, p<0.001), and left ventricular mass (320 g vs 194 g, p<0.001). However, only 9% of patients demonstrated enough recovery to have their LVAD explanted.

In a 2006 study, a series of 15 patients with severe heart failure due to nonischemic cardiomyopathy underwent implantation of LVADs, along with medical management designed to enhance myocardial recovery.[59] Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; two patients died after explantation. Among those who survived, the cumulate rate of freedom from recurring heart failure was 100% and 88.9%, respectively, at one- and four-years post explantation. The same group subsequently reported results of their LVAD explantation protocol among patients with severe heart failure due to nonischemic cardiopathy who had nonpulsatile LVADs implanted.[60] They included 20 patients who received a combination of angiotensin converting enzyme ACE inhibitors, beta blockers, and adosterol antagonists followed by the β2-agonist clenbuterol. One patient was lost to follow-up and died after 240 days of support. Of the remaining 19 patients, 12 (63.2%) were successfully explanted after a mean 286 days; estimated survival without heart failure recurrence was 83.3% at one and three years.

Section Summary

The studies previously outlined indicate that a subset of patients who receive a VAD as a bridge to transplant demonstrate improvements in their cardiac function, sometimes to the point that they no longer require the VAD. However, questions remain about defining and identifying the population most likely to experience cardiac recovery with VAD placement. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. Current evidence is insufficient to allow the identification of other heart failure patient populations who might benefit from the use of a VAD as a specific bridge-to-recovery treatment strategy. Ongoing research studies are addressing this question, along with protocols for transitioning patients off VAD use.

LEFT VENTRICULAR ASSIST DEVICES AS DESTINATION THERAPY

Technology Assessment

The policy statement regarding LVADs as destination therapy was initially based on a 2002 TEC assessment[61] that offered the following observations and conclusions:

- The available evidence comes from a single, well-designed and rigorously conducted randomized trial, known as the REMATCH study.[62] The study was a cooperative effort of Thoratec, Columbia University and the National Institutes of Health.

- The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have significantly better survival on an LVAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this group's better outcomes on function. NYHA Class was significantly improved, as was quality of life among those living to 12 months.

- LVAD patients spend a greater relative proportion of time inside the hospital than medical management patients do, but the survival advantage would mean a longer absolute time outside the hospital.

Randomized Controlled Trials

The MOMENTUM 3 trial compared HeartMate 3™ centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as a bridge to transplant or destination therapy; inclusion criteria included 1) NYHA Class III heart failure with dyspnea upon mild physical activity or NYHA Class IV; 1) left ventricular ejection fraction ≤ 25%; 3) inotrope-dependent OR cardiac index <2.2 liters/min/m2 while not on inotropes plus on optimal medical management for at least 45 of the last 60 days and failing to respond or with advanced heart failure for at least 14 days and dependent on intra-aortic balloon pump for ≥7 days.[63, 64] HeartMate 3 ™ received PMA approval as a bridge to transplant therapy in August 2017 and as destination therapy in October 2018. The destination therapy indication was based on 2-year results from MOMENTUM 3, which showed superiority of the HeartMate 3 device compared to HeartMate II on the composite primary outcome, survival at two years free of disabling stroke or reoperation to replace a malfunctioning device (relative risk 0.84; 95% CI, 0.78–0.91, p<.001). Prevalence of stroke at 2 years was lower in the HeartMate 3 than the HeartMate 2® group (10.1% vs 19.2%; p=.02). Measures of functional capacity and Health-Related QOL did not differ between the two devices at six months.

A prespecified subgroup analysis of MOMENTUM 3 published in 2020 did not find differences in outcomes based on preoperative categories of bridge to transplant, bridge to transplant candidacy, or destination therapy.[65] Additionally, nearly 15% of those initially deemed transplant ineligible were eventually transplanted within 2 years of follow-up, supporting that clinical categorizations based on transplant eligibility should no longer be used. Park (2005) published a further follow-up of patients in the REMATCH trial, mentioned in the above TEC assessment, which found that survival and quality of life benefits were still apparent with extended two-year follow-up.[66]

Slaughter (2009) published data from an unblinded randomized multicenter trial.[67] Subjects were randomized to continuous-flow or pulsatile-flow devices on a 2:1 block-randomization basis. The primary outcome measured was a composite endpoint of two-year survival, free of disabling stroke or need for device replacement. Continuous-flow patients (n=134) reached the primary outcome at a rate of 46% (95% CI 38 to 55) compared to pulsatile-flow patients (n=66) rate of 11% (95% CI 3 to 18), which was a significant difference (p<0.001). Analysis of constituent factors indicated that a lower rate of devices needing replacement in the continuous-flow group had the largest effect on the composite endpoint; two-year death rate also favored this device (58% vs. 24%, p=0.008). Stroke and death (within two years of implantation) were similar in the two groups (stroke rate 12% and death rate 36%). Quality of life scores were also similar in the two groups. Although unblinded, this randomized trial adds to the evidence favoring continuous-flow devices.

Nonrandomized Studies

Jorde (2014) published results from an FDA-required postapproval study of the HeartMate II® device for destination therapy.[68] The study included the first 247 HeartMate II® patients identified as eligible for the device as destination therapy, outcomes and adverse events did not differ significantly from those treated in the original trial, which compared patients who

received the HeartMate II® to earlier generation devices (Slaughter [2009], described below).[67] Survival in the postapproval cohort was 82% and 69% at one and two years postoperatively, respectively.

A subsequent prospective observational study comparing LVAD support (n=97) with optimal medical therapy (n=103) for patients with heart failure not requiring inotropes also reported superior survival and health-related quality of life in LVAD-treated patients.[69] Twelve-month survival was 80% in the LVAD group, compared with 63% in the best medical therapy group (p=0.022).

In addition, other case series suggest continuing improvement in outcomes related to ongoing improvements in the device and in patient management.[70] However, the durability of the HeartMate device used in the REMATCH trial is a concern; for example, at one participating institution, all six long-term survivors required device change-outs. Next generation devices consisting of smaller continuous flow devices are eagerly anticipated.

Section Summary

The primary evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is from the REMATCH study. This study reported that the use of LVADs led to improvements in survival, quality of life, and functional status.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of an RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous-flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes.[67] Other nonrandomized comparative studies, including a database study with large numbers of patients, have not reported important differences in clinical outcomes between devices.

CONTINUOUS-FLOW VS PULSATILE-FLOW DEVICES

Nonrandomized Studies

Mehra (2022) published a five year observational follow-up study in patients with Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial.[71] A total of 477 patients (295 enrolled between June 2019 and April 2021 and 182 provided limited data) of 536 patients still receiving LVAD support at 2 years contributed to the extended-phase analysis (median age, 62 y; 86 [18%] women). The 5-year Kaplan-Meier estimate of survival to transplant, recovery, or LVAD support free of debilitating stroke or reoperation to replace the pump in the centrifugal-flow vs axial-flow group was 54.0% vs 29.7% (hazard ratio, 0.55 [95% CI, 0.45-0.67]; P < .001). Overall Kaplan-Meier survival was 58.4% in the centrifugal-flow group vs 43.7% in the axial-flow group (hazard ratio, 0.72 [95% CI, 0.58-0.89]; P = .003). Serious adverse events of stroke, bleeding, and pump thrombosis were less frequent in the centrifugal-flow pump group. The authors conclude that these findings support the use of the fully magnetically levitated LVAD.

A post-pivotal trial continuous access protocol was initiated as a single-arm prospective study to assess the reproducibility of HeartMate3™ LVAD outcomes across centers used in the MOMENTUM 3 trail.[72] A total of 515 patients were included in the pivotal cohort. The primary outcomes for this extended study were survival to transplant, recovery, or ongoing LVAD support, free of disabling stroke or reoperation to replace or remove a malfunctioning pump, at

2 years post-implant. At 2 years post-implant, a similar proportion of patients in the continuous access group versus the pivotal cohort achieved the composite endpoint (76.7% vs 74.8%; adjusted HR, 0.87; 95% CI, 0.71 to 1.08; p=.21). Pump exchange rates were low in both cohorts with 98.4% of the continuous access cohort and 96.9% of the pivotal cohort being free of pump replacement at 2 years. Overall survival at 2 years was 81.2% in the continuous access cohort compared to 79% in the pivotal cohort. After controlling for baseline demographics between cohorts, the adjusted HR for continuous access versus pivotal cohort was 0.84 (95% CI, 0.67 to 1.06; p=.15). Survival based on if the HeartMate3 ™ was used as a bridge to transplant or as destination therapy was similar between the continuous access and pivotal trial cohorts (bridge to transplant adjusted HR, 0.70; 95% CI, 0.43 to 1.14; p=.15; destination therapy adjusted HR, 0.89; 95% CI, 0.68 to 1.16; p=.38). This additional trial in a larger cohort reproduced similar results to the initial MOMENTUM 3 study, especially in individuals using VADs as destination therapy.

Dell'Aquila (2014) compared outcomes for patients treated with a third-generation continuous flow device, the HeartWare® device, with those for patients treated with earlier generation devices in a single-center study.[73] Comparison-group patients received either an earlier generation continuous flow device or a pulsatile flow device. Of 287 patients who received VAD support from 1993 to 2012, 52 received a HeartWare® device, 76 an earlier generation continuous flow device, and 159 a pulsatile device. Survival was significantly better for patients who received a third-generation device, with 24 months survival of 70.4%, compared with 33.7% for patients who received an earlier generation continuous flow device and 33.8% for patients who received a pulsatile flow device (p=0.013). The difference in survival associated with third generation devices was more pronounced for higher scores on the INTERMACs scale.

Nativi (2011) published a nonrandomized comparison of pulsatile versus continuous flow devices using data from the registry of the International Society for Heart and Lung Transplantation on 8,557 patients undergoing transplant.[74] Comparisons were made among patients receiving a pulsatile LVAD, a continuous flow LVAD, and no LVAD. Two time periods were used for analysis, the first was pre-2004, when nearly all LVADs were pulsatile devices, and post-2004 when continuous use devices began to be used in clinical care. There was a significantly greater risk of mortality in the first time period compared to the second time period (RR 1.30, 95% CI 1.03 to 1.65, p=0.03). When analysis was confined to the second time period, there was no significant improvement in survival for the continuous group compared to the pulsatile group (RR 1.25, 95% CI 1.03 to 1.65, p=0.03).

Other nonrandomized studies that have compared outcomes from different types of LVADs have been smaller and/or focused on physiologic outcomes.[75-78] In some of these studies, the continuous flow devices exhibit greater improvement in physiologic measures, but none of these studies have reported significant differences between devices in clinical outcomes.

Section Summary

The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of two RCTs of two different centrifugal continuous-flow devices. The MOMENTUM3 trial compared HeartMate 3™ centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as a bridge to transplantation or destination therapy. HeartMate 3™ has been recalled. The ENDURANCE trial compared HeartWare® centrifugal continuous-flow device with the

HeartMate II® axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare® is FDA-approved for bridge to transplantation. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke and freedom from device failure. While there are fewer device failures with the centrifugal devices without significant increase in disabling stroke, the HeartWare® device was associated with increased risk of any stroke over a period of two years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of one RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes. Other nonrandomized comparative studies, including one database study with large numbers of patients, have not reported differences between devices on clinical outcomes.

AORTIC COUNTERPULSATION DEVICES

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved, and therefore the evidence for these devices is not reviewed in detail.

TOTAL ARTIFICIAL HEARTS

BRIDGE TO TRANSPLANTATION

Nonrandomized Studies

In 2004, the CardioWest Total Artificial Heart™ (now called the SynCardia Total Artificial Heart) received FDA approval for use as a bridge to transplant. The approval was based on the results of a nonrandomized, prospective study of 81 patients.[79] Patients had failed inotropic therapy and had biventricular failure and thus were not considered appropriate candidates for an LVAD. The rate of survival to transplant was 79%, which was considered comparable to the experience with LVAD in patients with left ventricular failure. The mean time from entry into the study until transplantation or death was 79.1 days.

Other case series have been reported on outcomes of the TAH as a bridge to transplant. For example, Copeland reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant.[80] All patients either met established criteria for mechanically assisted circulatory support or were failing medical therapy on multiple inotropic drugs. The mean support time was 87 days, with a range of 1 to 441 days. Survival to transplant was 68.3% (69/101). Of the 32 deaths prior to transplant, 13 were due to multiple organ failure, 6 were due to pulmonary failure, and four were due to neurologic injury. Survival after transplant at 1, 5, and 10 years, respectively, was 76.8%, 60.5%, and 41.2%.

DESTINATION THERAPY

In currently available studies, the AbioCor® Implantable Replacement Heart has only been used as destination therapy for end-stage patients with congestive heart failure.

Nonrandomized Studies

Torregrossa (2014) reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than one year.[81] Patients were implanted for dilated cardiomyopathy (n=23), ischemic cardiomyopathy (n=15), and "other" reasons (n=9). Over a median support time of 554 days (range, 365-1373 days), 34 patients (72%) were successfully transplanted, 12 patients (24%) died while on device support, and one patient (2%) was still supported. Device failure occurred in five patients (10%). Major complications were common, including systemic infection in 25 patients (53%), driveline infections in 13 patients (27%), thromboembolic events in nine patients (19%) and hemorrhagic events in seven patients (14%). Two of the deaths occurred secondary to device failure.

Dowling (2004) reported on the first seven patients in the AbioCor® clinical trial.[82] The 30-day survival rate was 71% compared with the predicted survival rate of 13% with only medical therapy. At 60 days, 43% were still alive and as of July 2006 two patients were still alive 234 and 181 days postoperatively and remain hospitalized. Deaths were due to intraoperative bleeding at the time of implantation, cerebrovascular accidents, pulmonary embolism, and multiorgan failure. No reports of serious device malfunction have been reported for the seven patients. Frazier (2004) reported information on four additional patients receiving the AbioCor®.[83] Using the same inclusion criteria as in the above RCT the device supported three patients for greater than 100 days, whereas a fourth patient expired at 53 days. There were no device related problems reported.

SECTION SUMMARY

There is little evidence on the use of TAH as a bridge to transplantation, or as destination therapy, compared with the use of LVADs. The type of evidence on bridge to transplant is similar to that for LVADs (i.e., case series reporting substantial survival rates in patients without other alternatives). Therefore, this evidence is sufficient to conclude that TAH improves outcomes for these patients similar to LVADs and is a reasonable alternative for patients who require bridge to transplantation but who are ineligible for other types of support devices. Although TAHs show promise for use as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. There is insufficient evidence on the use of TAH as destination therapy to support conclusions about the efficacy of TAH in this setting.

PRACTICE GUIDELINE SUMMARY

SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

In 2015, the Society for Cardiovascular Angiography and Interventions (SCAI), the Heart Failure Society of America (HFSA), the Society of Thoracic Surgeons (STS), the American Heart Association (AHA), and the American College of Cardiology (ACC) published a clinical expert consensus statement on the use of percutaneous mechanical circulatory support (MCS) devices in cardiovascular care.[84] This statement addressed intra-aortic balloon pumps (IABPs), left atrial (LA)-to-aorta assist device (eg, TandemHeart), left ventricle (LV)-to-aorta assist devices (eg, Impella), extracorporeal membrane oxygenation (ECMO), and methods of right-sided support. Specific recommendations are not made, but the statement reviews the use of MCS in patients undergoing high-risk percutaneous intervention (PCI), those with cardiogenic shock, and those with acute decompensated heart failure.

AMERICAN ASSOCIATION FOR THORACIC SURGERY/INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION[85]

In 2020, the American Association for Thoracic Surgery/International Society for Heart and Lung Transplantation published guidelines on selected topics in mechanical circulatory support. The guidelines noted that "Compared with IABP, contemporary percutaneous circulatory support devices provide a significant increase in cardiac index and mean arterial pressure; however, reported 30-day outcomes are similar." The level of evidence was graded at B and class of evidence was graded IIA.

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION / AMERICAN HEART ASSOCIATION / HEART FAILURE SOCIETY OF AMERICA (ACCF/AHA/HFSA)[86]

The 2013 ACCF/AHA practice guidelines for the management of heart failure included the recommendations below related to MCS which includes LVADs. All of these recommendations were rated II.a., level of evidence B, defined as a recommendation in favor of the treatment being useful, with some conflicting evidence from a single RCT or nonrandomized studies.

- MCS is considered beneficial in carefully selected patients with stage D heart failure with reduced ejection fraction (HFrEF) as a bridge to transplantation or recovery.
- Nondurable mechanical cardiac support including percutaneous and extracorporeal VADs are considered "reasonable" as a bridge to recovery or a bridge to decision for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.
- Durable (permanent) MCS is considered reasonable to prolong survival for carefully selected patients with stage D HFrEF.

The guidelines note that, although optimal patient selection for MCS is an area of investigation, general indications for referral for MCS therapy include patient with LVEF<25% and NYHA class III-IV functional status despite guideline-directed medical therapy (GDMT) including cardiac resynchronization therapy (CRT), when indicated, with either high predicted one- to two-year mortality or dependence on continuous parenteral inotropic support.

In 2017, the ACCF/AHA/HFSA published a focused update of the 2013 recommendations released by the ACCF and AHA.[87] LVAD was one of several treatment options recommended for patients with refractory NYHA class III or IV heart failure (stage D). If symptoms were not improved after guideline-directed management and therapy, which included pharmacologic therapy, surgical management and/or other devices, then LVAD was presented as an additional treatment option. The 2017 update focused on changes in sections regarding biomarkers, comorbidities, and prevention of heart failure, while many of the previous recommendations remained unchanged.

The AHA/ACC/HFSA published updated guidelines in 2022 to consolidate the 2013 and 2017 guidelines and to provide contemporary evidence.[88] The use of LVADs in patients with stage D HF is an included focus. The guidelines provide the highest class of recommendation (COR =1) and strongest level of evidence (LOE = A) that In select patients with advanced HFrEF with NYHA class IV symptoms who are deemed to be dependent on continuous intravenous inotropes or temporary MCS, durable LVAD implantation is effective to improve functional status, QOL, and survival. (Class or Recommendation (COR) level 1 and Level of Evidence (LOE) = A. Additionally, In select patients with advanced HFrEF who have NYHA class IV

symptoms despite GDMT, durable MCS can be beneficial to improve symptoms, improve functional class, and reduce mortality (COR II A; LOE B-R). Where COR A is high quality evidence from more than 1 RCT; B-R: Moderate-quality evidence from 1 or more RCTs; B-NR: Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies. The updated guidelines are silent on the use of artificial hearts.

THE HEART FAILURE SOCIETY OF AMERICA (HFSA)

The HFSA published guidelines in 2010 on surgical approaches to the treatment of heart failure. The guidelines are based on evidence and expert opinion.[79] The following recommendations were made regarding ventricular assist devices:

- Bridge to transplantation: Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant. (Strength of Evidence B - cohort and case-control studies)
- Bridge to recovery: Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a "bridge to decision." These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence C - expert opinion)
- Destination Therapy: Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center. (Strength of Evidence B - cohort and case-control studies)

SUMMARY

VENTRICULAR ASSIST DEVICES

There is enough research to show that implantable ventricular assist devices (VADs) as a bridge to transplantation or recovery, or as destination therapy, improve health outcomes in some patients with heart failure who might not otherwise survive. Therefore, implantable VADs may be considered medically necessary when the policy criteria are met.

There is not enough research to show that ventricular assist devices or aortic counterpulsation devices improve health outcomes for people with heart failure or other heart conditions when policy criteria are not met. Therefore, the use of ventricular assist devices or aortic counterpulsation devices when policy criteria are not met is considered investigational.

TOTAL ARTIFICIAL HEARTS

There is enough research to show that the use of a total artificial heart (TAH) as a bridge to heart transplantation improves survival and quality of life for patients in some specific

situations. Therefore, total artificial hearts may be considered medically necessary as a bridge to heart transplantation when policy criteria are met.

There is not enough research to show that total artificial hearts (TAHs) as destination therapy improves health outcomes for patients. Therefore, the use of TAHs as destination therapy is considered investigational.

REFERENCES

1. FDA Warns of Serious Risks With LVADs. [cited 12/27/2023]. 'Available from:' https://www.medpagetoday.com/cardiology/chf/52948.
2. Recalls Related to the HVAD System. PMID:
3. Alba AC, McDonald M, Rao V, et al. The effect of ventricular assist devices on long-term post-transplant outcomes: a systematic review of observational studies. *European journal of heart failure.* 2011;13(7):785-95. PMID: 21551162
4. Blue Cross and Blue Shield Association. Technology Evaluation Center (TEC). Ventricular Assist Devices in Bridging to Heart Transplantation. TEC Assessments 1996. Volume 11, Tab 26. [cited. 'Available from:'
5. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. *N Engl J Med.* 1998;339(21):1522-33. PMID: 9819452
6. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol.* 2010;55(17):1826-34. PMID: 20413033
7. Lahpor J, Khaghani A, Hetzer R, et al. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. *Eur J Cardiothorac Surg.* 2010;37(2):357-61. PMID: 19616963
8. Wieselthaler GM, Schima H, Lassnigg AM, et al. Lessons learned from the first clinical implants of the DeBakey ventricular assist device axial pump: a single center report. *Ann Thorac Surg.* 2001;71(3 Suppl):S139-43; discussion S44-6. PMID: 11265849
9. Goldstein DJ. Worldwide experience with the MicroMed DeBakey Ventricular Assist Device as a bridge to transplantation. *Circulation.* 2003;108 Suppl 1:II272-7. PMID: 12970245
10. Salzberg S, Lachat M, Zund G, et al. Left ventricular assist device as bridge to heart transplantation--lessons learned with the MicroMed DeBakey axial blood flow pump. *Eur J Cardiothorac Surg.* 2003;24(1):113-8. PMID: 12853054
11. Vitali E, Lanfranconi M, Ribera E, et al. Successful experience in bridging patients to heart transplantation with the MicroMed DeBakey ventricular assist device. *Ann Thorac Surg.* 2003;75(4):1200-4. PMID: 12683563
12. Grinda JM, Latremouille CH, Chevalier P, et al. Bridge to transplantation with the DeBakey VAD axial pump: a single center report. *Eur J Cardiothorac Surg.* 2002;22(6):965-70. PMID: 12467821
13. Frazier OH, Myers TJ, Westaby S, et al. Use of the Jarvik 2000 left ventricular assist system as a bridge to heart transplantation or as destination therapy for patients with chronic heart failure. *Ann Surg.* 2003;237(5):631-6; discussion 36-7. PMID: 12724629
14. Pagani FD, Mehra MR, Cowger JA, et al. Clinical outcomes and healthcare expenditures in the real world with left ventricular assist devices - The CLEAR-LVAD study. *J Heart Lung Transplant.* 2021;40(5):323-33. PMID: 33744086

15. Aissaoui N, Morshuis M, Maoulida H, et al. Management of end-stage heart failure patients with or without ventricular assist device: an observational comparison of clinical and economic outcomes. *Eur J Cardiothorac Surg.* 2018;53(1):170-77. PMID: 28950304
16. Grimm JC, Magruder JT, Crawford TC, et al. Duration of Left Ventricular Assist Device Support Does Not Impact Survival After US Heart Transplantation. *Ann Thorac Surg.* 2016;102(4):1206-12. PMID: 27319984
17. Grimm JC, Sciortino CM, Magruder JT, et al. Outcomes in Patients Bridged With Univentricular and Biventricular Devices in the Modern Era of Heart Transplantation. *Ann Thorac Surg.* 2016;102(1):102-8. PMID: 27068177
18. Cheng A, Trivedi JR, Van Berkel VH, et al. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. *Journal of cardiac surgery.* 2016;31(10):648-53. PMID: 27573150
19. Deo SV, Sung K, Daly RC, et al. Cardiac transplantation after bridged therapy with continuous flow left ventricular assist devices. *Heart, lung & circulation.* 2014;23(3):224-8. PMID: 23954004
20. Slaughter MS, Pagani FD, McGee EC, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant.* 2013;32(7):675-83. PMID: 23796152
21. Aaronson, KD, Slaughter, MS, Miller, LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. United States, 2012. p. 3191-200.
22. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med.* 2007;357(9):885-96. PMID: 17761592
23. FDA information on the Thoratec HeartMate II device. [cited 12/27/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf.
24. Patel ND, Weiss ES, Schaffer J, et al. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann Thorac Surg.* 2008;86(3):832-40; discussion 32-40. PMID: 18721570
25. John R, Kamdar F, Liao K, et al. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. *Ann Thorac Surg.* 2008;86(4):1227-34; discussion 34-5. PMID: 18805167
26. Struber M, Sander K, Lahpor J, et al. HeartMate II left ventricular assist device; early European experience. *Eur J Cardiothorac Surg.* 2008;34(2):289-94. PMID: 18571932
27. Frazier OH, Gemmato C, Myers TJ, et al. Initial clinical experience with the HeartMate II axial-flow left ventricular assist device. *Tex Heart Inst J.* 2007;34(3):275-81. PMID: 17948075
28. Kirklin JK, Naftel DC, Stevenson LW, et al. INTERMACS database for durable devices for circulatory support: first annual report. *J Heart Lung Transplant.* 2008;27(10):1065-72. PMID: 18926395
29. Starling, RC, Naka, Y, Boyle, AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). United States, 2011. p. 1890-8.
30. Shaikh AF, Joseph SM, Lima B, et al. HeartMate II Left Ventricular Assist Device Pump Exchange: A Single-Institution Experience. *The Thoracic and cardiovascular surgeon.* 2016. PMID: 27903010

31. Palazzolo T, Hirschhorn M, Garven E, et al. Technology landscape of pediatric mechanical circulatory support devices: A systematic review 2010-2021. *Artificial organs.* 2022;46(8):1475-90. PMID: 35357020
32. Zakaria D, Frazier E, Imamura M, et al. Improved Survival While Waiting and Risk Factors for Death in Pediatric Patients Listed for Cardiac Transplantation. *Pediatric cardiology.* 2016. PMID: 27803956
33. Davies RR, Russo MJ, Hong KN, et al. The use of mechanical circulatory support as a bridge to transplantation in pediatric patients: an analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg.* 2008;135(2):421-7, 27 e1. PMID: 18242279
34. Jeewa A, Imamura M, Canter C, et al. Long-term outcomes after transplantation after support with a pulsatile pediatric ventricular assist device. *J Heart Lung Transplant.* 2018. PMID: 30466802
35. Bulic A, Maeda K, Zhang Y, et al. Functional status of United States children supported with a left ventricular assist device at heart transplantation. *J Heart Lung Transplant.* 2017;36(8):890-96. PMID: 28363739
36. Almond, CS, Morales, DL, Blackstone, EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. United States, 2013. p. 1702-11.
37. Jordan LC, Ichord RN, Reinhartz O, et al. Neurological complications and outcomes in the Berlin Heart EXCOR(R) pediatric investigational device exemption trial. *Journal of the American Heart Association.* 2015;4(1):e001429. PMID: 25613996
38. Bryant R, 3rd, Zafar F, Castleberry C, et al. Transplant Survival Following Berlin Heart EXCOR(R) Support. *ASAIO J.* 2016. PMID: 27660899
39. Wehman B, Stafford KA, Bittle GJ, et al. Modern Outcomes of Mechanical Circulatory Support as a Bridge to Pediatric Heart Transplantation. *Ann Thorac Surg.* 2016;101(6):2321-7. PMID: 26912304
40. Reid G, Mork C, Gahl B, et al. Outcome of right ventricular assist device implantation following left ventricular assist device implantation: Systematic review and meta-analysis. *Perfusion.* 2022;37(8):773-84. PMID: 34112048
41. Monteagudo-Vela M, Krasopoulos G, Athanasiou T, et al. Impact of third-generation left ventricular assist devices on quality of life: Scoping review and meta-analysis. *Artificial organs.* 2022;46(6):1012-18. PMID: 35132647
42. Braunwald E, Zipes DP, Libby P. *Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Philadelphia: W.B. Saunders Company, 2001, pp.
43. John R, Long JW, Massey HT, et al. Outcomes of a multicenter trial of the Levitronix CentriMag ventricular assist system for short-term circulatory support. *J Thorac Cardiovasc Surg.* 2010. PMID: 20605026
44. Agrawal S, Garg L, Shah M, et al. Thirty-Day Readmissions After Left Ventricular Assist Device Implantation in the United States: Insights From the Nationwide Readmissions Database. *Circ Heart Fail.* 2018;11(3):e004628. PMID: 29519902
45. Adesiyun TA, McLean RC, Tedford RJ, et al. Long-term follow-up of continuous flow left ventricular assist devices: complications and predisposing risk factors. *The International journal of artificial organs.* 2017;40(11):622-28. PMID: 28777392
46. Kawajiri H, Manlhiot C, Ross H, et al. High-risk cardiac surgery as an alternative to transplant or mechanical support in patients with end-stage heart failure. *J Thorac Cardiovasc Surg.* 2017;154(2):517-25. PMID: 28495061

47. Raju S, MacIver J, Foroutan F, et al. Long-term use of left ventricular assist devices: a report on clinical outcomes. *Canadian journal of surgery Journal canadien de chirurgie.* 2017;60(4):236-46. PMID: 28730986
48. Takayama H, Soni L, Kalesan B, et al. Bridge-to-decision therapy with a continuous-flow external ventricular assist device in refractory cardiogenic shock of various causes. *Circ Heart Fail.* 2014;7:799-806. PMID: 25027874
49. Acharya D, Loyaga-Rendon RY, Pamboukian SV, et al. Ventricular Assist Device in Acute Myocardial Infarction. *J Am Coll Cardiol.* 2016;67(16):1871-80. PMID: 27102502
50. Wever-Pinzon O, Drakos SG, McKellar SH, et al. Cardiac Recovery During Long-Term Left Ventricular Assist Device Support. *J Am Coll Cardiol.* 2016;68(14):1540-53. PMID: 27687196
51. Topkara VK, Garan AR, Fine B, et al. Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices: Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). *Circ Heart Fail.* 2016;9(7). PMID: 27402861
52. Mohamedali B, Bhat G, Yost G, et al. Survival on biventricular mechanical support with the Centrimag(R) as a bridge to decision: a single-center risk stratification. *Perfusion.* 2015;30:201-8. PMID: 25524992
53. FDA information on Levitronix Centrimag RVAS device. [cited 12/27/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf7/H070004b.pdf.
54. Shuhaiber JH, Jenkins D, Berman M, et al. The Papworth experience with the Levitronix CentriMag ventricular assist device. *J Heart Lung Transplant.* 2008;27(2):158-64. PMID: 18267221
55. De Robertis F, Birks EJ, Rogers P, et al. Clinical performance with the Levitronix Centrimag short-term ventricular assist device. *J Heart Lung Transplant.* 2006;25(2):181-6. PMID: 16446218
56. De Robertis F, Rogers P, Amrani M, et al. Bridge to decision using the Levitronix CentriMag short-term ventricular assist device. *J Heart Lung Transplant.* 2008;27(5):474-8. PMID: 18442711
57. John R, Liao K, Lietz K, et al. Experience with the Levitronix CentriMag circulatory support system as a bridge to decision in patients with refractory acute cardiogenic shock and multisystem organ failure. *J Thorac Cardiovasc Surg.* 2007;134(2):351-8. PMID: 17662772
58. Maybaum, S, Mancini, D, Xydas, S, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. United States, 2007. p. 2497-505.
59. Birks, EJ, Tansley, PD, Hardy, J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. United States, 2006. p. 1873-84.
60. Birks, EJ, George, RS, Hedger, M, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. United States, 2011. p. 381-90.
61. TEC Assessment 2002. "Left Ventricular assist devices as destination therapy for end-stage heart failure." BlueCross BlueShield Association Technology Evaluation Center, Vol. 17
62. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med.* 2001;345(20):1435-43. PMID: 11794191

63. Colombo PC, Mehra MR, Goldstein DJ, et al. Comprehensive Analysis of Stroke in the Long-Term Cohort of the MOMENTUM 3 Study. *Circulation.* 2019;139(2):155-68. PMID: 30586698
64. Mehra MR, Naka Y, Uriel N, et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med.* 2017;376(5):440-50. PMID: 27959709
65. Goldstein DJ, Naka Y, Horstmanshof D, et al. Association of Clinical Outcomes With Left Ventricular Assist Device Use by Bridge to Transplant or Destination Therapy Intent: The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) Randomized Clinical Trial. *JAMA Cardiol.* 2020;5(4):411-19. PMID: 31939996
66. Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg.* 2005;129(1):9-17. PMID: 15632819
67. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 2009;361(23):2241-51. PMID: 19920051
68. Jorde UP, Kushwaha SS, Tatooles AJ, et al. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol.* 2014;63(17):1751-7. PMID: 24613333
69. Estep JD, Starling RC, Horstmanshof DA, et al. Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients: Results From the ROADMAP Study. *J Am Coll Cardiol.* 2015;66(16):1747-61. PMID: 26483097
70. Long JW, Kfoury AG, Slaughter MS, et al. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. *Congest Heart Fail.* 2005;11(3):133-8. PMID: 15947534
71. Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. *Jama.* 2022;328(12):1233-42. PMID: 36074476
72. Mehra MR, Cleveland JC, Jr., Uriel N, et al. Primary results of long-term outcomes in the MOMENTUM 3 pivotal trial and continued access protocol study phase: a study of 2200 HeartMate 3 left ventricular assist device implants. *European journal of heart failure.* 2021;23(8):1392-400. PMID: 33932272
73. Dell'Aquila AM, Schneider SR, Stypmann J, et al. Survival results after implantation of intrapericardial third-generation centrifugal assist device: an INTERMACS-matched comparison analysis. *Artificial organs.* 2014;38(5):383-90. PMID: 24117675
74. Nativi JN, Drakos SG, Kucheryavaya AY, et al. Changing outcomes in patients bridged to heart transplantation with continuous- versus pulsatile-flow ventricular assist devices: an analysis of the registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2011;30(8):854-61. PMID: 21571550
75. Pruijsten RV, Lok SI, Kirkels HH, et al. Functional and haemodynamic recovery after implantation of continuous-flow left ventricular assist devices in comparison with pulsatile left ventricular assist devices in patients with end-stage heart failure. *European journal of heart failure.* 2012;14(3):319-25. PMID: 22294758
76. Lim KM, Constantino J, Gurev V, et al. Comparison of the effects of continuous and pulsatile left ventricular-assist devices on ventricular unloading using a cardiac

electromechanics model. *The journal of physiological sciences : JPS.* 2012;62(1):11-9. PMID: 22076841
77. Kato TS, Chokshi A, Singh P, et al. Effects of continuous-flow versus pulsatile-flow left ventricular assist devices on myocardial unloading and remodeling. *Circ Heart Fail.* 2011;4(5):546-53. PMID: 21765125
78. Ventura PA, Alharethi R, Budge D, et al. Differential impact on post-transplant outcomes between pulsatile- and continuous-flow left ventricular assist devices. *Clinical transplantation.* 2011;25(4):E390-5. PMID: 21401721
79. Lindenfeld, J, Albert, NM, Boehmer, JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. United States, 2010. p. e1-194.
80. Copeland JG, Copeland H, Gustafson M, et al. Experience with more than 100 total artificial heart implants. *J Thorac Cardiovasc Surg.* 2012;143(3):727-34. PMID: 22245242
81. Torregrossa G, Morshuis M, Varghese R, et al. Results with SynCardia total artificial heart beyond 1 year. *ASAIO J.* 2014;60(6):626-34. PMID: 25158888
82. Dowling RD, Gray LA, Jr., Etoch SW, et al. Initial experience with the AbioCor implantable replacement heart system. *J Thorac Cardiovasc Surg.* 2004;127(1):131-41. PMID: 14752423
83. Frazier OH, Dowling RD, Gray LA, Jr., et al. The total artificial heart: where we stand. *Cardiology.* 2004;101(1-3):117-21. PMID: 14988633
84. Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care (Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie D'intervention). *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2015;85(7):E175-96. PMID: 25851050
85. Kirklin JK, Pagani FD, Goldstein DJ, et al. American Association for Thoracic Surgery/International Society for Heart and Lung Transplantation guidelines on selected topics in mechanical circulatory support. *J Heart Lung Transplant.* 2020;39(3):187-219. PMID: 31983666
86. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239. PMID: 23747642
87. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136(6):e137-e61. PMID: 28455343
88. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145(18):e895-e1032. PMID: 35363499

CODES

Note: There is no specific code for reporting prolonged extracorporeal percutaneous transseptal ventricular assist device; the appropriate code for reporting this procedure is 33999.

Codes	Number	Description
CPT	33927	Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy
	33928	Removal and replacement of total replacement heart system (artificial heart)
	33929	Removal of a total replacement heart system (artificial heart) for heart transplantation (list separately in addition to code for primary procedure)
	33975	Insertion of ventricular assist device; extracorporeal, single ventricle
	33976	Insertion of ventricular assist device; extracorporeal, biventricular
	33977	Removal of ventricular assist device; extracorporeal, single ventricle
	33978	Removal of ventricular assist device; extracorporeal, biventricular
	33979	Insertion of ventricular assist device, implantable intracorporeal, single ventricle
	33980	Removal of ventricular assist device, implantable intracorporeal, single ventricular
	33981	Replacement of extracorporeal ventricular assist device, single or biventricular, pump(s), single or each pump
	33982	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, without cardiopulmonary bypass
	33983	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, with cardiopulmonary bypass
	33990	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; left heart, arterial access only
	33991	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; left heart, both arterial and venous access, with transseptal puncture
	33992	Removal of percutaneous left heart ventricular assist device, arterial or arterial and venous cannula(s), at separate and distinct session from insertion
	33993	Repositioning of percutaneous right or left heart ventricular assist device with imaging guidance at separate and distinct session from insertion
	33995	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; right heart, venous access only
	33997	Removal of percutaneous right heart ventricular assist device, venous cannula, at separate and distinct session from insertion
	33999	Unlisted procedure, cardiac surgery
HCPCS	L8698	Miscellaneous component, supply or accessory for use with total artificial heart system
	Q0477 – Q0509	Ventricular assist device accessories, code range

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 58

Bariatric Surgery

Effective: February 1, 2024

Next Review: October 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Bariatric surgery is a major surgical intervention which aims to reduce weight, eliminate or improve comorbid conditions, and maintain weight loss in obese patients who have failed to achieve weight loss through lifestyle modifications.

MEDICAL POLICY CRITERIA

Note: Member contracts for covered services vary. Member contract language takes precedence over medical policy.

I. Bariatric surgery may be considered **medically necessary** in the treatment of obesity when all of the following criteria (A. and B.) are met**:**

A. All of the general Criteria (1.- 4.) must be met:

1. At the start of the medically-supervised, nonsurgical weight reduction program, one of the following must be met:

a. BMI greater than or equal to 40 kg/(meter squared); or

b. BMI greater than or equal to 35 kg/(meter squared) with at least one of the following comorbid conditions:

i. Type II diabetes mellitus; or

ii. Poorly controlled hypertension despite optimal medical management; or

iii. Coronary artery disease; or

iv. Obstructive sleep apnea as defined by an AHI equal to or greater than 15 per hour; and

2. The patient meets one of the following age requirements:
   a. Greater than or equal to 18 years; or
   b. Less than 18 years of age and has attained Tanner 4 or 5 pubertal development and one of the following must be met:
      i. BMI greater than or equal to 140 percent of the 95th percentile for age and sex; or
      ii. BMI greater than or equal to 120 percent of the 95th percentile for age and sex with at least one of the comorbid conditions listed in Criterion I.A.1.b.
3. Documentation of active participation for a total of at least 3 consecutive months in a structured, medically supervised pre-operative training program. The program must be provided by or approved and monitored under the supervision of the bariatric program.

   Documentation from the clinical medical records must indicate that the structured medical supervision meets all of the following Criteria:
   a. Program participation occurs during a total of at least 3 consecutive months within the 12 months prior to the request for surgery; and
   b. Include at least 2 visits for medical supervision, during the 3 consecutive months of program participation. One visit must occur at the initiation, and another at least 3 months later (90 days); and
   c. Be provided by an MD, DO, NP, PA, or RD in conjunction with the bariatric program; and
   d. Include assessment and counseling concerning weight, nutrition and diet that should be related to the type of planned bariatric surgery, exercise, and behavior modification; and
4. Preoperative evaluation to include both of the following:
   a. A licensed psychologist, psychiatrist, LCSW/LICSW, licensed masters-level counselor, or NP in a behavioral health practice, documents the absence of significant psychopathology that can limit an individual's understanding of the procedure or ability to comply with medical/surgical recommendations (e.g., active substance abuse, eating disorders, schizophrenia, borderline personality disorder, uncontrolled depression); and
   b. Clinical documentation that the patient is an appropriate candidate for the surgery and is committed to the treatment plan; and

B. The request is for one of the following procedures:

1. Sleeve gastrectomy as a stand-alone procedure; or
2. Gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less
3. Biliopancreatic bypass with duodenal switch in patients ages greater than or equal to 18 years with BMI greater than or equal to 50 kg/(meter squared)

II. Reoperation may be considered **medically necessary** when one or more of the following criteria (A. or B.) are met:

A. Reoperation with revision of a bariatric procedure (i.e. sleeve gastrectomy, biliopancreatic bypass with duodenal switch, or gastric bypass), conversion of a sleeve gastrectomy to a gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less, or adjustable gastric band removal when one or more of the following documented significant complications is present:

1. Leak or bowel perforation, including band erosion; or
2. Documentation of band migration (slippage), that cannot be corrected with fluid adjustment.; or
3. Band infection; or
4. Obstruction exceeding the inherent obstruction of the original bariatric procedure, documented by imaging or endoscopic findings; or
5. Staple-line failure (such as, Gastro-gastric fistula); or
6. Weight loss to 90% or less of ideal body weight; or
7. One or more of the following severe, clinically-objective conditions that have been unresponsive to optimal medical management for at least 4 months:
   a. Severe esophagitis (may include Barrett's esophagus); or
   b. Cameron lesion(s); or
   c. Gastro-jejunal anastomotic ulcer(s).

B. Removal of adjustable gastric band with conversion to a gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less when Criterion I. A. is met. Note: Criterion I. A. must be met during the period after placement of the adjustable gastric band.

III. Sleeve gastrectomy, biliopancreatic bypass with duodenal switch, or gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less is considered **not medically necessary** when Criterion I. above is not met including but not limited to biliopancreatic bypass with duodenal switch in patients younger than 18 years of age or in patients with BMI less than or equal to 50kg/(meter squared).

IV. The vertical banded gastroplasty and adjustable gastric banding are no longer a standard of care and are therefore considered **not medically necessary**.

V. Reoperation or conversion of a prior bariatric procedure is considered **not medically necessary** when Criterion II. is not met, including but not limited to reoperation for

early satiety, nausea, patient dissatisfaction, or gastroesophageal reflux disease (GERD).

VI. Repair of sliding or paraesophageal hiatal hernia when performed at the time of any bariatric surgery would be considered **a component of and incidental** to the primary bariatric surgery.

VII. The following procedures are considered **investigational** for the treatment of:

A. Obesity including distal or partial gastrectomy (other than standard sleeve gastrectomy) performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction; and gastric restrictive procedure without gastric bypass for obesity (other than sleeve gastrectomy)

B. Obesity using only hiatal hernia repair including repair of sliding or paraesophageal hernia.

C. Any condition *other than obesity* (e.g. gastroesophageal reflux disease or gastroparesis) including sleeve gastrectomy, biliopancreatic bypass with duodenal switch or gastric bypass using a Roux-en-Y anastomosis.

D. Any condition including but not limited to obesity and gastroesophageal reflux disease:

1. Mini-gastric bypass (gastric bypass using a Billroth II type of anastomosis)
2. Distal gastric bypass (long limb gastric bypass, i.e., >150 cm)
3. Biliopancreatic bypass (i.e., the Scopinaro procedure)
4. Duodenal switch with single anastomosis, D-Loop surgery, or stomach intestinal pylorus sparing surgery (SIPS)
5. Two-stage bariatric surgery procedures (e.g., sleeve gastrectomy followed by gastric bypass, sleeve gastrectomy followed by biliopancreatic diversion, removal of gastric band followed by sleeve gastrectomy or gastric bypass)
6. Any combination of adjustable gastric banding (e.g., Fobi pouch with silastic band) or adjustable gastric banding with Roux-en-Y gastric bypass, or sleeve gastrectomy, or other bariatric surgical procedure.
7. Parietal cell separating gastrojejunostomy
8. Gastric plication

VIII. Endoscopic procedures are considered **investigational** for the following:

A. As the primary bariatric procedure

B. Secondary bariatric procedures (See Policy Guidelines) to treat complications of primary bariatric surgery including but not limited to weight gain due to a large gastric stoma or large gastric pouch and dumping syndrome.

C. Balloon dilatation of strictures when Criterion II.A.4 is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Examples of endoscopic devices/procedures include but are not limited to the following:

1. StomaphyX (EndoGastric Solutions, Inc)
2. ROSE procedure (Restorative Obesity Surgery, Endoscopic)
3. EndoCinch (Bard)
4. EndoSurgical Operating System (EOS) (USGI Medical, Inc.)
5. Sclerotherapy of stoma
6. Endoscopic gastroplasty
7. Endoscopically placed duodenal-jejunal sleeve
8. Endoscopic stoma revision
9. Gastric balloon systems
10. AspireAssist
11. OverStitch Endoscopic Suturing System (Apollo Endosurgery, Inc.)

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could our impact review and decision outcome:

1. If patient is less than 18 years of age, documentation is provided of Tanner 4 or 5 pubertal development. For patients under 18 years of age, greater consideration should be given to psychosocial and informed consent issues.
2. Clinical documentation of a medically supervised nonsurgical pre-operative training program approved and monitored under the supervision of the healthcare practitioner providing medical oversight, that includes:
    A. BMI at the start of the program
    B. Comorbid conditions
    C. The program occurred during at least 3 consecutive months within the 12 months prior to request for surgery
    D. At least 2 visits for medical supervision during the 3 consecutive months of program participation. One visit must occur at the initiation, and another at least 3 months later.
    E. Assessment and counseling concerning weight, diet, exercise and behavior modification
    F. Documentation the program was provided by an MD, DO, NP, PA, or RD under the supervision of the bariatric program.
3. Preoperative evaluation by a licensed psychologist, psychiatrist, LCSW/LICSW, licensed masters-level counselor, or NP in behavioral health that includes:

A. Documentation of the absence of significant psychopathology that can limit an individual's understanding of the procedure or ability to comply with medical/surgical recommendations (e.g., active substance abuse, eating disorders, schizophrenia, borderline personality disorder, uncontrolled depression)

4. Clinical documentation that the patient is an appropriate candidate for the surgery and is committed to the treatment plan.
5. History and Physical including current medications.
6. Specific procedure being requested.
7. For Reoperation, Revision or Removal requests:
   A. Complication present
   B. Interventions attempted. NOTE: For band migration (slippage), that cannot be corrected with manipulation or adjustment. Records must demonstrate that manipulation or adjustment to correct band slippage has been attempted.
   C. Imaging or endoscopic findings. NOTE: For obstruction, records must demonstrate endoscopic findings or imaging has been performed.
   D. For severe esophagitis, Cameron lesions, or gastro-jejunal anastomotic ulcers, documentation must demonstrate medical management has been tried for at least 4 months.

CROSS REFERENCES

1. Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD), Surgery, Policy No. 110
2. Gastric Electrical Stimulation, Surgery, Policy No. 111
3. Gastroesophageal Reflux Surgery, Surgery, Policy No. 186
4. Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease, Surgery, Policy No. 190

BACKGROUND

Levels of overweight and obesity are currently determined by Body Mass Index (BMI) – which is calculated as weight (kg) / height (meters) squared. A normal BMI range is 18.5 to < 25.0 kg/m^2) – overweight and obesity is classified as follows:

Overweight:	25 to < 30.0 kg/m^2
Obesity:	Class I: 30 to < 35.0 kg/m^2
	Class II: 35 to < 40 kg/m^2
	Class III: ≥ 40.0 kg/m^2 (also referred to as severe obesity)

Note: BMI may be calculated by using the BMI calculator.

Individuals with class III obesity are at high risk for developing weight-related complications such as diabetes, hypertension, obstructive sleep apnea, and various types of cancers (colon, prostate, breast, uterus, and ovaries). In addition, class III obesity is associated with a shortened life span.[1]

The first-line treatment of severe obesity involves dietary and lifestyle changes. Although this strategy may be effective in some patients, a majority of patients with severe obesity do not achieve significant weight loss through lifestyle modifications. In addition, the weight loss may

not be durable, as only a small number of patients are able to comply with the changes on a long-term basis. When conservative measures fail, some patients may consider surgery for severe obesity (bariatric surgery).

Several bariatric procedures have been developed, but based on the underlying mechanism of weight loss, all fall into one or both of the following categories:

Restrictive procedures

- Decrease the size of the stomach and limit food intake

Malabsorptive procedures

- Limit the absorption of calories and nutrients by altering the way food moves through the intestinal track

Multiple variants exist, differing in the reconfiguration of the small intestines and consequently the extent of malabsorption.

The following table briefly summarizes different bariatric procedures:

Procedure	CPT Code	Description
Gastric Bypass with Roux-en-Y Anastomosis (RYGBP) AKA: Proximal or Short Limb Gastric Bypass	43846 43644	• Involves both restrictive and malabsorptive components: o A small gastric pouch is created from the upper part of the stomach by segmentation or resection to restrict the amount of food that can be ingested o The mid portion of the jejunum is divided and the cut end of the distal limb (≤ 150 cm) is attached to the gastric pouch outlet (Roux limb). The cut end of the proximal limb (the limb consisting of the duodenum and proximal jejunum) is attached to the side of the Roux limb (the limb connected to the pouch). This creates the Y configuration of the small intestine, allowing food to bypass the duodenum and proximal jejunum, resulting in malabsorption.
Distal (Long Limb) Gastric Bypass	43847	• The procedure involves both restrictive and malabsorptive components and is a variant of the standard gastric bypass with the longer (>150 cm) Roux limb. The longer the Roux limb, the greater the bypass of the small intestine and consequently the degree of malabsorption.
Biliopancreatic Diversion (Bypass) Procedure AKA Scopinaro procedure	43847	• Involves both restrictive and malabsorptive components: o Subtotal (distal) gastrectomy creates small gastric pouch at the top of the stomach to limit food intake o A long limb Roux-en-Y anastomosis (>150 cm) results in the biliopancreatic juices being diverted into the distal ileum, significantly increasing malabsorption • Designed to preferentially inhibit the absorption of fat • Only partially reversible
Biliopancreatic Diversion (Bypass) with Duodenal Switch (BPD-DS)	43845	• This procedure is an adaptation of the standard biliopancreatic bypass: o The restrictive component involves subtotal gastrectomy resulting in a tube or sleeve-like stomach remnant that leaves the pyloric valve and the initial segment of duodenum intact. o The long limb Roux-en-Y anastomosis (>150 cm) provides malabsorption in this variant as well, but the distal ileum is connected to the duodenal segment leading from the stomach sleeve, instead of the stomach pouch itself.
Laparoscopic duodenal switch with single anastomosis AKA Single loop duodenal switch	No specific CPT code	• Restrictive and malabsorptive procedure • Simplified version of the BPD-DS procedure • Surgery consists of: o Creation of a small gastric pouch by section the curvature of the stomach o Duodenum is transected while keeping the pylorus intact o A 1-loop duodenal switch is performed with creation of a 200-250 cm anastomosis
Mini-Gastric Bypass	no specific code	• The procedure is a variant of the gastric bypass and involves both restrictive and malabsorptive components: o The stomach is segmented to create a small gastric pouch similar to traditional gastric bypass o Instead of creating a Roux-en-Y anastomosis, the loop of jejunum is anastomosed directly to the stomach pouch (similar to a Billroth II procedure)
Sleeve Gastrectomy	43775	• Greater curvature of the stomach is resected resulting in a gastric remnant shaped like a tube or sleeve. • The pyloric sphincter is preserved leaving stomach function unaltered. • Not reversible • Can be performed as: o A stand-alone procedure (restrictive) o The first part of a two-stage surgical procedure for the very high-risk patients (BMI ≥50 kg/m^2) who need to lose some weight before they can proceed with a malabsorptive procedure (most commonly BPD-DS or RYGBP)

Procedure	CPT Code	Description
Adjustable Gastric Banding	43770-43774 43886-43888	• Restrictive procedure • An adjustable, external, constrictive band is wrapped around the upper portion of the stomach to create a small stomach pouch • The band can be adjusted through a subcutaneous access port, foregoing the need to enter the gastric cavity when adjusting the band • The least invasive and least technically complex bariatric procedure • Lap-Band® (original applicant, Allergan, Inc.; sold to Apollo Endosurgery, Inc.) and the REALIZE™ (Ethicon Endo-Surgery, Inc.) have received approval from the U.S. Food and Drug Administration (FDA).
Vertical Banded Gastroplasty AKA Vertically banded gastric partition or Gastric stapling	43842	• The vertical banded gastroplasty is no longer a standard of care. • Restrictive procedure • Surgical stapling is used to create a small, vertical gastric pouch at the top of the stomach • The pouch outlet (stoma) is reinforced with an external mesh collar
Endoscopic (Endoluminal) Bariatric Procedures	43290, 43291	• The access to the stomach is gained through the mouth, so no incisions are necessary. • Endoluminal procedures being developed: o Primary bariatric procedure o Revision (e.g. for treatment of enlarged gastric stoma and/or enlarged gastric pouches that may be associated with weight gain after bariatric surgery) • Examples of the endoscopic revision bariatric procedures include: o Gastroplasty using an endoscopically guided stapler (reduces the size of the gastric pouch) o Placement of gastric balloon (soft, silicone balloon inserted into the stomach and filled with sterile saline to induce feeling of satiety) o Placement of duodenal-jejunal sleeve (sleeve placed inside duodenum and upper jejunum to prevent contact between food and the intestine). • StomaphyX®, an endoscopically guided system intended for tissue plication and ligation, has received 510(k) FDA approval. The device is also being investigated for endoscopic treatment of gastroesophageal reflux. • OverStitch™ Endoscopic Suturing System is intended for endoscopic placement of sutures and approximation of soft tissue, and has received FDA approval. The system may be used as an incisionless revision surgery, with the intent to reduce the size of a stomach pouch that has stretched out following a previous bariatric procedure.
Laparoscopic Gastric Plication	No specific CPT code	• Sutures are laparoscopically placed over the greater curvature (laparoscopic greater curvature plication) or anterior gastric region (laparoscopic anterior curvature plication) to create a tube-like stomach. • The procedure involves 2 main steps: o Mobilization of the greater curvature of the stomach, and o Suture plication of the stomach to achieve gastric restriction

EVIDENCE SUMMARY

- Roux-en-Y Gastric Bypass (RYGBP)

  The Roux-en-Y gastric bypass is a commonly performed procedure with the most accumulated evidence in the published literature.[2] Consequently, in order to determine the safety and efficacy of other bariatric surgical procedures, they need to be compared to RYGBP in well-designed, well-executed randomized controlled trials (RCTs).

- Laparoscopic Adjustable Gastric Banding (LAGB)

  RCT data comparing LAGB and RYGBP are limited, however:

  - LAGB is reversible and the least invasive of all bariatric procedures.
  - Weight loss following LAGB is less than what is usually seen following RYGBP.
  - LAGB has low perioperative complications; however inadequate weight loss or long term complications of band erosion, slippage, or malfunction may require additional surgery.

- Sleeve Gastrectomy (SG)

  - SG has gained acceptance in clinical practice and is a commonly performed procedure.
  - SG offers an alternative to adjustable gastric banding with potentially greater weight loss but without the complications associated with malabsorptive procedures, such as RYGBP.

- Other Bariatric Surgical Procedures

  Randomized Controlled Trials

  Very few randomized controlled trials compared other bariatric procedures with RYGBP. Overall, the trials were of poor quality and the findings unreliable due to at least one of the following design flaws:

  - The trials had very small study populations, limiting the ability to rule out the role of chance as an explanation of findings.
  - The randomization scheme was either inadequate or not explained. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics, which in turn may affect the outcome.
  - The studies have short follow-up times so there is no long-term (5-10 years or longer) evidence regarding:

    - durability of weight loss
    - complications (e.g. metabolic side effects, nutritional deficiencies, anastomotic ulcers, esophagitis, procedure-specific complications such as band erosion)
    - resolution of comorbidities (e.g. diabetes, hypertension, obstructive sleep apnea, increased cholesterol)
    - need for reoperations

- Short-term complications, adverse events, morbidity, resolution of comorbidities, and reoperation rates are inconsistently reported, limiting conclusions and comparisons across studies.
- There is limited understanding of appropriate patient selection criteria for each of the non-RYGBP bariatric procedures (e.g. superobese patients vs. morbidly obese patients).

Nonrandomized Studies

Although the published, peer-reviewed literature on non-RYGBP bariatric procedures is voluminous, it consists mostly of case series and retrospective, nonrandomized comparisons. Evidence from these studies is unreliable due to design flaws, such as non-random allocation of treatment, lack of adequate comparison groups, and short-term follow-up. In addition, the inconsistent reporting of weight loss, resolution of comorbidities, adverse events, morbidity, and reoperation rates further limit meaningful comparisons across these studies.

- Bariatric Surgery in the Pediatric Population

  Overall, there is enough evidence on the role of bariatric surgery in treating pediatric patients with severe obesity. Moreover, the evidence mostly comes from small, nonrandomized and therefore unreliable studies. Specifically:

  - There is enough evidence that bariatric surgery leads to clinically significant, long-term sustained weight loss and resolution of obesity-related comorbidities in the pediatric population.
  - There is still a lack of evidence regarding the long-term potential impact of bariatric procedures on growth and development in the pediatric population.

- Bariatric Surgery as a Treatment for Gastroesophageal Reflux Disease (GERD)

  In order to determine the safety and efficacy of bariatric surgical procedures as treatments for GERD, they need to be compared to standard medical or surgical treatments of this condition in well-designed, well-executed randomized controlled trials.

- Endoscopic Bariatric Procedures

  There is insufficient evidence to determine the safety and efficacy of any endoluminal procedure as either a primary bariatric procedure or a revision procedure. The published evidence is limited and consists of only a few case series and randomized trials with a high risk of bias.

- Multidisciplinary Approach to the Clinical Management of Bariatric Surgery Patients

  The National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) clinical practice guidelines state the importance of a multidisciplinary approach to the clinical management of bariatric surgery patients. Comprehensive programs should address nursing, nutrition, exercise, behavior modification, and psychological support, and they should provide lifelong follow-up for treated patients.[1]

- Bariatric Surgery Centers of Excellence

The published evidence indicates that high volume bariatric centers are more likely to be successful in achieving optimal outcomes and lower complication and mortality rates than low volume bariatric centers.[3-5] These data have led to national efforts to establish bariatric surgery centers of excellence by the American Society for Metabolic and Bariatric Surgery, the American College of Surgeons, and the BlueCross BlueShield Association.

The following literature appraisal is based on randomized controlled trials (RCT), Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessments, Cochrane reviews, Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness reviews, Washington State Health Technology Assessment and evidence-based guidelines.

DISTAL (LONG LIMB) GASTRIC BYPASS

SYSTEMATIC REVIEWS

The 2005 Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment identified six comparative trials of long limb gastric bypass with Roux-en-Y anastomosis (LL-RYGBP) vs. standard RYGBP.[2] However, only two were randomized controlled trials (RCT). The assessment determined that there was not sufficient evidence to reach conclusions on the efficacy and safety of LL-RYGBP compared to standard RYGBP:

- In both RCTs, there was no significant difference in weight loss between the two groups at 1 year.
- The evidence for the super obese (BMI ≥50 kg/m^2) population was weak and did not allow conclusions concerning whether LL-RGYBP is superior in this subgroup of patients
- The adverse events were poorly reported in all comparative studies. Some of the reports contradicted one another.
- There was no definite cut-off for “long” vs. “standard” limb, making comparisons even more challenging.

RANDOMIZED CONTROLLED TRIALS

Salman (2023) published a single site RCT comparing outcomes of one-anastomosis gastric bypass (OAGB) and long BPL RYGB regarding weight loss and comorbidity resolution.[6] This study included 62 patients equally allocated to OAGB or long BPL RYGB, with no dropouts during follow-up. At 6 months, there was no statistically significant difference between the two groups regarding postoperative BMI ($p = 0.313$) and the EBWL ($p = 0.238$). There was comparable remission of diabetes, hypertension, OSA, joint pain, and low back pain. Seven patients in the OAGB group experienced reflux symptoms ($p = 0.011$), which were managed by proton pump inhibitors. The authors noted that long BPL RYGB should be preserved for cases whom are more risky for bile reflux.

One RCT evaluated the effectiveness of the distal gastric bypass for weight loss and control of comorbidities.[7] The study included only severely obese patients (BMI ≥50 kg/m^2). There was no significant difference in the control or improvement of hypertension, sleep apnea, or gastroesophageal reflux disorder between the patients who underwent long-limb (Roux limb = 250 cm) and short-limb gastric bypass (Roux limb = 150 cm). In addition, there was no difference in excess weight loss between the groups. Although the study reports better control of lipid disorders and diabetes in patients who underwent the long-limb gastric bypass, several design flaws undermine the reliability of the study findings:

- The small study population (n=105) limits the ability to rule out the role of chance as an explanation of findings.
- The randomization scheme was not explained. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics.
- The short-term follow-up limits conclusions regarding the long-term complications and the effectiveness of the distal gastric bypass in controlling weight loss and comorbidities.
- The study included only super obese patients limiting the generalizability of the study findings to other patient populations (i.e. morbidly obese).
- The need for nutritional supplementation after the surgery was reported for the two treatment groups, but there was a failure to include statistical testing for this outcome.

NONRANDOMIZED STUDIES

A number of nonrandomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing distal gastric bypass.[2, 8-10] As noted at the beginning of the evidence section, conclusions cannot be reached from these studies as the evidence is considered unreliable.

SECTION SUMMARY

Evidence regarding long limb gastric bypass with Roux-en-Y anastomosis (LL-RYGBP) vs. standard RYGBP is limited to three RCTs which showed either no benefit to the LL approach compared to the RYGBP and/or had numerous methodological limitations. In addition, without a standardized cut-off for long vs. standard limb length, comprehensive assessment of the long limb procedure is unlikely. Therefore, current evidence is insufficient to recommend LL-RYGBP over standard RYGBP, including in individuals with class III obesity.

BILIOPANCREATIC BYPASS AND BILIOPANCREATIC BYPASS WITH DUODENAL SWITCH

SYSTEMATIC REVIEWS

In 2013, Colquitt updated a 2009 Cochrane review[11] which compared outcomes for a variety of surgical weight loss procedures.[12] Two RCTs were identified which assessed outcomes of biliopancreatic diversion with duodenal switch (BPD-DS) compared to RYGBP. At a mean three year follow-up, data from the two trials were pooled (n= 107) and the following conclusions were reached:

- BPD-DS resulted in significantly greater weight loss than RYGBP.
- Quality of life measures were similar between the two groups.
- Reoperation rates were higher in the BPD-DS group (16.1%-27.6%) compared to the RYGBP group (4.3%-8.3%), with one death reported in the BPD-DS group.

The 2005 BCBSA TEC Assessment identified only one comparative trial that compared RYGBP with BPD-DS.[2] Although the trial included 237 RYGBP and 113 BPD-DS patients, it was not a randomized clinical study (the choice of the surgery was determined by surgeon and/or patient) and it followed participants for only one year. The TEC Assessment did not find this data sufficient to determine the risk/benefit ratio for this procedure or that it results in greater weight loss than RYGBP:

- The % estimated weight loss (EWL) at one year was the same for both the RYGBP and BPD-DS groups.
- Data on short-term adverse events was limited, except for the mortality and wound infection rates which were equivalent in both groups.
- More anastomotic leaks were reported in BPD-DS group.
- Long-term complications were not reported.
- Nutritional concerns were not adequately addressed. This is of concern because BPD-DS further reduces fat absorption, affecting the absorption of fat soluble vitamins.

RANDOMIZED CONTROLLED TRIALS

Moller (2023) published a RCT comparing long-term outcome of BPD/DS and RYGB in patients with super obesity (BMI > 50 kg/m2).[13] This is a 13- to 17-year follow-up study of a single-center, single-blinded randomized trial in which 47 patients (BMI > 48 and eligible for bariatric surgery) were randomized 1:1 to BPD/DS and RYGB (25 men, 24 BPD/DS, 39.1 ± 9.9 years, BMI 54.5 ± 6.1 kg/m2). The primary outcome was weight loss. Thirty-four (18 BPD/DS) of the living 42 patients (81.0%) participated. BPD/DS resulted in higher BMI loss (20.4 ± 7.9 vs. 12.4 ± 8.6, p = .008) and higher percent of total body weight loss (37.5% ± 12.2 vs. 22.8% ± 14.8, p = 0.004). BPD/DS was associated with lower fasting glucose, glycated hemoglobin (HbA1c), and low-density lipoprotein (LDL) as well as lower hemoglobin. Adverse events were more common after BPD/DS (2.7 vs. 0.9 per patient, p = 0.004). The global assessment tool BAROS (Bariatric Analysis and Reporting Outcome System) demonstrated superior scores for BPD/DS (p = 0.047).

Two prospective randomized trials compared the experiences of obese patients undergoing RYGBP vs. BPD. The first trial compared weight loss, metabolic deficiencies, and resolution of comorbidities in morbidly obese patients undergoing RYGBP vs. a variant of BPD (BPD with RYGBP).[14] The study reports comparable nutritional deficiencies between the two procedures. Although better weight loss and resolution of diabetes and hypercholesterolemia was reported in the BPD group, several design flaws undermine the reliability of the study findings:

- The study employed an inadequate randomization scheme: the report states that patients were chosen to undergo RYGBP or BPD, but fails to provide any further explanation of how the treatment was assigned. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics.
- The RYGBP group had a significantly higher level of preexisting comorbidities (p = 0.01), suggesting a difference between the treatment groups that may have affected the outcome.
- The small study population (65 patients/surgery group) limits the ability to rule out the role of chance as an explanation of findings.
- The short-term follow-up (2 years) limits conclusions regarding the long-term metabolic complications and the long-term effectiveness of the BPD in controlling weight loss and comorbidities.

Another small randomized trial (n=60) compared laparoscopic RYGBP and BPD-DS for superobese patients (BMI 50-60 kg/m^2).[15] The study found comparable 30-day perioperative safety and greater weight loss following BPD-DS in the first year.

In 2015, long-term 5-year follow-up results were published on data from 55 patients (92%).[16] Results indicated a mean reduction of body mass index was greater with duodenal switch compared to bypass (mean between-group difference was 8.5 [95% CI, 4.9-12.2; P < .001]); however, duodenal switch was associated with more surgical, nutritional and gastrointestinal adverse effects.

NONRANDOMIZED STUDIES

A number of non-randomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing biliopancreatic diversion with or without duodenal switch.[17-35] Many of these studies show successful weight loss after BPD compared to other bariatric procedures.

SLEEVE GASTRECTOMY

There are various types of gastrectomy, which include distal, partial (including sleeve gastrectomy) or complete gastrectomy which may be performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction. There is insufficient evidence regarding the use of gastrectomy, other than sleeve gastrectomy, as a treatment of obesity. Numerous studies were identified which evaluated outcomes of these alternative gastrectomy methods as a treatment of other conditions, including gastric cancer; however, no studies or clinical practice guidelines were identified which evaluated the efficacy of these alternative types of gastrectomy as a treatment of obesity. Therefore, the following evidence review will focus on the use of sleeve gastrectomy as a treatment of obesity, in the context of systematic reviews and well-designed randomized controlled trials:

SYSTEMATIC REVIEWS

Numerous recent systematic reviews have compared SG and RYGB with regard to effects on weight, comorbidities, and complications.

Osland (2023) systematic review and meta-analysis of RCTs to investigate the comparative 5-year outcomes of both procedures in adults.[36] Three RCTs (LVSG=254, LRYGB=255) met inclusion criteria and reported on chronic disease outcomes. Improvement and/or resolution of hypertension favored LRYGB (odds ratio 0.49, 95% CI 0.29, 0.84; p = 0.03). Trends favoring LRYGB were seen for type 2 diabetes and dysplidemia, and LVSG for sleep apnea and back/joint conditions (p >0.05). The certainty of evidence associated with each assessed outcome ranged from low to very low, in the setting of 'some' to 'high' bias assessed as being present. The authors conclude that the limited certainty of the evidence does not allow for strong clinical conclusions to be made at this time regarding benefit of one procedure over the other.

Kermansaravi (2023) published an umbrella review with meta-analyis comparing the safety and efficacy of sleeve gastrectomy versus Roux-en-Y gastric bypass in elderly (>60 years) with severe obesity.[37] The umbrella review included six meta-analyses. The risk of early-emerging and late-emerging complications decreased by 55% and 41% in the patients underwent SG than in those receiving RYGB, respectively. The chance of the remission of hypertension and obstructive sleep apnea, respectively increased by 43% and 6%, but type-2 diabetes mellitus decreased by 4% in the patients underwent RYGB than in those receiving SG. RYGB also increased excess weight loss by 15.23% in the patients underwent RYGB than in those receiving SG. The authors conclude that lower levels of mortality and early-emerging and late-

emerging complications were observed in the older adults undergoing SG than in those receiving RYGB, which was, however, more efficient in term of weight loss outcomes and recurrence of obesity-related diseases.

Vanetta (2023) published a SR and meta-analysis evaluate the safety and success of same day discharge following SG and RYGB.[38] A total of 14 studies with 33,403 patients who underwent SDD SG (32,165) or RYGB (1238) were included in the qualitative synthesis. Seven studies with 5000 patients who underwent SDD SG were included in the quantitative analysis, and pooled proportions (PPs) were calculated for the outcomes of interest. The SDD success rate was 63%-100% (PP: 99%) after SG and 88%-98.1% after RYGB. The readmission rate ranged from 0.6% to 20.8% (PP: 4.0%) after SDD SG and 2.4%- 4.0% after SDD RYGB. Overall morbidity, reoperation, and mortality were 1.1%-10% (PP:4.0%), 0.3%-2.1% (PP: 1.0%), and 0%- 0.1% (PP: 0%), respectively, for SDD SG, and 2.5%-4.0%,1.9%-2.5%, and 0%- 0.9%, respectively, for SDD RYGB. SDD after SG seems feasible and safe. The outcomes of SDD RYGB seem promising, but the evidence is limited to draw definitive conclusions. Selection criteria and perioperative protocols must be standardized to adequately introduce this practice.

Gu (2020) completed a meta-analysis of the medium- and long-term effects of laparoscopic SG and RYGB.[39] The evaluation included 9038 patients from 28 studies. Overall, 5 year follow-up results revealed that laparoscopic RYGB was associated with an improvement in percentage of EWL and remission of T2D, hypertension, and dyslipidemia as compared to laparoscopic SG.

Han (2020) also published a systematic review and meta-analysis involving 18 studies (N=2917) that compared weight loss and comorbidity resolution between laparoscopic SG and RYGB.[40] Results from this analysis revealed no significant difference in EWL or T2D resolution between the 2 procedures. Laparoscopic RYGB was found to be superior to SG with regard to dyslipidemia, hypertension, and GERD management; however, patients who underwent laparoscopic SG experienced fewer postoperative complications and reoperation rates.

Sharples (2020) performed a systematic review and meta-analysis evaluating long-term (5 years) outcomes of RYGB and SG.[41] Overall, both RYGB and SG resulted in sustained weight loss and comorbidity control with RYGB associated with a greater percent EWL, improved dyslipidemia outcomes, and a reduced incidence of GERD (Table 5).

Shenoy (2020) published a systematic review and meta-analysis of 9 studies that compared laparoscopic SG and RYGB in 2240 elderly (>55 years) patients.[42] Results revealed no significant differences between the 2 bariatric procedures with regard to the rate of early complications (3.6% LSG versus 5.8% LRYGB; p=0.15) and mortality (0.1% versus 0.8%; p=0.27). Additionally, there was no difference in EWL between the procedures at 1 year; however, the authors recommended SG for high-risk elderly patients due to the reduced mortality and complication rates with this procedure.

Another systematic review and meta-analysis by Xu (2020) involving 19 studies also concluded that SG was the preferable option for elder obese patients 60 years and older as it was found to be non-inferior to RYGB with regard to efficacy, but overall had an improved safety profile.[43]

Osland (2017) published a systematic review and meta-analysis of RCTs comparing laparoscopic vertical SG with RYGB.[44] The literature search, conducted from 2000 to November 2015, identified 9 RCTs for inclusion (N=865 patients). Four trials were included in meta-analyses comparing percent EWL between the 2 groups. Results at both 6- and 12-month follow-ups showed that the procedures are comparable. Osland (2020) recently published a continuation of their work that focused exclusively on long-term (5 year) weight outcomes of laparoscopic vertical SG versus RYGB.[45] This systematic review and meta-analysis included 5 studies (SG=520; RYGB=508) and results revealed that a statistically significant BMI loss was seen with both SG: -11.37 kg/m^2 (range: -6.3 to -15.7 kg/m^2) and RYGB: -12.6 kg/m^2 (range: -9.5 to -15.4 kg/m^2) at 5 years. However, differences in reporting parameters limit the ability to reliably compare outcomes using statistical methods and the results may have been impacted by large dropout rates and per protocol analyses of the 2 largest included studies.

In 2017, Juodeikis evaluated five-year results following sleeve gastrectomy in a systematic review of the literature through May 2016.[46] The review was conducted according to PRISMA guidelines. Twenty studies were included for evaluation, however, only one study was a randomized controlled trial. Of the 2,713 patients included amongst all the studies combined, 1,626 reached at least five years follow-up (duration ranged from 5-11 years follow-up). Although mean percentage excess weight loss of greater than 56% was achieved at each time point from 5 to 11 years' time, the review was substantially limited by the lack of RCT data.

In 2016, Osland compared the efficacy of Roux-En-Y gastric bypass versus vertical sleeve gastrectomy in randomized controlled trials.[44] Six RCTs performed between 2005 and 2015 were included (N = 695; 347 for SG and 348 for RYGB). The authors summarized recent publications, without pooled analysis. Although the results stated comparable efficacy and improvement or resolution in comorbidities, the authors also noted the significant limitation of short follow-up time (one year, with significant loss of follow-up), and lack of blinding in five of the six studies included. In 2017, Osland published an additional meta-analysis, again comparing vertical sleeve gastrectomy in RCT's to LRYGB (N=865 patients; 437 for SG and 428 for LRYGB).[47] The authors concluded once again that a significant gap exists in the literature with respect to well-designed studies using intent-to-treat analysis.

In 2015, Zhang published a separate review comparing LSG to laparoscopic RYGBP (LRYGBP) which included 21 studies involving 18,766 morbidly obese patients.[48] Data regarding percentage of excess weight loss (%EWL), resolution or improvement of comorbidities, and adverse events were pooled. Although no difference in %EWL was observed between the two groups in the first 6 months-1.5 year follow-up, LRYGBP achieved higher %EWL compared to LSG ($p<0.05$). Except for improvements in type 2 diabetes, comorbidities did not differ significantly between the two groups. Adverse events were more frequent following Roux-en-Y bypass (OR for major complication: 1.29; 95% CI 1.22 to 3.22; $P<0.01$). Results of this review must be interpreted with caution as 13 of the 21 included studies were nonrandomized, limiting the ability to control for confounding factors.

A 2014 review by Zellmer compared complication rates of laparoscopic RYGBP to LSG in 61 publications which included 10,906 laparoscopic RYGBP patients and 4,816 LSG patients.[49] Authors reported similar leak and mortality rates in both groups; laparoscopic RYGBP (leak: 1.9%, mortality: 0.4%) vs. LSB (leak: 2.3%, mortality: 0.2%).

The 2013 Cochrane review of bariatric surgery identified only one randomized controlled trial that compared sleeve gastrectomy to gastric bypass with Roux-en-Y anastomosis (RYGBP).[11, 12, 50] This very small (n=32) and short trial that followed participants for only 1 year reported that:

- Weight loss and BMI were similar between the two procedures, but % excess weight loss was greater with sleeve gastrectomy.
- Two patients had diabetes at baseline, both in the RYGBP group. The condition was resolved at 1 year in both patients. The outcome of other comorbidities reported at baseline was not reported for the RYGBP or SG groups.
- Although the study reported no conversions to open surgery and no intraoperative and postoperative complications, the other complications and additional operative procedures were not reported.
- The study did not assess a two-stage approach using sleeve gastrectomy prior to another bariatric procedure and consequently no conclusions about the two-stage approach could be made.
- The short duration of the follow-up results in underestimation of the impact of late complications and the need for revision surgery.

In 2013, Trastulli published a systematic review of randomized trials that compared sleeve gastrectomy to other bariatric procedures.[51] A total of 15 RCTs with 1191 patients were included. In six trials laparoscopic sleeve gastrectomy (LSG) was compared to laparoscopic RYGBP. The authors reported mean complication rates with sleeve gastrectomy of 12.1% (range 10%-13.2) compared with 20.9% with laparoscopic gastric bypass (range 10%-26.4%). Percentage of excess weight loss ranged from 49%-81% with sleeve gastrectomy compared with 62.1%-94.4% with laparoscopic gastric bypass. Included studies which compared LSG to laparoscopic RYGBP were small[52-54] (n<60) and several contained a risk for bias which included unclear blinding, randomization methods and outcome data.

A 2013 meta-analysis by Li pooled data from five trials, four of which were included in the Trastulli review, to compare the impact of these procedures on type 2 diabetes rates.[55] Laparoscopic Roux-en-Y gastric bypass was associated with higher rates of type 2 diabetes remission and greater estimated weight loss, but higher rates of complications.

RANDOMIZED CONTROLLED TRIALS

Pajecki (2023) published three year outcomes of a RCT comparing SG and RYGBP in obese patients older than 65 years.[36] Of the 36 patients who underwent randomization, none were lost to follow-up through the 36 months of data collection. The baseline mean BMI was 45 ± 5.2 kg/m2. Weight loss was significantly better after LRYGB compared to LSG in the third year of follow-up, both on %TWL (30.3 ± 2.2% vs. 17.2 ± 2.2%, p = 0.001) and %EWL (63.1 ± 4.3 vs. 43.5 ± 6.7%, p = 0.018). After LRYGB, HbA1c (p < 0.001), HDL (p < 0.001), LDL (p = 0.007), and triglyceride (p < 0.001) levels improved significantly. After LSG, a significant difference was only seen in HDL levels (p = 0.004). Adherence to micronutrient supplementation was significantly more frequent in the LSG group (72.2% vs. 22.2%, p = 0.003). Hemoglobin and albumin levels remained stable for both procedures. The data in this study is limited to methodology concerns as all follow-up was via telephone contact only due to COVID-19.

Hofsø (2019) published the results of a single-center, triple-blind RCT comparing the efficacy of Roux-en-Y gastric bypass (RYGB) (n=54) vs sleeve gastrectomy (SG)(n=55) on diabetes

remission and ß-cell function in patients with obesity and T2D. Inclusion criteria included previously verified BMI ≥35 kg/m2 and current BMI ≥33.0 kg/m2, hemoglobin A1c (HbA1c) ≥6.5% or use of antidiabetic medications with HbA1c ≥6.1%, and age ≥18 years. One-year follow-up was completed by 107 (98%) of 109 patients, with 1 patient in each group withdrawing after surgery. In the intention-to-treat population, diabetes remission rates were superior in the gastric bypass group than in the sleeve gastrectomy group (risk difference 27%; relative risk [RR] 1.57). Results were similar in the per-protocol population (risk difference 27%; RR 1.57). The two procedures had a similar beneficial effect on ß-cell function.

Peterli (2018) published a randomized study of adults with morbid obesity treated with either laparoscopic sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).[56] Two hundred five patients treated at four bariatric centers were randomly assigned to receive SG (n=101) or RYGB (n=104) with 5-year follow-up. Excess BMI loss was 61.6% for SG and 68.3% for RYGB. Gastric reflux remission was seen in 25.0% of SG and 60.4% of RYGB patients. Reoperations or interventions were necessary for 15.8% in the SG group and 22.1% of the RYGB group. The study was limited by the lack of analysis of diabetes remission information and the results may not be generalizable.

Salminen (2018) published a randomized trial (SLEEVEPASS) comparing 5-year outcomes of morbidly obese patients who underwent either laparoscopic sleeve gastrectomy (SG; n=121) or Roux-en-Y gastric bypass (RYGB; n=119).[35] Five-year estimated mean percentage excess weight loss was 49% for sleeve gastrectomy and 57% for gastric bypass. For SG and RYGB, respectively, rates of remission of type 2 diabetes were 37% and 45%. Medication for hypertension was discontinued in 20/68 (29%) SG patients and 37/73 (51%) RYGB patients. Overall 5-yr morbidity rate was 19% for SG and 26% for RYGB, and there was no significant difference in QOL between groups. The study was limited by the following: the study having a higher reoperation rate for sleeve gastrectomy than other trials reported, approximately 20% of patients were lost to follow-up, and there was a lack of reliable information for diabetes duration at baseline.

CLINICAL PRACTICE GUIDELINES

In 2012, the American Society for Metabolic & Bariatric Surgery (ASMBS) updated their position statement on *Sleeve Gastrectomy as a Bariatric Procedure.*[57] The ASMBS recognizes sleeve gastrectomy as an acceptable option as a primary bariatric procedure and as a first stage procedure in high risk patients as part of a planned staged approach. In addition, the group noted that substantial comparative and long-term data have now been published which demonstrate durable weight loss, improved medical comorbidities, long-term patient satisfaction, and improved quality of life after SG. However, the ASMBS Statement does not include a critical appraisal of the reviewed evidence.

SECTION SUMMARY

Recent systematic reviews of existing trials indicate sleeve gastrectomy (SG) is a comparable procedure to RYGBP. Although the evidence regarding SG with RYGBP compared to standard RYGBP is limited by short-term follow-up, SG has become a recognized surgical option in clinical practice for the treatment of morbid obesity.

ADJUSTABLE GASTRIC BANDING

SYSTEMATIC REVIEWS

Park (2019) conducted a systematic review with a network meta-analysis evaluating the comparative efficacy of various bariatric surgery techniques against standard-of-care in the treatment of morbid obesity and diabetes.[58] The literature search was conducted through February 2018, identifying 45 RCTs for inclusion on Roux-en-Y gastric bypass (RYGB; 2 studies), sleeve gastrectomy (SG; 3 studies), laparoscopic adjustable gastric band (LAGB; 5 studies), and biliopancreatic diversion with duodenal switch (BPD-DS; 3 studies vs RYGB). Based on 33 trials, superior efficacy for % excess weight loss compared to standard-of-care was seen for BPD-DS (mean difference [MD] 38.2%), RYGB (MD 32.1%), and SG (MD 32.5%) at 6 months post procedure. LAGB was not superior to standard-of-care (MD -0.2%). At 3 years post-procedure, superior efficacy for %EWL compared to standard-of-care was seen for RYGB (MD 45%) and SG (MD 39.2%). BPD-DS (RR 7.51), RYGB (RR 7.51), and SG (RR 6.69) were all superior to standard-of-care with respect to remission rates at 3-5 years post-procedure and remission rates were not significantly different among procedures. SG was found to have a relatively lower risk of adverse events compared to RYGB.

A 2017 systematic review by Kang reported results from a network meta-analysis of RCTs evaluating the three most commonly performed bariatric procedures – Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and laparoscopic adjustable gastric band (LAGB).[59] The review was conducted with literature through July 2016, and in accordance with PRISMA guidelines. Evidence was synthesized from 11 trials (8 RYGB vs SG; 2 RYGB vs LAGB; 1 SG vs LAGB) in order to evaluate the primary outcome of changes in weight loss, expressed as the mean difference in BMI reduction and in percentage excess weight loss (%EWL) following 1 year after the surgery. The smallest treatment effect was observed in LAGB (8 trials, totalling 656 patients). The mean %EWL for RYGB, SG, and LAGB were 67.3% (n=294), 71.2% (n=209), and 40.6% (n=153), respectively. Heterogeneity between studies was low (as evaluated by calculating the I^2 statistic), and the studies were consistent between direct and indirect comparisons – both demonstrated strengths of the analysis. The study was limited by fewer trials evaluating LAGB, and inclusions of RCTs with a lack of blinding.

The 2013 Cochrane review of bariatric surgery identified three randomized controlled trial that compared laparoscopic adjustable gastric banding (LAGB) to laparoscopic gastric bypass with Roux-en-Y anastomosis (RYGBP).[11, 12, 60] At five-year follow-up, the review reported the following conclusions:

- RYGBP was superior to LAGB on more than one measure of weight loss (% excess weight loss, mean BMI).
- Quality of life measures and comorbidities were not assessed due to the low quality of the evidence.
- RYGBP resulted in a greater duration of hospitalization and a greater number of late major complications.
- One study reported high rates of reoperation for removal of LAGB (9 patients, 40.9%).

In 2012, TEC conducted an updated Assessment, focusing on LAGB in patients with BMIs less than 35 kg/m^2.[61] TEC made the following observations and conclusions:

- The evidence on LAGB for patients with lower BMIs is limited both in quantity and quality. There was only one small randomized, controlled trial, which had methodologic limitations, one nonrandomized comparative study based on registry data, and several case series. Using the GRADE evaluation, the quality of evidence on the comorbidity outcomes was

judged to be low and the quality of the evidence on the weight loss outcomes was judged to be moderate.

- The evidence was sufficient to determine that weight loss following LAGB was greater than with nonsurgical therapy.
- Direct data on improvement in weight-related comorbidities was lacking. The limited evidence was not sufficient to conclude that the amount of weight loss was large enough that improvements in weight-related comorbidities could be assumed.
- There was very little data on quality of life in this population of patients.
- The frequency and impact of long-term complications following LAGB was uncertain, thus it was not possible to determine whether the benefit of LAGB outweighed the risk for this population. TEC concluded that while the short-term safety of LAGB was well-established, the long-term adverse effects occur at a higher rate and are less well-defined.

RANDOMIZED CONTROLLED TRIALS

An updated literature search failed to identify any additional randomized controlled trials that compare LAGB with RYGBP.

NONRANDOMIZED STUDIES

A number of non-randomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing LAGB.[34, 62-69] As noted at the beginning of the evidence section, conclusions cannot be reached as the evidence from these studies is considered unreliable.

SECTION SUMMARY

The evidence regarding the laparoscopic adjustable gastric banding (LAGB) compared to standard RYGBP is limited. Additionally, LAGB may have higher rates of reoperation and revisions. LAGB is no longer considered a standard of care.

LAPAROSCOPIC DUODENAL SWITCH WITH SINGLE ANASTOMOSIS

Several nonrandomized studies were identified which describe the experiences of patients undergoing laparoscopic duodenal switch with single anastomosis (LSDSA).[70-74] As noted at the beginning of the evidence section, conclusions cannot be reached from these studies as the evidence is considered unreliable. Well-designed RCTs which compare LSDSA with RYGBP are needed in order to evaluate the safety and efficacy of this procedure compared to accepted surgical treatments of morbid obesity.

SYSTEMATIC REVIEWS

Balamurugan (2023) published a systematic review comparing the safety and efficacy between Roux-en-Y gastric bypass (RYGB), one anastomosis gastric bypass (OAGB) and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S). Eighteen eligible studies were included. Weight loss outcomes were greater with SADI-S (5 years) and OAGB (10 years). SADI-S offered better resolution of diabetes whereas hypertension and dyslipidaemia resolution were better with OAGB. Although early complications and mortality were higher with SADI-S, late complications were more frequent with RYGB. Both SADI-S and OAGB are as effective as RYGB for weight loss, but OAGB offers lesser complications. The authors conclude that more data is imperative to determine the next gold standard procedure.

Nakanishi (2022) published a systematic review of six studies including 1,846 patients with obesity who underwent either single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S) or a biliopancreatic diversion with duodenal switch (BPD-DS).[75] The BPD-DS group had a greater % excess body mass index loss (MD=-10.16%, 95% confidence interval: -11.80, -8.51) at two years compared with the SADI-S group. There was no difference observed in preoperative comorbidities and remission, including diabetes, hypertension, and dyslipidemia between SADI-S and BPD-DS cohorts. The SADI-S group had shorter hospital stays and fewer long-term complications. The authors concluded that additional randomized trials with extended follow-up periods are necessary to establish the safety and efficacy of the procedure.

Spinos (2021) conducted a systematic review to evaluate the effectiveness of patients who have undergone single-anastomosis duodenal bypass with sleeve gastrectomy/one anastomosis duodenal switch (SADI-S/OADS).[76] There were 14 studies included in the review including five retrospective cohort and nine case series. A total of 1086 patients were included in the analysis with preoperative BMI of 51.3 ± 9.5 kg/m2. The average body mass index (BMI) following SADI-S was 32.1 ± 6.7 kg/m2. Mean total body weight (TBW) loss ranged from 11.3% to 17.3% at three months, 21.5% to 41.2% at 12 months, and 25.8% to 46.3% at 24 months. Mean excess body weight (EBW) loss ranged from 21.8% to 40.2% at three months, 60.9% to 91.0% at 12 months, and 44.3% to 86.0% at 24 months. Mean excess BMI (EBMI) ranged from 9.4% to 31.1% at three months, 17.9% to 86.6% at 12 months, and 19.5% to 80.8% at 24 months. The comorbidity resolution rates were 72.6% for diabetes mellitus, 77.2% for dyslipidemia, 59% for hypertension, 54.8% for obstructive sleep apnea, and 25% for gastroesophageal reflux disease. The most common early postoperative complications after SADI-S included the need for reoperation (3.1%), bleeding (1.1%), wound infection (1.0%), anastomotic leak (0.9%), and intrabdominal collection/abscess (0.6%). Late postoperative complications were the need for reoperation (5.3%) and dumping syndrome (1.3%). The major limitation of this review is that studies were either retrospective cohort studies or case series with short-term follow ups.

CLINICAL PRACTICE GUIDELINES

In 2020, ASMBS published an updated statement on single-anastomosis duodenal switch (SADI-S) "in response to numerous inquiries made...by patients, physicians, society members, hospitals, and others regarding [this procedure] as a treatment for obesity and metabolic diseases."[77] The following recommendations were endorsed regarding SADI-S for the primary treatment of obesity or metabolic disease:

> "SADI-S, a modification of classic Roux-en-Y duodenal switch, is an appropriate metabolic bariatric surgical procedure."
>
> "Publication of long-term safety and efficacy outcomes is still needed and is strongly encouraged, particularly with published details on sleeve gastrectomy size and common channel length."
>
> "There remain concerns about intestinal adaptation, nutritional issues, optimal limb lengths, and long-term weight loss/regain after this procedure. As such, ASMBS recommends a cautious approach to the adoption of this procedure, with attention to ASMBS-published guidelines on nutritional and metabolic support of bariatric patients, in particular for duodenal switch patients."

MINI-GASTRIC BYPASS

SYSTEMATIC REVIEWS

In 2014, Georgiadou published a systematic review regarding the safety and efficacy of laparoscopic mini gastric bypass.[78] The review included a search of the literature through July 2013, and was conducted according to PRISMA guidelines. Ten articles with a total of 4,899 patients were included for review, of which three were comparative studies (two versus LRYGB and one versus LAGB). Excess weight loss at two years ranged from 64.4% ± 8.8% to 80%. Minor postoperative complication rates ranged from 3.6%-7.5%, and major early postoperative complication rates ranged from 0-7%. Authors noted a major concern for postoperative esophagitis and gastritis caused by bile reflux, and the risk for gastric cancer. Overall, the study was limited by the limitations of the included studies (e.g., short term follow-up and noncomparative design).

RANDOMIZED CONTROLLED TRIALS

One small RCT compared the safety and effectiveness of laparoscopic RYGBP and mini-gastric bypass (MGBP).[79] The study found a comparable rate of late complications (>30 days post-op), weight loss, and comorbidity resolution. MGBP was associated with fewer early complications (<30 days post-op). However, the following design flaws undermine reliability of the study findings:

- The small study population (n=80) limits the ability to rule out the role of chance as an explanation of findings.
- Short-term follow-up (2 years) limits comparisons regarding the longer-term complications rates and the effectiveness of the two procedures in controlling weight loss and comorbidities

NONRANDOMIZED STUDIES

In 2017, Plamper reported a comparison of mini gastric bypass and sleeve gastrectomy in super-obese patients (i.e., BMI > 50 kg/m^2) at a single institution.[80] At one-year follow-up, 90.8% (99 of 109) and 78.7% (74 of 94) of the MGB and SG patients were available for follow-up, respectively. Reasons for loss of follow-up were not discussed. One patient in the SG group died within 30 days of the operation due to multi-organ failure after staple line leakage. Percent excess weight loss was statistically significantly greater in the MGB group at 12 months. The authors cited limitations of their review to include the retrospective design, and short-term results.

Several other nonrandomized studies (retrospective comparisons, case series), describe experiences of patients undergoing MGBP.[81-85] As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

SECTION SUMMARY

Data regarding the mini-gastric bypass (MGBP) is limited to a small RCT, prohibiting conclusions regarding the efficacy of this procedure compared to RYGBP.

VERTICAL BANDED GASTROPLASTY (VBG)

VBG has largely been abandoned in the United States due to insufficient weight loss and high reoperation rates (approximately 30%).[11, 86]

HIATAL HERNIA REPAIR

Numerous studies[87-91] were identified which evaluated outcomes of hiatal hernia repair performed in conjunction with other bariatric surgical procedures; however, no studies or clinical practice guidelines were identified which evaluated the efficacy of hiatal hernia repair as an independent treatment of obesity.

CLINICAL PRACTICE GUIDELINES

In 2018, the ASMBS and the American Hernia Society published a consensus guideline on bariatric surgery and hernia surgery.[92] The guideline contained the following conclusions and summary recommendations:

- "There is a significant link between obesity and hernia formation both after abdominal surgery and de novo. There is also evidence that abdominal wall hernia can more commonly present with obstruction or strangulation in patients with obesity."
- "There is a higher risk for complications and recurrence after hernia repair in patients with obesity."
- "In patients with severe obesity and ventral hernia, and both being amenable to laparoscopic repair, combined hernia repair and metabolic/bariatric surgery may be safe and associated with good short-term outcomes and low risk of infection. There is a relative lack of evidence, however, about the use of synthetic mesh in this setting."
- "In patients with severe obesity and abdominal wall hernia that is not amenable to laparoscopic repair, a staged approach is recommended. Weight loss prior to hernia repair is likely to improve hernia repair outcomes. Metabolic/bariatric surgery appears to provide far more significant and rapid weight loss than other modalities and would be a good option for selected patients with severe obesity and large, symptomatic abdominal wall hernia."

The 2022 ASMBS guidelines include the following recommendations: MBS is an effective treatment of clinically severe obesity in patients who need other specialty surgery, such as joint arthroplasty, abdominal wall hernia repair, or organ transplantation.[93]

TWO-STAGE BARIATRIC SURGERY PROCEDURES

Bariatric surgeries that are performed in two stages have been proposed as a treatment option, particularly for patients with “super-obesity” defined as a BMI greater than 50. The rationale for a two-stage procedure is that the risk of an extensive surgery is prohibitive in patients with extreme levels of obesity. Therefore, an initial procedure with low risk, usually a sleeve gastrectomy, is performed first. After a period of time in which the patient loses some weight, thus lowering the surgical risk, a second procedure that is more extensive, such as a biliopancreatic diversion (BD), is performed.

RANDOMIZED CONTROLLED TRIALS

Coffin (2017) published results on the use of intragastric balloon (IGB) prior to a laparoscopic gastric bypass in patients with super-obesity.[56] Patients with BMI greater than 45 kg/m^2 were randomized to an IGB (n=55) or standard medical care (n=60) during the 6 months prior to a

planned laparoscopic gastric bypass procedure. Five patients had the IGB removed earlier than 6 months due to complications (n=3) or patient request (n=2). Patients receiving IGBs during the first 6 months of the study experienced significantly more BMI reduction (2.8 kg/m^2; range 1.7-6.2 kg/m^2) than patients receiving standard care (0.4 kg/m^2; range 0.3-2.2 kg/m^2). Weight loss during months 6 through 12, after the laparoscopic gastric bypass procedure, was greater in the patients who received standard of care before the procedure. Duration of hospitalization after laparoscopic gastric bypass and quality of life did not differ between groups.

NONRANDOMIZED STUDIES

Case series on two-stage procedures for patients undergoing sleeve gastrectomy (SG) as the initial procedure generally did not report on the second-stage operation, and in those that did, only a minority of patients undergoing the first stage actually proceeded to the second-stage surgery. For example, Cottam[94] reported on 126 patients with a mean BMI of 65 who underwent laparoscopic SG as the first portion of a planned two-stage procedure. A total of 36 patients (29%) proceeded to the second-stage procedure, which was laparoscopic gastric bypass. In a similar study, Alexandrou.[95] reported on 41 patients who underwent SG as the first stage of a planned 2-stage procedure. After 1-year follow-up, 12 patients (29%) achieved a BMI less than 35 and were not eligible for the second-stage procedure. Of the remaining 28 patients, 10 (24% of total) underwent the second-stage procedure. The remaining 18 patients (44% of total) were eligible for, but had not undergone, the second-stage procedure at the last follow-up.

Patients who undergo two-stage procedures are at risk for complications from both procedures. Silecchia.[96] described the complication rates in 87 patients undergoing a stage I SG followed by a BPD in 27 patients. For the first stage of the operation, 16.5% of patients had complications of bleeding, fistula, pulmonary embolism, acute renal failure, and abdominal abscess. For the 27 patients who underwent the second-stage BPD, major complications occurred in 29.6% including bleeding, duodenoileal stenosis, and rhabdomyolysis.

SECTION SUMMARY

The current evidence does not indicate that a two-stage bariatric surgery procedure improves outcomes for patients with extreme levels of obesity. There is no evidence to suggest that weight loss is improved or that complications are reduced by this approach. A majority of patients who received SG as the initial procedure lost sufficient weight during the first year such that a second procedure was no longer indicated. In addition, patients undergoing a two-stage procedure are at risk for complications from both procedures; therefore, it is possible that overall complications are increased by this approach.

ENDOSCOPIC (ENDOLUMINAL) BARIATRIC PROCEDURES

SYSTEMATIC REVIEWS

Several systematic reviews of RCTs evaluating intragastric balloon (IGB) devices for the treatment of obesity have been published; none was limited to FDA-approved devices.[97-99]Weitzner (2023) published a SR comparing the efficacy of endoscopic bariatric procedures as compared to other existing treatments.[100] Thirty-seven studies (15,639 patients) were included. Intragastric balloons achieved greater %TBWL with a range of 7.6-14.1% compared to 3.3-6.7% with lifestyle modification at 6 months, and 7.5-14.0% compared to 3.1-7.9%, respectively, at 12 months. When endoscopic sleeve gastroplasty (ESG) was compared to

laparoscopic sleeve gastrectomy (LSG), ESG had less %TBWL at 4.7-14.4% compared to 18.8-26.5% after LSG at 6 months, and 4.5-18.6% as compared to 28.4-29.3%, respectively, at 12 months. For the AspireAssist, there was greater %TBWL with aspiration therapy compared to lifestyle modification at 12 months, 12.1-18.3% TBWL versus 3.5-5.9% TBWL, respectively. All endoscopic interventions had higher adverse events rates compared to lifestyle modification. The authors conclude that endoscopic therapies result in greater weight loss compared to lifestyle modification, but not as much as bariatric surgery.

Loo (2022) published a systematic review evaluating the utility of intragastric balloon as a bridge therapy to bariatric surgery in patients with severe obesity.[101] A total of 13 studies were included and the IGB resulted in a BMI reduction of 6.60 kg/m2 and post-operative complication rate of 8.13%. There was no evaluation of the risk reduction for subsequent bariatric surgeries or an assessment of long-term weight loss outcomes after the use of the bridge therapy. Additional follow-up and long-term studies are needed to assess the utility of IGB as a bridge therapy to bariatric surgeries.

Kotinda (2020) published a systematic review and meta-analysis that evaluated the efficacy of IGB devices in comparison to sham or lifestyle interventions in overweight and obese adults.[102] Thirteen RCTs with 1,523 patients were included. Results revealed that the mean percent EWL difference between the IGB and control groups was 17.98% (95% CI, 8.37 to 27.58; p<0.001), significantly favoring IGB. IGB was also significantly favored when evaluating the mean percent TWL difference between the groups: 4.40% (95% CI, 1.37 to 7.43; p<0.001). Similarly, the difference in actual weight loss and BMI loss was 6.12 kg and 2.13 kg/m2, respectively. Overall, IGB was found to be more effective than lifestyle intervention alone for weight loss. The majority of included RCTs used one fluid-filled IGB and there was significant heterogeneity between the included studies.

The systematic review by Tate (2017) focused on recent RCTs, published between 2006 and 2016.[103] Additional inclusion criteria were: sham, lifestyle modification, or pharmacologic agent as a comparator; at least 1 outcome of body weight change; and study duration of 3 or more months. Eight RCTs were included in the review, with four contributing to the meta-analysis. The meta-analysis included 777 patients and showed a significant improvement in percent TBWL with IGB compared with control (5.5%; 95% CI, 4.3% to 6.8%). However, there was significant heterogeneity among the trials (I^2=62%), so interpretation of results is limited. The percent TBWL with IGB is lower than expected with RYGB (reported 27%) or with the most efficacious pharmacologic agent (reported 9%).

Saber (2017) identified 20 RCTs reporting weight loss outcomes after IGB implantation or a non-IGB control intervention.[99] IGB was compared with sham in 15 trials, behavioral modification in 4 trials, and pharmacotherapy in 1 trial. In 17 trials, patients received lifestyle therapy in addition to other interventions. Studies were published between 1987 and 2015 and sample sizes varied from 21 to 326 participants. Outcomes were reported between 3 and 6 months. In a meta-analysis of 7 RCTs reporting BMI loss as an outcome, there was a significantly greater BMI loss in the IGB group than in the control group (mean effect size [ES], 1.59 kg/m^2; 95% CI, -0.84 to 4.03 kg/m^2; p<0.001). Findings on other outcomes were similar. A meta-analysis of 4 studies reporting percent EWL favored the IGB group (ES=14.25%; 95% CI, 2.09% to 26.4%; p=0.02). Also, a meta-analysis of 6 studies reporting absolute weight loss favored the IGB group (ES=4.6 kg; 95% CI, 1.6 to 7.6 kg; p=0.003).

Although the review was not limited to FDA-approved devices, older devices were air-filled and newer devices, including the two approved by FDA in 2015, are fluid-filled. Sufficient data were available to conduct a sensitivity analysis of 3-month efficacy data. A meta-analysis of 4 studies did not find a significant difference in weight loss with air-filled IGB devices or a control intervention at 3 months (ES= 0.26; 95% CI, -0.12 to 0.64; p=0.19). In contrast, a meta-analysis of 8 studies of fluid-filled devices found significantly better outcomes with the IGB than with control (ES=0.25; 95% CI, 0.05 to 045; p=0.02).

In 2017, Vargas performed a systematic review of two observational studies with no comparator group combined with results from a multi-center study of 130 consecutive patients.[104] Between the three studies, 330 endoscopic transoral outlet reduction (TORe) cases were performed with the Apollo OverStitch system. TORe was performed in patients experiencing weight regain following RYGB. Study quality was evaluated using the Newcastle-Ottawa Quality Assessment Scale for cohort studies; all were rated to be of moderate overall quality. Using a random effects model, the pooled absolute weight loss at 6, 12, and 18–24 months was 9.5 kg (95% CI 7.9–11.1), 8.4 kg (95% CI 6.5–10.3), 8.4 kg (95% CI 5.9–10.9), respectively. Given the fluctuation of absolute weight loss reported between timelines by each of the three studies, longer term follow-up would aid in evaluating the overall efficacy of TORe.

A systematic review of the effect of EndoBarrier® on weight loss and diabetic outcomes was published in 2015.[105] There were five small RCTs included with a total of 235 individuals (range, 18-77) and follow-up ranging from 12 to 24 weeks. The comparators were diet and/or other lifestyle modifications, and 2 studies had sham controls. All studies were judged to be at high risk of bias using the Cochrane risk of bias tool. Combined results demonstrated that the EndoBarrier® group had 12.6% greater EWL (95% CI, 9.0 to 16.2) compared to medical therapy. For diabetic outcomes, there were trends toward greater improvement in the EndoBarrier® group that did not reach statistical significance. The mean difference in HgA1c was -0.8% (95% CI, -1.8 to 0.3) and the relative risk of reducing or discontinuing diabetic medications was 3.28 (95% CI, 0.54 to 10.73).

RANDOMIZED CONTROLLED TRIALS

In June 2016 the AspireAssist (Aspire Bariatrics, King of Prussia, PA) weight loss therapy system was approved by the FDA to assist in weight reduction in adults aged 22 and older with a BMI of 35.0-55.0 kg/m^2 who have failed to achieve and maintain weight loss with non-surgical weight loss therapy. Feasibility data for the AspireAssist was reported by Sullivan and colleagues in 2013.[106] Preliminary results from the ongoing PATHWAY Pivotal Trial (sponsored by Aspire Bariatrics) are included in the FDA Summary of Safety and Effectiveness Data, though results have not been published in peer-reviewed literature at this point in time.[107]

In 2014, Eid reported results from a single-center RCT of the StomaphX device compared with a sham procedure for revision procedures in patients with prior weight loss after Roux-en-Y gastric bypass at least two years earlier.[108] Enrollment was initially planned for 120 patients, but the trial was stopped prematurely after 1-year follow up was completed by 45 patients in the StomaphyX group and 29 patients in the sham control group after preliminary analysis failed to achieve the primary efficacy endpoint in at least 50% of StomaphyX patients. The primary efficacy end point (reduction in pre-Roux-en-Y gastric bypass excess weight by 15% or more, excess BMI loss, and BMI less than 35, at 12 months post-procedure) was achieved by 10/45 (22.2%) of the StomaphyX group and 1/29 (3.4%) of the sham control group

(P<0.01). Conclusions regarding the use of the StomaphX device as a primary procedure for the treatment of obesity may not be drawn due to the discontinuation of the trial and the limited use of the device as a revision procedure in patients who had failed a prior bariatric surgery.

In 2014, Koehestanie published results from an RCT of duodenal-jejunal bypass liner (DJBL) treatment in comparison with dietary intervention for obesity and type 2 diabetes mellitus (T2DM).[109] A total of 77 patients were included in the trial with 38 patients randomized to 6 months DJBL in combination with dietary intervention and 39 patients were randomized to dietary interventions only. The total study duration for both groups was 12 months, including 6 months of post-DJBL removal follow-up. At 6 months follow-up, prior to DJBL removal, the DJBL group lost a higher percentage of excess weight compared to the dietary only group, 32% (22%-46.7%) vs. 16.4% (4.1%-34.6%) respectively. However, better HbAIc levels improvement was observed in the dietary only group compared to the DJBL at both 6 and 12 month follow-ups. Conclusions are limited in this study as both groups underwent dietary interventions limiting the isolation of the effects of DJBL upon obesity and type 2 diabetes.

In 2013, Sullivan reported results from a small feasibility pilot RCT (n=18) comparing the AspireAssist siphon assembly (Aspire Bariatrics, King of Prussia, PA) combined with lifestyle therapy (AT) versus lifestyle therapy (LT) alone.[106] Only fourteen subjects completed the 12-month trial (10 in the AT group and four in the LT group). Although weight loss in the AT group was greater at 52 weeks than the LT group (18.6% ± 2.3% of body weight vs 5.9% ± 5.0%) the study was limited by the very small sample size, and unblinded design. The study was partially funded by the manufacturer. The authors all disclosed having previously performed contracted research for the manufacturer of the device and one author also disclosed having consulted on a pivotal trial for the company.

In 2013, Fuller published a small RCT (n=66) which evaluated intragastric balloons (IGB) compared to behavioral modification as a treatment of obesity.[110] Subjects were either randomized to IGB and 12 months behavior modification (BH) and or 12 months BH alone. At six months the IGB treatment group demonstrated superior weight loss compared to the BH group (-14.2 vs. -4.8; P < 0.0001). However, at 12 months the difference in weight loss between groups, although still statistically significant, diminished (-9.2 vs. -5.2; P = 0.007). There were numerous adverse events related to IGB placement which typically resolved in two weeks. Limitations of this study include a relatively small population size and short-term follow-up with which to evaluate the lasting effects of weight reduction with IGB. In addition, RCTs which evaluate IGB to other standard surgical treatments of obesity are needed.

Additional, small RCTs assessing IGB were identified[111-113]; however, large, long-term data remain lacking with which to evaluate the safety and sustained benefit of IGB in weight reduction compared to conservative measures and accepted bariatric procedures.

NONRANDOMIZED STUDIES

A small number of non-randomized studies, primarily case series, describe experiences of patients undergoing different endoluminal procedures, such as endoscopic gastroplasty and endoscopically placed sleeves, gastric balloons or tissue anchors.[104, 114-131] As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

LAPAROSCOPIC GASTRIC PLICATION

Similar to the data for endoscopic bariatric procedures, the data for laparoscopic gastric plication (also known as laparoscopic gastric imbrication) is limited to case series and case reports and few, small RCT's.

RANDOMIZED CONTROLLED TRIALS

Sullivan (2017) published results from the ESSENTIAL trial, a randomized sham-controlled trial evaluating the efficacy and safety of endoscopic gastric plication.[132] Patients (N=332) were randomized 2:1 to the active or sham procedure. All patients were provided low-intensity lifestyle therapy. The primary end point was total body weight loss (TBWL) at 12-month follow-up. The mean difference in TBWL for patients receiving the procedure compared with patients receiving the sham procedure was 3.6% (95% CI, 2.1% to 5.1%). Significant differences between the active and sham groups were also reported in a change in weight from baseline, percent excess weight loss, BMI, and improvement in diabetes. No significant differences were detected in improvements in hyperlipidemia or hypertension between the treatment groups.

Talebpour (2017) randomized patients to laparoscopic gastric plication (n=35) or laparoscopic SG (n=35).[133] Patients were followed for 2 years. Both procedures were equally effective based on weight reduction outcomes. Adverse events (eg, nausea, hair loss, vitamin D deficiency, iron deficiency) were similar between groups. One death due to pulmonary thromboembolism occurred in the gastric plication group.

NONRANDOMIZED STUDIES

Additional studies describe patient outcomes after different laparoscopic plication procedures.[134-138] As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

REVISION BARIATRIC SURGICAL PROCEDURES

There are a number of reasons why patients who are treated with accepted forms of bariatric surgery may not lose weight or may regain weight that is initially lost. These reasons include issues of adherence (compliance), as well as technical (structural) issues. A number of studies[139-142] have evaluated the efficacy of revision procedures after failed bariatric surgery and reported satisfactory weight loss and resolution of co-morbidities with somewhat higher complication rates than for primary surgery. However, criteria for classifying what constitutes a failed, primary bariatric procedure, has not been clearly established.[143]

Vitiello (2023) published a SR with meta-analysis comparing weight loss and gastroesophageal reflux disease (GERD) remission after one-anastomosis gastric bypass (OAGB) versus Roux-en-Y gastric bypass (RYGB) as revisional procedures after laparoscopic sleeve gastrectomy (LSG).[144] Six retrospective comparative articles were included. Weight loss analysis showed a mean difference = 5.70 (95% CI 4.84-6.57) in favor of the OAGB procedure (p = 0.00001) with no significant heterogeneity (I2 = 0.00%). There was no significant risk difference (RD) for leak, bleeding, or marginal ulcer after the two revisional procedures. After conversion to OAGB, remission from GERD was 68.6% (81/118), and it was 80.6% (150/186) after conversion to RYGB with a RD = 0.10 (95% CI -0.04, 0.24; p = 0.19), with high heterogeneity (I2 = 96%). De novo GERD was 6.3% (16/255) after conversional OAGB, and it was 0.5% (1/180) after conversion to RYGB with a RD = -0.23 (95% CI -0.57, 0.11; p = 0.16), with high heterogeneity (I2 = 92%).

Franken (2023) published a SR with meta-analysis evaluating revisional techniques for addressing weight regain and insufficient weight loss after Roux-en-Y gastric bypass through a systematic review and meta-analysis.[145] Thirty-nine studies were included: four studies reported on argon plasma coagulation, four studies on transoral outlet reduction, nine studies on transoral outlet reduction + argon plasma coagulation, four studies on pouch/gastrojejunal anastomosis revision, five on laparoscopic gastric banding, two studies on laparoscopic gastric banding + pouch resizing, 10 on distalization-RYGB, and one on duodenal switch. All techniques resulted in short-term clinically relevant weight loss. Endoscopic procedures had a short follow-up and resulted in modest and temporary weight loss. Surgical revision techniques were successful for weight loss in longer term follow-up, at the expense of high complication rates.

Kermansaravi (2021) published a systematic review of 1,771 patients from 26 studies evaluating the efficacy of one anastomosis/mini gastric bypass (OABG-MGB) as a revisional procedure.[146] Mean initial BMI was 45.7 which decreased to 30.5 at five year follow up with remission of type 2 diabetes reaching 78.1%. Leakage was the most common complication in the included patients and 7.4% of patients developed de novo GERD following OABG-MGB. Although the authors concluded that OAGB-MGB is a safe and effective choice for revisional bariatric surgery, RCTs on this topic are needed as currently only retrospective cohort studies with heterogenous data are available.

Parmar (2020) published a systematic review of 1,075 patients (n=17 studies) who underwent one anastomosis/mini gastric bypass as a revisional bariatric procedure after failure of a primary LAGB and SG.[147] No RCTs were available on this topic and no meta-analyses were performed as part of this systematic review. The most commonly reported reason for revisional surgery was poor response (81%) followed by gastric band failure (35.9%), GERD (13.9%), intolerance (12.8%), staple line disruption (16.5%), pouch dilatation (17.9%), and stomal stenosis (10.3%). Results revealed that after the revisional OABG-MGB, the mean percent EWL was 50.8% at 6 months, 65.2% at one year, 68.5% at two years, and 71.6% at five years. Resolution of comorbidities after OAGB-MGB was significant with 80.5% of patients with T2D, 63.7% of patients with hypertension, and 79.4% of patients with GERD reporting resolution. The overall readmission rate following OAGB-MGB was 4.73%, the mortality rate was 0.3%, and the leak rate was 1.54%. Although the authors concluded that OAGB-MGB is a safe and effective choice for revisional bariatric surgery, RCTs on this topic are needed as currently only retrospective cohort studies with heterogenous data are available.

In 2018, Almalki published a retrospective analysis of patients diagnosed with failed restrictive procedure who underwent revision bariatric surgery.[47] One hundred sixteen patients between 2001 and 2015 had revision RY gastric bypass (R-RYGB) or revision single-anastomosis (mini-) gastric bypass (R-RSAGB); the primary indications for revisional procedures were weight regain (50.9%), inadequate weight loss (31%), and intolerance (18.1%). Major complications occurred in 12 patients without significant difference between groups. At one year after revision surgery, the R-SAGB group (76.8% EWL) showed better weight loss than R-RYGB (32.9% EWL). In the 37.1% of patients available for follow-up at five years, R-SAGB had significantly lower hemoglobin levels than R-RYGB (8.2 ± 3.2 g/dl vs 12.8 ± 0.5 g/dl). The study was limited by its retrospective nature, relatively short follow-up time, and lack of consideration of data related to patient compliance.

In 2016, Dang reported results from a systematic review and meta-analysis comparing revisional single-step versus two-step bariatric surgery from laparoscopic adjustable gastric

banding (LAGB) to Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG).[148] Single-step procedures involved revisional surgery wherein the LAGB was removed and replaced by RYGB or SG in the same operation; two-step procedures allowed a delay before the second bariatric procedure was performed. Although the authors found comparable rates of complications, morbidity and mortality between the one- and two-step procedures, the study was not designed to evaluate differences in patient outcomes between the second bariatric procedure (i.e., RYGB vs SG).

In 2014, Sudan reported safety and efficacy outcomes for reoperative bariatric surgeries using data from a national registry, the Bariatric Outcomes Longitudinal Database.[149] The Bariatric Outcomes Longitudinal Database is a large multi-institutional bariatric surgery-specific database to which data was submitted from June 2007 through March 2012 by 1,029 surgeons and 709 hospitals participating in the Bariatric Surgery Centers of Excellence (BSCOE) program. Surgeries were classified as primary or reoperative bariatric surgery. Reoperations were further divided into corrective operations (when complications or incomplete treatment effect of a previous bariatric operation was addressed but the initial operation was not changed) or conversions (when an index bariatric operation was changed to a different type of bariatric operation or a reversal restored original anatomy.) There were a total of 449,473 bariatric operations in the database of which 420,753 (93.6%) operations had no further reoperations (primary operations) while 28,270 (6.3 %) underwent reoperations. Of the reoperations, 19,970 (69.5%) were corrective operations and 8,750 (30.5%) were conversions. The primary bariatric operations were Roux-en-Y gastric bypass (N=204,705, 49.1 %), adjustable gastric banding (N=153,142, 36.5 %), sleeve gastrectomy (N=42,178, 10 %), and BPD±DS (N=4,260, 1 %), with the rest classified as miscellaneous. Adjustable gastric banding was the most common primary surgery among conversions (57.5% of conversions; most often [63.5%] to Roux-en-Y gastric bypass). Compared with primary operations, mean length of stay was longer for corrections (2.04±6.44 vs 1.8±4.9, P<0.001) and for conversions (2.86±4.58 vs 1.8±4.9, P<0.001). The mean % excess weight loss at one year was 43.5 % after primary operation, 39.3 % after conversions, and 35.9 % after corrective operations (statistical comparison not reported). One-year mortality was higher for conversions compared with primary operations (0.31% vs 0.17%, P<0.001), but not for corrections compared with primary operations (0.24% vs0.17%, P=NS). One-year serious adverse event rates were higher for conversions compared with primary operations (3.61% vs 1.87%, P<0.001), but not for corrections compared with primary operations (1.9% vs 1.87%, P=NS). The authors conclude that reoperation after primary bariatric surgery is relatively uncommon, but generally safe and efficacious when it occurs.

As part of the American Society for Metabolic and Bariatric Surgery Revision Task Force, Brethauer conducted a systematic review of reoperations after primary bariatric surgery that included 175 studies, most of which were single-center retrospective reviews.[150] The review was primarily descriptive, but the authors made the following conclusions:

> "The current evidence regarding reoperative bariatric surgery includes a diverse group of patient populations and procedures. The majority of the studies are single institution case series reporting short- and medium-term outcomes after reoperative procedures. The reported outcomes after reoperative bariatric surgery are generally favorable and demonstrate that additional weight loss and co-morbidity reduction is achieved with additional therapy. The risks of reoperative bariatric surgery are higher than with primary bariatric surgery and the evidence highlights the need for careful patient selection and surgeon expertise."

REVISION OR REMOVAL OF ADJUSTABLE GASTRIC BAND

Evidence regarding the indications for band removal or revision procedure is primarily limited to small cohort[151] and case series studies; however, reoperation or removal rates are estimated to range from 4.1%- 53%, depending on the time of reported follow-up.[152-155] Several of the largest cohort studies have reported the following complications which resulted in reoperation or band removal:

Arapis reported the following complications in 87 patients who underwent reoperation:[156] chronic dilatation of the proximal gastric pouch (27 patients - 14.5%), acute dilatation (21 patients - 11.3%), intragastric migration of the prosthesis (6 patients - 3.2%), reflux esophagitis (6 patients - 3.2%), infection of the gastric band (1 patient - 0.5%), and Barrett's esophagus (1 patient - 0.5%).

Perathoner reported on 108 patients who underwent laparoscopic conversion of gastric banding to gastric bypass due to the following complications: band migration, inadequate weight loss, pouch dilation, band leakage, band intolerance, band infection and esophageal dilation.[157]

Other reported complications included: band erosion,[154, 158, 159] gastric obstruction,[12] and gastric slippage.[154, 159]

Avriel reported major respiratory complications and chronic disease development in 30 patients who underwent LAGB.[160] Reported complications included aspiration pneumonia (19 patients) including pulmonary abscess (4 patients) and empyema (2 patients), exacerbation of asthma (3 patients), hemoptysis (1 patient), interstitial lung disease (5 patients) and bronchiectasis (3 patients). However, the impact of LAGB upon the development of these conditions is unclear given that 83% of the patients smoked or had a smoking history (mean pack years 34).

Studies which evaluated band conversion to a second bariatric surgery primarily indicated that bypass was the preferred revision surgery due to better long-term outcomes compared to sleeve gastrectomy.[161-164] In one large retrospective study published in 2014, bypass was compared to sleeve gastrectomy after band removal and conversion.[165] National Surgical Quality Improvement Project data from 2005-2011 were analyzed and included 495 patients who converted from LAGB to bypass and 130 patients who converted to sleeve gastrectomy. Conversion to bypass was not associated with higher morbidity or mortality compared to primary RYGB; however, conversion to sleeve gastrectomy was independently associated with a higher rate of major complications and mortality compared to primary sleeve gastrectomy (OR 8.02, 95 % CI 1.08-59.34, p = 0.04).

SECTION SUMMARY

For surgical revision of bariatric surgery after failed treatment, evidence from nonrandomized studies suggests that revisions are associated with improvements in weight similar to those seen in primary surgery. However, evidence from large long-term studies is required to determine the appropriate clinical indications for band removal or reoperation.

BARIATRIC SURGERY IN PATIENTS WITH DIABETES WITH BMI < 35KG/M²

SYSTEMATIC REVIEWS

Zhou (2023) published a SR comparing the effect of surgical and nonsurgical treatment on patients with a BMI < 35 kg/m2 to reach diabetes remission.[166] Seven studies were included (544 participants) of which five reported number of patients reaching diabetes remission. Bariatric surgery is more effective than non-surgical treatment to reach diabetes remission [OR 25.06, 95%CL 9.58-65.54]. Bariatric surgery was more likely to result in reductions in HbA1c [MD -1.44, 95%CL (-1.84) - (-1.04)] and FPG [MD -2.61, 95%CL (-3.20) - (-2.20)]. Bariatric surgery resulted in reductions in BMI [MD -3.14, 95%CL (-4.41) - (-1.88)], which was more significant in individuals of Asian race. Limitations include time frame for data collection (different years) resulting in criteria difference defining T2DM remission, inconsistent follow-up time and small sample sizes.

In 2015 Muller-Stich published a systematic review comparing surgical versus medical treatment of type II diabetes in patients with a BMI less than 35 kg/m².[167] The analysis included data from five RCTs and six observational studies for a total of 702 patients. The follow-up of included studies ranged from 12-36 months. Authors concluded that surgery was associated with higher diabetes remission rate (OR: 14.1, 95% CI: 6.7–29.9, P < 0.001), higher rate of glycemic control (OR: 8.0, 95% CI: 4.2–15.2, P < 0.001) and lower HbA1c level (MD: −1.4%, 95% CI −1.9% to −0.9%, P < 0.001) compared to medical treatment. However, results are limited by inclusion of studies in which the BMI of some patients was greater than 35 kg/m² and short-term follow-up, limiting conclusion regarding the long-term benefits of bariatric surgery upon glycemic control.

In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of bariatric surgery and nonsurgical therapy in adults with metabolic conditions, including diabetes, and a BMI of 30.0-34.9 kg/m².[168] The report evaluated key issues which included the effectiveness of bariatric surgery compared to nonsurgical therapies, short and long-term effects in symptom control and racial and demographic disparities regarding benefits and harms of surgery in patients with metabolic conditions and a BMI of 30.0-34.9 kg/m². Evidence was gathered from global literature searches, reference mining and titles identified from external sources. A total of 24 studies reported bariatric surgery results, with a majority of studies evaluating RYGBP or LAGB procedures in diabetic patients with a BMI of 30-35 kg/m². The AHRQ report concluded that there was moderate strength evidence of efficacy for certain bariatric procedures as a treatment for diabetes in the short term. However, the report noted that the evidence contained many limitations, “(m)ost importantly, very few studies of this target population have long-term follow-up. Only two studies followed patients for more than 2 years; one has a followup rate of only 13.8 percent and the other includes only seven patients. Thus, we have almost no data on long-term efficacy and safety.” In addition, the AHRQ report noted the lack of evidence on major clinical outcomes such as all-cause mortality, cardiovascular risks, or peripheral arterial disease. Although short-term studies suggest an improvement in glucose control, the AHRQ report pointed out that, “…the available evidence from the diabetes literature indicates it may be premature to assume that controlling glucose to normal or near normal levels completely mitigates the risk of microvascular and macrovascular events. Thus, claims of a “cure” for diabetes based on glucose control within 1 or 2 years require longer term data before they can be substantiated.”

RANDOMIZED CONTROLLED TRIALS

Since the publication of the AHRQ report, two RCTs have been reported on bariatric surgery compared to medical therapy in diabetic patients with a BMI between 30-40 kg/m².

Ikramuddin performed an unblinded RCT of gastric bypass versus intensive medical therapy on 120 patients with type II diabetes for at least 6 months and an HgbA1C of at least 8.0%.[169] Patients were followed for 12 months with the primary endpoint being a composite of HgA1C less than 7.0%, low-density lipoprotein (LDL) cholesterol less than 100 mg/dl and systolic blood pressure less than 130 mm Hg. A total of 28 patients in the surgery group achieved the primary outcome compared to 11 patients in the medical therapy group (odds ratio [OR]: 4.8, 95% CI: 1.9-11.7). The percent of patients achieving HgbA1C of less than 7.0% was 75% in the surgery group compared to 32% of patients in the medical therapy group (OR: 6.0, 95% CI: 2.6-13.9). There were 22 serious complications in the surgery group, including 4 perioperative complications, compared to 15 serious complications in the medical group. A limitation of this study was that results were not provided separately for patients who were above and below a BMI of 35 kg/m², thus restricting conclusions regarding the benefits of bariatric surgery compared to medical management in diabetic patients with a BMI < 35 kg/m².

In 2014, Prikh published a small (n=57), short-term (6-month follow-up) RCT which compared intensive medical weight management to bariatric surgery in patients with a BMI of 30-35 kg/m² and type 2 diabetes.[170] Significant improvements in primary outcome measures of homeostatic model of insulin resistance and higher diabetes remission rates were observed in the surgical group compared to the MWM group. Additional small RCTs have been identified;[171] however, larger, long-term RCTs are needed to confirm these findings.

In 2015, Mingrone published results of a small (n=60) RCT comparing long-term outcomes of either medical treatment or surgery by Roux-en-Y gastric bypass or biliopancreatic diversion in patients with type II diabetes.[172] A total of 53 patients were included in the 5-year follow-up assessment. Primary outcome measures included the rate of diabetes remission at 2 years which was defined as glycated HbA1c concentration of 6.5% or less (≤47.5 mmol/mol) and a fasting glucose concentration of 5.6 mmol/L or less without active pharmacological treatment for 1 year. At 5-year follow-up 19 (50%) of the 38 surgical patients (7 of 19 [37%] in the gastric bypass group and 12 of 19 in the [63%] bilipancreatic diversion group) maintained diabetes remission at 5 years, compared with none of the 15 medically treated patients (p=0.0007). Fifteen incidents of hyperglycemic relapse occurred in 34 surgical of the patients who achieved 2-year remission, suggesting continued monitoring of glycemic control may be necessary. Authors also reported that both surgical procedures were associated with significantly lower plasma lipids, cardiovascular risk, and medication use and no late complications or deaths.

CLINICAL PRACTICE GUIDELINES

American College of Cardiology, American Heart Association, and the Obesity Society

In 2013, the American College of Cardiology (ACC), American Heart Association (AHA), and the Obesity Society published guidelines on the management of obesity and overweight in adults.[173] The guidelines were based upon a high-quality systematic review of the evidence which included transparent methods for grading the strength of the evidence and subsequent recommendations. The guidelines make the following recommendations related to bariatric surgery:

> “For adults with a BMI >40kg/m2 or BMI >35 kg/m2 with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment (with or without pharmacotherapy) with sufficient weight loss to achieve targeted health outcome goals, advise that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and

evaluation." (Grade A: Indicating a strong recommendation, indicating there is a high certainty based on the evidence that the net benefit is substantial).

"For individuals with a BMI <35 kg/m2, there is insufficient evidence to recommend for or against undergoing bariatric surgical procedures." (No recommendation given, indicating there is insufficient evidence or evidence is unclear or conflicting).

American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery

In 2022 the American Association of Clinical Endocrinology published an updated Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan.[174] They include the following recommendations:

- Persons with a BMI 35 kg/m2 and one or more severe obesity-related complications remediable by weight loss, including T2D, high risk for T2D (insulin resistance, prediabetes, and/or metabolic syndrome), poorly controlled hypertension, NAFLD/NASH, OSA, osteoarthritis of the knee or hip, and urinary stress incontinence, should be considered for a bariatric procedure.

- Persons with BMI 30 to 34.9 kg/m2 and T2D with inadequate glycemic control despite optimal lifestyle and medical therapy should be considered for a bariatric procedure.

In 2019, an update to the 2013 joint guidelines were published by the American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery (AACE/ASM/Obesity Society) regarding the perioperative nutritional, metabolic and nonsurgical support of the bariatric surgery patient.[175, 176] Recommendations regarding which patients should be offered bariatric surgery indicated the following:

- "Patients with a BMI≥40 kg/m^2 without coexisting medical problems and for whom bariatric surgery would not be associated with excessive risk should be eligible for a bariatric procedures."

- "Patients with a BMI≥35 kg/m^2 and 1 or more severe obesity-related complications remediable by weight loss, including T2D, high risk for T2D, poorly controlled hypertension, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, OSA, osteoarthritis of the knee or hip, and urinary stress incontinence, should be considered for a bariatric procedure."

- "Patients with the following comorbidities and BMI≥35 kg/m^2 may also be considered for a bariatric procedure, though the strength of evidence is more variable; obesity-hypoventilation syndrome and Pickwickian syndrome after a careful evaluation of operative risk; idiopathic intracranial hypertension; GERD; severe venous stasis disease; impaired mobility due to obesity, and considerably impaired quality of life."

- "Patients with BMI of 30 to 34.9 kg/m^2 with T2D with inadequate glycemic control despite optimal lifestyle and medical therapy should be considered for a bariatric procedure; current evidence is insufficient to support recommending a bariatric procedure in the absence of obesity." or metabolic syndrome may also be offered a bariatric procedure although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit."

- "The BMI criterion for bariatric procedures should be adjusted for ethnicity (eg, 18.5 to 22.9 kg/m^2 is normal range, 23 to 24.9 kg/m^2 overweight, and ≥25 kg/m^2 obesity for Asians)." “There is insufficient evidence for recommending a bariatric surgical procedure specifically for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone, independent of BMI criteria.”
- "Bariatric procedures should be considered to achieve optimal outcomes regarding health and quality of life when the amount of weight loss needed to prevent or treat clinically significant obesity-related complications cannot be obtained using only structured lifestyle change with medical therapy."

American Society for Metabolic & Bariatric Surgery[93]

The American Society for Metabolic and Bariatric Surgery (ASMBS), in combination with International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), updated their guideline on indications for metabolic and bariatric surgery. They recommend the following:

- Metabolic and bariatric surgery (MBS) is recommended for individuals with a BMI greater than or equal to 35 kg/m^2 regardless of presence, absence, or severity of co-morbidities.
- MBS should be considered for individuals with metabolic disease and BMI of 30-34.9 kg/m^2
- BMI thresholds should be adjusted in the Asian population such that a BMI greater than or equal to 25 kg/m^2 suggests clinical obesity and individuals with a BMI greater than or equal to 27.5 kg/m^2 should be offered MBS.

Institute for Clinical Systems Improvement

In 2014, the Institute for Clinical Systems Improvement (ICSI) published revised guidelines regarding the diagnosis and management of type 2 diabetes mellitus in adults and indicated:[177]

A clinician may recommend a patient diagnosed with T2DM and a BMI >35 kg/m^2 consider bariatric surgery if diabetes or comorbidities are difficult to control with lifestyle and pharmacologic therapy. [Quality of Evidence: Moderate, Strength of Recommendation: Weak]

SECTION SUMMARY

Evidence regarding the efficacy of bariatric surgery as a treatment for diabetes in patients with a BMI< 35 kg/m² primarily consists of small cases series with short-term follow-up as noted in the AHRQ report. Since the publication of these reports a single RCT was identified which was limited by the inclusion of obese (BMI 35-40 kg/m²) and non-obese (BMI 30-34.9 kg/m²) patients, precluding conclusions regarding the clinically non-obese population. Clinical practice guidelines have recommended bariatric surgery in diabetic patients who do not meet the clinical definition of obesity; however, a lack of long-term data was noted. There are clinical concerns about durability and long-term outcomes at 5 to 10 years as well as potential variation in observed outcomes in community practice versus clinical trials. Overall, the current evidence does not demonstrate the safety and efficacy of bariatric surgery as a treatment for diabetes in patients with a BMI< 35 kg/m².

ADOLESCENT AND PEDIATRIC BARIATRIC SURGERY

SYSTEMATIC REVIEWS

Wu (2023) published a SR with meta-analysis aimed to evaluate the long-term outcomes of bariatric surgery in adolescents with obesity.[178] They included 29 cohort studies (4970 patients with age ranges from 12- 21 years). Body mass index ranged from 38.9 to 58.5 kg/m2. Females were the predominant gender (60.3%). After at least 5-year of follow-up, the pooled BMI decline was 13.09 kg/m2 (95%CI 11.75-14.43), with sleeve gastrectomy (SG) was 15.27 kg/m2, Roux-en-Y gastric bypass (RYGB) was 12.86 kg/m2, and adjustable gastric banding (AGB) was 7.64 kg/m2. The combined remission rates of type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension (HTN), obstructive sleep apnea (OSA), and asthma were 90.0%, 76.6%, 80.7%, 80.8%, and 92.5%, (95%CI 83.2-95.6, 62.0-88.9, 71.5-88.8, 36.4-100, and 48.5-100), respectively. Postoperative complications were underreported. Combined with the current study, we found a low level of postoperative complications. Iron and vitamin B12 deficiencies were the main nutritional deficiency complications identified so far.The authors conclude that for adolescents with severe obesity, bariatric surgery (especially RYGB and SG) is an effective treatment option. After at least five years of follow-up, bariatric surgery in adolescents showed a desirable reduction in BMI and significant remission of T2DM, dyslipidemia, and HTN. Surgical and nutrition-related complications still need to be further explored by more long-term studies.

Qi (2017) published a SR and meta-analysis on the use of bariatric surgery for the treatment of adolescents with obesity. 49 studies were identified for inclusion and study quality was assessed using the Newcastle-Ottawa Scale. Age of patients ranged from 14 to 20 years. BMI ranged from 34 to 63 kg/m2. Overall results showed significant improvements in BMI as well as glycemic and lipid control with various bariatric surgery techniques. RYGB showed the largest improvements compared with other procedures, with LAGB and sleeve gastrectomy also showing improvements in this population.

The 2007 Washington State Health Technology Assessment evaluated the published, peer reviewed scientific literature describing bariatric surgery in the pediatric population.[179] Data from 17 studies that enrolled a total of 553 pediatric patients were included. Only one study was clearly prospective. Eight studies reported outcomes after LAGB, six after RYGBP, two after VBG, and one after banded bypass. The report concluded that:

- The evidence that LAGB for morbidly obese pediatric patients leads to sustained and clinically significant weight loss compared to non-operative approaches was weak at the longest follow-up after surgery (1.7 to 3.3 years).
- The evidence that RYGBP for morbidly obese pediatric patients leads to sustained and clinically significant weight loss compared to non-operative approaches was weak at the longest follow-up after surgery (1 to 6.3 years).
- The evidence was insufficient to permit quantitative estimates of the precise amount of weight loss after any bariatric surgical procedure for pediatric patients.
- The evidence was insufficient to permit any conclusions about weight loss after other bariatric surgical procedures for pediatric patients.
- The evidence was insufficient to permit any conclusions about weight loss in specific age subgroups (18-21, 13-17, 12 or less) within the pediatric population.

- The evidence that LAGB for morbidly obese pediatric patients does resolve comorbid conditions linked to obesity (diabetes, hypertension) compared to non-operative approaches was weak.
- The evidence that RYGBP for morbidly obese pediatric patients does resolve comorbid conditions linked to obesity (diabetes, hypertension) compared to non-operative approaches was weak.
- The evidence was insufficient to permit quantitative estimates of the likelihood of comorbidity resolution, quality of life improvement, or survival after any bariatric surgical procedure for pediatric patients.
- The evidence was insufficient to permit any conclusions about comorbidity resolution in specific age subgroups (18-21, 13-17, 12 or less) within the pediatric population.
- The LAGB studies reported no in-hospital or postoperative death. However, the most commonly reported complication was band slippage. Reoperations were performed on 7.9% of the LAGB patients to correct various complications (band slippage, intragastric migration, port/tubing problems).
- The RYGBP studies reported one postoperative death. The most frequently reported complication was related to malnutrition and micronutrient deficiency. In addition, potentially life-threatening complications (shock, pulmonary embolism, severe malnutrition, bleeding, gastrointestinal obstructions) were reported.
- The evidence was insufficient to permit any conclusions on potential impacts of bariatric surgery on growth and development of pediatric patients.
- The evidence was insufficient to permit any conclusions on potential harms in specific age groups (18-21, 13-17, 12 or less).

In summary, the assessment found that longer term, prospective collection of data on physical growth, quality of life, weight loss, persistence or resolution of comorbid conditions, and long-term survival are needed in order to fully understand the role of bariatric surgical procedures in treating morbidly obese pediatric patients.

In 2013, Black published a systematic review and meta-analysis of 23 studies (22 nonrandomized) that included 637 young patients (age 6-18 years) who underwent bariatric surgery.[180] Although significant weight loss was reported at the 1-year follow-up, limitations of the evidence were similar to those reported in the Washington State Health Technology Assessment. Included studies were limited by small sample size with a median number of 24 patients per study (range: 10-108) and short-term follow-up (range: 6-12 months). Authors reported that complications were inconsistently reported and indicated that, “long-term, prospectively designed studies, with clear reporting of complications and comorbidity resolution, alongside measures of [health-related quality of life], are needed to firmly establish the harms and benefits of bariatric surgery in children and adolescents.”

In 2015, the Washington State Health Technology Assessment compared various bariatric procedures and also re-examined the role of bariatric surgery in children and adolescents upon obesity related comorbidities.[181] The group concluded that there was, “a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents.” Only two studies were identified which were deemed to be of sufficient quality and only one of those was a RCT. In addition, no comparative studies were identified which evaluated any bariatric procedure exclusively in children (under 13 years).

Additional reviews were identified; however, conclusions were limited due to a lack of long-term follow-up.[182-186]

RANDOMIZED CONTROLLED TRIALS

Jarvholm (2023) published a small randomized, open-label, multicentre trial (The adolescent morbid obesity surgery 2; AMOS2).[187] Adolescents aged 13-16 years with a BMI of at least 35 kg/m2, who had attended treatment for obesity for at least 1 year, passed assessments from a pediatric psychologist and a pediatrician, and had a Tanner pubertal stage of at least three, were randomly assigned (1:1) to MBS or intensive non-surgical treatment. 25 (19 females and six males) were randomly assigned to receive MBS and 25 (18 females and seven males) were assigned to intensive non-surgical treatment. Three participants (6%; one in the MBS group and two in the intensive non-surgical treatment group) did not participate in the 2-year follow-up, and in total 47 (94%) participants were assessed for the primary endpoint. Mean age of participants was 15·8 years (SD 0·9) and mean BMI at baseline was 42·6 kg/m2 (SD 5·2). After two years, BMI change was -12·6 kg/m2 (-35·9 kg; n=24) among adolescents undergoing MBS (Roux-en-Y gastric bypass [n = 23], sleeve gastrectomy [n = 2]) and -0·2 kg/m2 (0·4 kg; [n = 23]) among participants in the intensive non-surgical treatment group (mean difference -12·4 kg/m2 [95% CI -15·5 to -9·3]; p < 0·0001). Five (20%) patients in the intensive non-surgical group crossed over to MBS during the second year. Adverse events (n=4) after MBS were mild but included one cholecystectomy. Regarding safety outcomes, surgical patients had a reduction in bone mineral density, while controls were unchanged after 2 years (z-score change mean difference -0·9 [95% CI -1·2 to -0·6]). There were no differences between the groups in vitamin and mineral levels, gastrointestinal symptoms (except less reflux in the surgical group), or in mental health at the 2-year follow-up.

A small randomized trial compared the outcomes of gastric banding with an optimal lifestyle program in adolescents 14-18 years of age with a BMI >35.[188] Although the study reports that gastric banding resulted in greater percentage achieving a loss of 50% of excess weight, several flaws undermine the reliability of the study findings:

- The small study population (n=50) limits the ability to rule out the role of chance as an explanation of findings.
- The study had significant loss to follow-up suggesting a difference that may affect the outcome.
- Short-term follow-up (2 years) limits comparisons regarding the longer-term complications rates and the effectiveness of the procedure in controlling weight loss and comorbidities.

NONRANDOMIZED STUDIES

Studies with short follow-up time

A small number of nonrandomized comparative studies reported significant weight loss and resolution of some of the comorbidities in pediatric patients undergoing bariatric surgery.[189-191] However, the studies were small and had a very short follow up time. In 2014, Inge reported results from Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, a prospective, multicenter observational study of bariatric surgery in patients aged 19 or under.[192] The study enrolled 242 participants, with mean age 17.1 and median BMI 50.5 (IQR 45.2-58.2) at the time of operation. All patients had at least 1 obesity-related comorbidity, most commonly dyslipidemia (74%), followed by sleep apnea (57%), back and joint pain (46%), hypertension (45%), and fatty liver disease (37%). Roux-en-Y gastric bypass, adjustable gastric banding, and vertical sleeve gastrectomy were performed in 66.5%, 5.8%, and 27.7%, respectively. Within 30 days of surgery, 20 major complications occurred in 19 patients (7.9%),

most of which were perioperative complications. The cohort will be followed to assess longer-term outcomes.

Studies with mid-term follow-up time

Alqahtani (2021) conducted a prospective, noncomparative, cohort study analyzing durability of weight loss and comorbidity resolution, growth velocity, and adverse events associated with LSG in children and adolescents with severe obesity over 10 years.[193] Children and adolescents with class II or III obesity underwent LSG between 2008 and 2021. Overall, 2504 children and adolescents were included, with a mean age ± standard deviation (SD) 15.7 ± 3.7 years (range, 5 to 21 years) at the time of operation. In the 15- to 18-year age group specifically, there were 1517 children enrolled (61%). Mean ± SD baseline BMI was 44.8 ± 12.6 kg/m2, with a BMI z-score of 3.0 ± 0.5, representing 165% above the 95th percentile for age and sex, on average. In the overall cohort in the short- (1 to 3 years, n = 2051), medium- (4 to 6 years, n=1268), and long-term (7 to 10 years, n = 632) follow-up, mean %EWL was 82.3% ± 20.5%, 76.3% ± 29.1%, and 71.1% ± 26.9%, respectively. At baseline, 263 patients (10.5%) were diagnosed with T2D, 227 (9.1%) were diagnosed with dyslipidemia, and 377 (15.1%) had hypertension. At long-term follow-up, complete comorbidity remission was observed in 74% of T2D cases, 59% of dyslipidemia cases, and 64% of hypertension cases. Mean height z-score change at short-, medium-, and long-term follow-up was 0.1 ± 0.5, 0.1 ± 1.2, and 0.0 ± 0.8, respectively, representing no significant change in growth velocity at each follow-up stage (p= 0.95, p= 0.21, and p= 0.40, respectively). There were 27 (1%) reported adverse events within the first 90 days after operation, including 2 patients with a staple line leak, 22 patients with nausea and vomiting, and three patients with signs of metabolic neuropathy, with no procedure-related mortality. None of those patients with adverse events had long-standing sequelae or disability.

Dumont (2018) published a retrospective study of obese adolescents who underwent LAGB. Between 2006 and 2015, 97 consecutive teenagers (average age at surgery 17.2 ± 0.7 years; mean BMI of 44.9 ± 6.1 kg/m^2) who had achieved full growth and sexual maturity and had previously failed a medical nutritional and dietary management program for at least 1 year were enrolled in the study. After a mean follow-up time of 56.0 ± 22.0 months, mean total weight loss was 20.0 ± 16.6% and mean excess weight loss was 46.6 ± 39.5%. Nineteen patients underwent band removal (mean 43.0 ± 28.0 months). No limitations to the study were reported.

Two observational studies with mid-term follow-up times (≤10 and ≤8 years) reported experiences of pediatric patients undergoing LAGB (sample size 41 and 107 respectively).[194, 195] The first study found that weight loss was initially successful and resulted in resolution of some comorbidities, but it slowly increased over the time and ultimately was unsatisfactory in many patients. The second study reported 65.5% excess weight loss at eight years. Both studies reported high complication and reoperation rates (Lanthaler: 46% patients had complications that required reoperation; Mittermaier: 46% patients had complications and 29% required reoperation).

CLINICAL PRACTICE GUIDELINES FOR PEDIATRIC BARIATRIC SURGERY

American College of Physicians

The 2005 American College of Physicians (ACP) evidence-based guideline on use of bariatric surgery in adolescents and children states that the current evidence on surgical treatment of

pediatric populations is limited to a few case series which do not permit quantitative analysis.[196] Further, the guideline states that it is unclear whether extrapolation of adult data for bariatric surgery to the pediatric population is appropriate and that RCTs are needed (and feasible) to establish the role of bariatric surgery in this population.

American Academy of Pediatrics

In 2023, the American Academy of Pediatrics (AAP) published their first evidence-based clinical practice guideline for the evaluation and treatment of children and adolescents (ages two to 18 years) with obesity.[187] The recommendations put forth in the guideline are based on evidence from RCTs and comparative effectiveness trials, along with high-quality longitudinal and epidemiologic studies gathered in a systematic review process described in their methodology. The AAP's recommendation related to bariatric surgery is below:

"Pediatricians and other PHCPs [pediatric health care providers] should offer referral for adolescents 13 years and older with severe obesity (BMI ≥ 120% of the 95th percentile for age and sex) for evaluation for metabolic and bariatric surgery to local or regional comprehensive multidisciplinary pediatric metabolic and bariatric surgery centers (Grade C Evidence Quality)."

They list indications for adolescent metabolic and bariatric surgery that align with the 2019 indications.

American Heart Association

In 2013, the American Heart Association (AHA) published a statement regarding severe obesity in children and adolescents which concluded:[197]

> “Current treatment approaches using lifestyle modification and medications to reduce BMI and improve chronic disease risk factors are insufficient for most patients and significant residual risk (unacceptably high BMI and risk factor levels) remains. Although experts recommend stepped intensification of interventions, the “step” after behavior-based and pharmaceutical interventions to the next established alternative, bariatric surgery, is unacceptably large because of its limited applicability and availability.”

The AHA indicated that the following evidence was needed before bariatric surgery could be widely recommended in children and adolescents:

> “Generation of additional safety and efficacy data (especially long-term) on bariatric surgery, including studies describing improvements in vascular structure and function, insulin resistance, and β-cell function.”

Society of American Gastrointestinal and Endoscopic Surgeons

The 2008 the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) evidence-based guidelines state:[198]

> “RGB is well tolerated and produces excellent weight loss in patients younger than 18 years with 10-year follow-up… Well-designed prospective studies are just emerging to better define the place for adolescent bariatric surgery.”

This statement is based on eight publications of which six are retrospective studies, each with less than 35 participants and most with limited follow-up. Two of the supporting articles are opinion papers.

Endocrine Society

In 2017, the Endocrine Society published an updated clinical practice regarding the assessment, treatment, and prevention of pediatric obesity.[199] The guideline was developed according to the GRADE system. The following statements were given a rating of "we suggest", i.e., weak recommendations, and were based on "very low quality" to "low quality" evidence. Given the evidence quality, and the suggestion as opposed to a *recommendation*, the following statements are ultimately, expert opinion.

For pre-adolescent children, pregnant or breast-feeding adolescents (and those planning on becoming pregnant within two years of surgery), and in any patient who has not mastered the principles of healthy dietary and activity habits and/or has unresolved substance abuse, eating disorder or untreated psychiatric disorder, the Society suggests against bariatric surgery.

The Endocrine Society suggests that bariatric surgery be considered for adolescents only under the following conditions:

- The patient has attained Tanner 4 or 5 pubertal development and final or near-final adult height, the patient has a BMI of >40 kg/m2 or has a BMI of >35 kg/m2 and significant, extreme comorbidities
- extreme obesity and comorbidities persist despite compliance with a formal program of lifestyle modification, with or without pharmacotherapy
- psychological evaluation confirms the stability and competence of the family unit [psychological distress due to impaired quality of live (QOL) from obesity may be present, but the patient does not have an underlying untreated psychiatric illness]
- the patient demonstrates the ability to adhere to the principles of healthy dietary and activity habits
- there is access to an experienced surgeon in a pediatric bariatric surgery center of excellence that provides the necessary infrastructure for patient care, including a team capable of long-term follow-up of the metabolic and psychosocial needs of the patient and family.

Institute for Clinical Systems Improvement

In 2013, ICSI published updated guidelines regarding the prevention and management of obesity for children and adolescents.[200] The group noted that, "there is limited information on the long-term efficacy and safety of bariatric surgery in children and adolescents." However, ICSI concluded that bariatric surgery may be considered at centers of excellence when specific criteria where met and should not be considered in preadolescent children.

National Heart, Lung and Blood Institute

In 2011, National Heart, Lung and Blood Institute (NHLBI) published guidelines regarding cardiovascular health and risk reduction in overweight and obese children and adolescents which indicated bariatric surgery may be considered:[201]

> "For adolescents with BMI far above 35 kg/m2 and associated comorbidities, bariatric surgery on a research protocol, in conjunction with a comprehensive lifestyle weight loss program, improved weight loss, BMI, and other outcomes—such as IR, glucose tolerance, and cardiovascular (CV) measures—in a small case series."

This guideline is based on a Grade D recommendation which is defined as, “Expert opinion, case reports, or reasoning from first principles (bench research or animal studies).”

American Society of Bariatric and Metabolic Surgery

In 2022, the ASMBS updated their guideline on indications for metabolic and bariatric surgery.[93] They noted that prospective data demonstrated durable weight loss and maintained co-morbidity remission in patients as young as five years of age. Additionally, the ASMBS stated that metabolic and bariatric surgery do not negatively impact pubertal development or linear growth, and therefore a specific Tanner stage and bone age should not be considered a requirement for surgery. Other statements supported 2018 recommendations, including that syndromic obesity, developmental delay, autism spectrum, or a history of trauma would not be considered a contraindication to bariatric surgery in children or adolescents.

In 2018, ASBMS published an update to the 2012 guideline.[202] Summary of major changes in the guideline included:

- "Vertical sleeve gastrectomy has become the most used and most recommended operation in adolescents with severe obesity for several reasons, near-equivalent weight loss to RYGB in adolescents, fewer reoperations, better iron absorption, and near-equivalent effect on comorbidities as RYGB in adolescents. However, given the more extensive long-term data available for RYGB, we can recommend the use of either RYGB or VSG in adolescents. Long-term outcomes of GERD after vertical sleeve gastrectomy are still not well understood."
- "There are no data that the number of preoperative weight loss attempts correlated with success after metabolic/bariatric surgery. Compliance with a multidisciplinary preoperative program may improve outcomes after metabolic/bariatric surgery but prior attempts at weight loss should be removed as a barrier to definitive treatment for obesity."
- "The use of the most up to date definitions of childhood obesity are as follows: (1) BMI cut offs of 35 kg/m^2 or 120% of the 95th percentile with a comorbidity, or (2) BMI >40 kg/m^2 or 140% of the 95th percentile without a comorbidity (whichever is less). Requiring adolescents with a BMI >40 to have a comorbidity (as in the old guidelines) puts children at a significant disadvantage to attaining a healthy weight. Earlier surgical intervention (at a BMI <45 kg/m^2) can allow adolescents to reach a normal weight and avoid lifelong medication therapy and end organ damage from comorbidities."
- "Certain comorbidities should be considered in adolescents, specifically the psychosocial burden of obesity, the orthopedic diseases specific to children, GERD, and cardiac risk factors. Given the poor outcomes of medical therapies for T2D in children, these comorbidities may be considered an indication for metabolic/bariatric surgery in younger adolescents or those with lower obesity percentiles."
- "Vitamin B deficiencies, especially B1 appear to be more common in adolescents both preoperatively and postoperatively; they should be screened for and treated. Prophylactic B1 for the first 6 months postoperatively is recommended as is education of patients and primary care providers on the signs and symptoms of common deficiencies."
- "Developmental delay, autism spectrum, or syndromic obesity should not be a contraindication to metabolic/bariatric surgery. Each patient and caregiver team will need to be assessed for the ability to make dietary and lifestyle changes required for surgery. Multidisciplinary teams should agree on the specific needs and abilities of the

given patient and caregiver and these should be considered on a case-by-case basis with the assistance of the hospital ethics committee where appropriate."

- "Because metabolic/bariatric surgery results in better weight loss and resolution of comorbidities in adolescents at lower BMI's with fewer comorbidities, referrals should occur early, as soon as a child is recognized to suffer from severe obesity disease (BMI >120% of the 95th percentile or BMI of 35). Prior weight loss attempts, Tanner stage, and bone age should not be considered when referring patients to a metabolic/bariatric surgery program."
- "Unstable family environments, eating disorders, mental illness, or prior trauma should not be considered contraindications for metabolic/bariatric surgery in adolescents; however, these should be optimized and treated where possible before and surrounding any surgical intervention for obesity."
- "Routine screening of alcohol use is imperative across all procedures. Conservative clinical care guidelines, which strongly advocate abstinence, while appropriate, must also include information for this age group on harm reduction (i.e., lower consumption levels, how to avoid or manage situations related to alcohol-related harm) to mitigate clinical and safety risks. Risks of nicotine should be discussed and smoking or vaping nicotine should be discouraged."
- "The recognition of obesity as a chronic disease that requires multimodal therapies justifies the treatment of such a disease in a multidisciplinary team that can provide surgical, pharmacologic, behavioral, nutritional, and activity interventions. Pharmacologic therapies as adjuncts to surgical therapies may provide improved outcomes long term in the pediatric population; more studies are needed.

SECTION SUMMARY

There is evidence to suggest bariatric surgery may provide the benefits of weight reduction and improved comorbidities compared to non-surgical treatments in the obese children and adolescents.

GASTROESOPHAGEAL REFLUX DISEASE

This section focuses on evidence related to gastroesophageal reflux disease (GERD) as it relates to bariatric procedures as a treatment for obesity. See Cross References section, above, for policies focused on treatment of GERD.

SYSTEMATIC REVIEWS

In 2016, Osland compared the efficacy of Roux-En-Y gastric bypass versus vertical sleeve gastrectomy in randomized controlled trials.[44] Six RCTs performed between 2005 and 2015 were included (N = 695; 347 for SG and 348 for RYGB). The authors summarized recent publications, citing worsened GERD symptoms following sleeve gastrectomy in patients with preoperative symptoms, and new symptoms in 9% of patients with no previous symptoms. Preexisting GERD in those who undergo sleeve gastrectomy is noted as being the cause of frequent revisional surgeries, and high rates of surgical complications. In addition those with preexisting GERD were found to have failure to achieve weight loss, and failure to resolve weight related comorbidities such as diabetes, obstructive sleep apnea, and hypertension.

In 2016, Oor reported results from a systematic review and meta-analysis of studies reporting prevalence of GERD symptoms, the use of anti-reflux medication, and/or outcome of esophageal function tests before and after laparoscopic sleeve gastrectomy (LSG) in patients

with a BMI of more than 35.[203] Pooled data from seven studies using validated symptom questionnaires for new-onset of GERD symptoms resulted in a 20% incidence following LSG (follow-up time ranging from one- to 60-months). There was heterogeneity amongst these studies (I^2=68%). For difference in prevalence of GERD before and after LSG, the pooled risk difference was found to be 4.3%; with heterogeneity present (I^2=89%). Of the 24 studies reviewed, the authors found new-onset GERD symptom incidence to range from zero to 34.9%. The authors therefore concluded that LSG could induce serious GERD symptoms in patients with no preoperative GERD complaints. The heterogeneity found in analyses may be due to a lack of a standardized approach to LSG, as well has the variability in follow-up length. The authors also noted that range in prevalence of GERD symptoms may be in part due to the variability in reported preoperative BMI, as the LSG will be a more technically challenging procedure in those with a BMI of 60 kg/m^2 versus those with a BMI of 40 kg/m^2.

Li and colleagues (2016) conducted a systematic review and meta-analysis comparing Roux-en-Y gastric bypass (LRYGB) with LSG for treating morbid obesity.[204] Randomized controlled trials and nonrandomized studies were included. Amongst five studies that reported GERD resolution post-operation (147 in the LRYGB group and 93 in the LSG group), symptoms resolved significantly more after LRYGB as compared to LSG (OR = 8.99, 95% CI 4.77-16.95). Heterogeneity was not detected between these groups (I^2 = 48% P=0.12).

NONRANDOMIZED STUDIES

Several nonrandomized studies have retrospectively reviewed weight reduction and GERD symptoms following Roux-en-Y gastric bypass surgery for treatment of morbid obesity.[205-210] Authors have reported reduction in self-reported GERD symptoms, prescribed medications, and weight loss. As demonstrated in small case series, in combination with takedown of fundoplication, Roux-en-Y gastric bypass for morbid obesity has been effective in weight reduction as well as self-reported GERD symptom improvement.[208, 209] Evidence regarding high incidence of GERD following laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy makes Roux-en-Y gastric bypass the ideal procedure in the presence of already existing reflux symptoms.[46, 211-215]

CLINICAL PRACTICE GUIDELINES

Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

The SAGES clinical practice guidelines for the surgical treatment of GERD (2010) state the following:[216]

> Due to concerns for higher failure rates after fundoplication in the morbidly obese patient (BMI >35 kg/m2) and the inability of fundoplication to address the underlying problem (obesity) and its associated comorbidities, gastric bypass should be the procedure of choice when treating GERD in this patient group (Grade B). The benefits in patients with BMI > 30 is less clear and needs further study.

SECTION SUMMARY

Systematic review of GERD symptoms following laparoscopic sleeve gastrectomy (LSG) as a treatment for severe obesity is limited by heterogeneity in the technical approach to the procedure, therefore presenting statistical challenges to analyzing pooled results. In comparing LSG with Roux-en-Y gastric bypass (RYGB) directly, GERD symptoms resolve significantly more post-RYGB as compared to LSG. In the presence of GERD, the Society of American

Gastrointestinal and Endoscopic Surgeons (SAGES) clinical practice guidelines state that gastric bypass is the procedure of choice in patients who are morbidly obese. In those who are not morbidly obese, evidence does not indicate that bariatric surgery is an appropriate treatment for GERD, and SAGES states this is an area in need of further study.

SAFETY OF BARIATRIC SURGERY

GENERAL SURGICAL RISKS

Bariatric procedures are associated with all the potential risks of any major abdominal surgical procedure including but not limited to:

- Bleeding
- Death
- Infection
- Injury to internal organs or gastrointestinal tract
- Thromboembolic complications

PROCEDURE-SPECIFIC SURGICAL RISKS

The following table summarizes the most common procedure-specific risks. However, other adverse events are also possible.

RYGBP[2, 217-219]	**LL-RYGBP**[2]	**BPD/BPD-DS**[2, 11, 217]	**SG**[11, 217, 220-223]	**LAGB**[63, 217]	**MGB**[79]	**Endoluminal Procedures**
• Cholecystitis • Depression • Dilated stomach pouch • Dumping syndrome† • Gastritis • Leaks or obstructions at the anastomotic site • Marginal ulcer • Reoperations††† • Staple line failure • Vitamin/mineral deficiencies (iron, folate, B_{12}) • Kidney stones	• All RYGBP risks • Additional unknown risks associated with the greater bypass of the small intestine and consequent increase in malabsorption††	• Dilated stomach pouch • Gastric obstruction • GERD • Leaks or stenoses at anastomotic sites • Malnutrition and/or vitamin deficiencies • Nausea/vomiting • Wound dehiscence	• Abscesses • Frequent vomiting • Gastric fistulas • GERD • Leaking from the stomach pouch • Reoperations††††	• Band slippage • Dilated stomach pouch • Erosion of the device through gastric wall • GERD • Malnutrition and vitamin deficiencies • Nausea and vomiting	• Bile reflux • Gastrojejunostomy leak • Marginal ulcer • Reoperations††† • Vitamin/mineral deficiency	The safety concerns are specific to the endoluminal procedure performed: <u>Transoral circular stapler (SurgASSIST®):</u>[224] • Bowel obstruction • Intra-abdominal adhesions <u>Dduodenal-jejunal bypass sleeve (DJBS):</u>[117] • Abdominal pain • Implant site inflammation • Nausea and vomiting <u>TOGa system endoscopic stapling:</u>[118] • Nausea • Vomiting • Pain • Transient dysphagia

† Abdominal pain, diarrhea, and/or vomiting shortly after eating due to reduced transit time in the intestine;
††The evidence, especially from the studies with long-term follow-up, is limited and not much is known about the long-term complications of LL-RYGBP;
†††Due to insufficient weight loss or technical issues;

SUMMARY

ROUX-EN-Y GASTRIC BYPASS, BILIOPANCREATIC BYPASS WITH DUODENAL SWITCH, AND SLEEVE GASTRECTOMY

Roux-en-Y gastric bypass is well established in clinical practice as a safe and effective bariatric procedure Sleeve gastrectomy as a stand-alone procedure gained acceptance in clinical practice. Sleeve gastrectomy offers an alternative to adjustable gastric banding with potentially greater weight loss and fewer complications. Therefore, Roux-en-Y gastric bypass, biliopancreatic bypass with duodenal switch, and sleeve gastrectomy may be considered medically necessary in the treatment of class III obesity when policy Criteria are met.

There is not enough research to show that Roux-en-Y gastric bypass, biliopancreatic bypass with duodenal switch, or sleeve gastrectomy improves health outcomes for any condition other than class III obesity. Therefore, Roux-en-Y gastric bypass, biliopancreatic bypass with duodenal switch, and sleeve gastrectomy are considered investigational for the treatment of any condition other than class III obesity, including, but not limited to gastroesophageal reflux disease.

There is not enough research to show that any other bariatric procedures improves health outcomes. Therefore, the use of distal, partial (not including sleeve gastrectomy) or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction, are considered investigational as a treatment of obesity.

MINI-GASTRIC BYPASS, DISTAL GASTRIC BYPASS, BILIOPANCREATIC BYPASS, AND LAPAROSCOPIC DUODENAL SWITCH WITH SINGLE ANASTOMOSIS

There is not enough research for these procedures on health outcomes. Therefore, mini-gastric bypass, distal gastric bypass, biliopancreatic bypass, and laparoscopic duodenal switch with single anastomosis are considered investigational for the treatment of class III obesity, gastroesophageal reflux disease or any other condition.

HIATAL HERNIA REPAIR

There is not enough research regarding the use of hiatal hernia repair as an independent treatment of obesity. In addition, no evidence-based clinical practice guidelines were identified which addressed the use of hiatal hernia repair as a treatment of obesity. Therefore, hiatal hernia repair is considered investigational as an independent treatment of obesity.

VERTICAL BANDED GASTROPLASTY AND ADJUSTABLE GASTRIC BANDING

Due to higher complications, insufficient weight loss, and high reoperation rates, vertical banded gastroplasty and adjustable gastric banding are no longer considered a standard of care and are therefore considered not medically necessary.

ENDOSCOPIC BARIATRIC PROCEDURES

There is not enough evidence to establish the safety and efficacy of any endoscopic bariatric

procedure. Therefore, endoscopic bariatric procedures are considered investigational for all indications.

LAPAROSCOPIC GASTRIC PLICATION

There is not enough evidence to establish the safety and efficacy of any laparoscopic gastric plication bariatric procedure. Therefore, laparoscopic gastric plication procedures are considered investigational for all indications.

REVISION BARIATRIC SURGICAL PROCEDURES

Research regarding reoperation of a primary bariatric surgery is limited to noncomparative studies without long-term outcome data. In addition, current research shows that the complication and mortality rate is slightly higher in cases of reoperation. However, reoperation appears to be beneficial for patients with serious complications related to the primary bariatric surgery and may be considered medically necessary when Criteria are met.

Research regarding the revision or removal of an adjustable gastric band is limited to noncomparative studies with short-term follow-up. These studies suggest band removal or revision is associated with improvement in band related complications. In addition, studies indicate gastric bypass is the preferred secondary procedure in cases of adjustable band conversion as bypass is associated with fewer complications and lower mortality rates compared to sleeve gastrectomy. Therefore, adjustable gastric band removal and/or conversion to gastric bypass may be considered medically necessary when Criteria are met.

The research is insufficient to determine the safety or efficacy of all other bariatric surgery reoperations or revisions; therefore, reoperations or revisions are considered not medically necessary when Criteria are not met.

TWO-STAGED BARIATRIC PROCEDURES

There is not enough research to establish the safety and efficacy of any two-stage bariatric procedure. Therefore, two-stage bariatric procedures are considered investigational for all indications.

ADOLESCENT AND PEDIATRIC BARIATRIC SURGERY

There is evidence to suggest bariatric surgery may provide the benefits of weight reduction and improved comorbidities compared to non-surgical treatments in children and adolescents under the age of 18 with obesity. Clinical practice guidelines suggest that bariatric surgery may be beneficial for patients under the age of 18 when they have achieved Tanner pubertal development of 4 or 5 and additional consideration is given to the psychosocial and informed consent issues. Therefore, bariatric procedures in patients younger than 18 years of age may be considered medically necessary when Criteria are met.

BARIATRIC SURGERY IN PATIENTS WITH DIABETES WITH BMI < 35KG/M²

Research for the safety and effectiveness of bariatric procedures as a treatment for diabetes in patients with a BMI < 35 kg/m² is limited by small study sizes and short-term follow-up. High-quality studies that include long-term follow-up are needed in order to evaluate the impact of bariatric surgery on health outcomes in this population. In addition, the majority of

evidence-based clinical practice guidelines do not recommend bariatric surgery in diabetic patients with a BMI < 35 kg/m². Therefore, bariatric procedures in diabetic patients with a BMI < 35 kg/m² are considered not medically necessary.

REFERENCES

1. Overweight and obesity. In: Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Bethesda (MD): National Heart, Lung, and Blood Institute; 2011. p. 282-321.
2. TEC Assessment 2005. "Newer Techniques in Bariatric Surgery for Morbid Obesity: Laparoscopic Adjustable Gastric Banding, Biliopancreatic Diversion, and Long-limb Gastric Bypass." BlueCross BlueShield Association Technology Evaluation Center, Vol. 20, Tab 5.
3. Nguyen NT, Paya M, Stevens CM, et al. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. *Ann Surg.* 2004;240(4):586-93; discussion 93-4. PMID: 15383786
4. Liu JH, Zingmond D, Etzioni DA, et al. Characterizing the performance and outcomes of obesity surgery in California. *Am Surg.* 2003;69(10):823-8. PMID: 14570356
5. Courcoulas A, Schuchert M, Gatti G, et al. The relationship of surgeon and hospital volume to outcome after gastric bypass surgery in Pennsylvania: a 3-year summary. *Surgery.* 2003;134(4):613-21; discussion 21-3. PMID: 14605622
6. Salman MA, Abelsalam A, Nashed GA, et al. Long Biliopancreatic Limb Roux-En-Y Gastric Bypass Versus One-Anastomosis Gastric Bypass: a Randomized Controlled Study. *Obes Surg.* 2023;33(7):1966-73. PMID: 37178225
7. Pinheiro JS, Schiavon CA, Pereira PB, et al. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. *Surg Obes Relat Dis.* 2008;4(4):521-5; discussion 26-7. PMID: 18539540
8. Sugerman HJ, Kellum JM, DeMaria EJ. Conversion of proximal to distal gastric bypass for failed gastric bypass for superobesity. *J Gastrointest Surg.* 1997;1(6):517-24; discussion 24-6. PMID: 9834387
9. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. *Ann Surg.* 2006;244(5):734-40. PMID: 17060766
10. Gleysteen JJ. Five-year outcome with gastric bypass: Roux limb length makes a difference. *Surg Obes Relat Dis.* 2009;5(2):242-7; discussion 47-9. PMID: 18996751
11. Colquitt JL, Picot J, Loveman E, et al. Surgery for obesity. *Cochrane Database Syst Rev.* 2009(2):CD003641. PMID: 19370590
12. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults. *Cochrane Database Syst Rev.* 2014;8:CD003641. PMID: 25105982
13. Möller F, Hedberg J, Skogar M, et al. Long-term Follow-up 15 Years After Duodenal Switch or Gastric Bypass for Super Obesity: a Randomized Controlled Trial. *Obes Surg.* 2023;33(10):2981-90. PMID: 37584851
14. Skroubis G, Anesidis S, Kehagias I, et al. Roux-en-Y gastric bypass versus a variant of biliopancreatic diversion in a non-superobese population: prospective comparison of the efficacy and the incidence of metabolic deficiencies. *Obes Surg.* 2006;16(4):488-95. PMID: 16608616

15. Sovik TT, Taha O, Aasheim ET, et al. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. *Br J Surg.* 2010;97(2):160-6. PMID: 20035530
16. Risstad H, Sovik TT, Engstrom M, et al. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body mass index of 50 to 60: a randomized clinical trial. *JAMA surgery.* 2015;150(4):352-61. PMID: 25650964
17. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. *Obes Surg.* 1998;8(3):267-82. PMID: 9678194
18. Scopinaro N, Gianetta E, Adami GF, et al. Biliopancreatic diversion for obesity at eighteen years. *Surgery.* 1996;119(3):261-8. PMID: 8619180
19. Slater GH, Ren CJ, Siegel N, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. *J Gastrointest Surg.* 2004;8(1):48-55; discussion 54-5. PMID: 14746835
20. Dolan K, Hatzifotis M, Newbury L, et al. A clinical and nutritional comparison of biliopancreatic diversion with and without duodenal switch. *Ann Surg.* 2004;240(1):51-6. PMID: 15213618
21. Grimm IS, Schindler W, Haluszka O. Steatohepatitis and fatal hepatic failure after biliopancreatic diversion. *Am J Gastroenterol.* 1992;87(6):775-9. PMID: 1590319
22. Langdon DE, Leffingwell T, Rank D. Hepatic failure after biliopancreatic diversion. *Am J Gastroenterol.* 1993;88(2):321. PMID: 8424445
23. Marceau P, Hould FS, Simard S, et al. Biliopancreatic diversion with duodenal switch. *World J Surg.* 1998;22(9):947-54. PMID: 9717420
24. Marceau P, Biron S, Hould FS, et al. Duodenal switch improved standard biliopancreatic diversion: a retrospective study. *Surg Obes Relat Dis.* 2009;5(1):43-7. PMID: 18440876
25. Baltasar A, del Rio J, Escriva C, et al. Preliminary results of the duodenal switch. *Obes Surg.* 1997;7(6):500-4. PMID: 9730508
26. Larrad-Jimenez A, Diaz-Guerra CS, de Cuadros Borrajo P, et al. Short-, mid- and long-term results of Larrad biliopancreatic diversion. *Obes Surg.* 2007;17(2):202-10. PMID: 17476873
27. Dapri G, Himpens J, Cadiere GB. Laparoscopic conversion of Roux-en-Y gastric bypass to biliopancreatic diversion. *Surg Endosc.* 2010;24(6):1490-3. PMID: 20044768
28. Mitchell MT, Carabetta JM, Shah RN, et al. Duodenal switch gastric bypass surgery for morbid obesity: imaging of postsurgical anatomy and postoperative gastrointestinal complications. *AJR Am J Roentgenol.* 2009;193(6):1576-80. PMID: 19933650
29. Kasama K, Tagaya N, Kanehira E, et al. Laparoscopic sleeve gastrectomy with duodenojejunal bypass: technique and preliminary results. *Obes Surg.* 2009;19(10):1341-5. PMID: 19626382
30. Piazza L, Pulvirenti A, Ferrara F, et al. Laparoscopic biliopancreatic diversion: our preliminary experience with 201 consecutive cases. *Chir Ital.* 2009;61(2):143-8. PMID: 19536986
31. Vila M, Ruiz O, Belmonte M, et al. Changes in lipid profile and insulin resistance in obese patients after Scopinaro biliopancreatic diversion. *Obes Surg.* 2009;19(3):299-306. PMID: 19137381
32. Gracia JA, Martinez M, Elia M, et al. Obesity surgery results depending on technique performed: long-term outcome. *Obes Surg.* 2009;19(4):432-8. PMID: 19002740
33. Prachand VN, Davee RT, Alverdy JC. Duodenal switch provides superior weight loss in the super-obese (BMI > or =50 kg/m2) compared with gastric bypass. *Ann Surg.* 2006;244(4):611-9. PMID: 16998370

34. Parikh M, Ayoung-Chee P, Romanos E, et al. Comparison of rates of resolution of diabetes mellitus after gastric banding, gastric bypass, and biliopancreatic diversion. *J Am Coll Surg.* 2007;205(5):631-5. PMID: 17964437
35. Salminen P, Helmio M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. *JAMA.* 2018;319(3):241-54. PMID: 29340676
36. Osland EJ, Yunus RM, Khan S, et al. Five-year Comorbidity Outcomes in Laparoscopic Vertical Sleeve Gastrectomy (LVSG) and Laparoscopic Roux-en-Y Gastric Bypass (LRYGB): A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Surg Laparosc Endosc Percutan Tech.* 2023;33(3):241-48. PMID: 37058440
37. Kermansaravi M, Vitiello A, Valizadeh R, et al. Comparing the safety and efficacy of sleeve gastrectomy versus Roux-en-Y gastric bypass in elderly (>60 years) with severe obesity: an umbrella systematic review and meta-analysis. *Int J Surg.* 2023;109(11):3541-54. PMID: 37800553
38. Vanetta C, Dreifuss NH, Angeramo CA, et al. Outcomes of same-day discharge sleeve gastrectomy and Roux-en-Y gastric bypass: a systematic review and meta-analysis. *Surg Obes Relat Dis.* 2023;19(3):238-49. PMID: 36209031
39. Gu L, Huang X, Li S, et al. A meta-analysis of the medium- and long-term effects of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. *BMC Surg.* 2020;20(1):30. PMID: 32050953
40. Han Y, Jia Y, Wang H, et al. Comparative analysis of weight loss and resolution of comorbidities between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: A systematic review and meta-analysis based on 18 studies. *Int J Surg.* 2020;76:101-10. PMID: 32151750
41. Sharples AJ, Mahawar K. Systematic Review and Meta-Analysis of Randomised Controlled Trials Comparing Long-Term Outcomes of Roux-En-Y Gastric Bypass and Sleeve Gastrectomy. *Obes Surg.* 2020;30(2):664-72. PMID: 31724116
42. Shenoy SS, Gilliam A, Mehanna A, et al. Laparoscopic Sleeve Gastrectomy Versus Laparoscopic Roux-en-Y Gastric Bypass in Elderly Bariatric Patients: Safety and Efficacy-a Systematic Review and Meta-analysis. *Obes Surg.* 2020;30(11):4467-73. PMID: 32594469
43. Xu C, Yan T, Liu H, et al. Comparative Safety and Effectiveness of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy in Obese Elder Patients: a Systematic Review and Meta-analysis. *Obes Surg.* 2020;30(9):3408-16. PMID: 32277330
44. Osland E, Yunus RM, Khan S, et al. Changes in Non-Diabetic Comorbid Disease Status Following Laparoscopic Vertical Sleeve Gastrectomy (LVSG) Versus Laparoscopic Roux-En-Y Gastric Bypass (LRYGB) Procedures: a Systematic Review of Randomized Controlled Trials. *Obes Surg.* 2017;27(5):1208-21. PMID: 27896647
45. Osland EJ, Yunus RM, Khan S, et al. Five-Year Weight Loss Outcomes in Laparoscopic Vertical Sleeve Gastrectomy (LVSG) Versus Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) Procedures: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Surg Laparosc Endosc Percutan Tech.* 2020;30(6):542-53. PMID: 32658120
46. Juodeikis Z, Brimas G. Long-term results after sleeve gastrectomy: A systematic review. *Surg Obes Relat Dis.* 2017;13(4):693-99. PMID: 27876332
47. Almalki OM, Lee WJ, Chen JC, et al. Revisional Gastric Bypass for Failed Restrictive Procedures: Comparison of Single-Anastomosis (Mini-) and Roux-en-Y Gastric Bypass. *Obes Surg.* 2018;28(4):970-75. PMID: 29101719

48. Zhang Y, Ju W, Sun X, et al. Laparoscopic sleeve gastrectomy versus laparoscopic roux-en-y gastric bypass for morbid obesity and related comorbidities: a meta-analysis of 21 studies. *Obes Surg.* 2015;25(1):19-26. PMID: 25092167
49. Zellmer JD, Mathiason MA, Kallies KJ, et al. Is laparoscopic sleeve gastrectomy a lower risk bariatric procedure compared with laparoscopic Roux-en-Y gastric bypass? A meta-analysis. *American journal of surgery.* 2014;208(6):903-10. PMID: 25435298
50. Karamanakos SN, Vagenas K, Kalfarentzos F, et al. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. *Ann Surg.* 2008;247(3):401-7. PMID: 18376181
51. Trastulli S, Desiderio J, Guarino S, et al. Laparoscopic sleeve gastrectomy compared with other bariatric surgical procedures: a systematic review of randomized trials. *Surg Obes Relat Dis.* 2013;9(5):816-29. PMID: 23993246
52. Peterli R, Wolnerhanssen B, Peters T, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. *Ann Surg.* 2009;250(2):234-41. PMID: 19638921
53. Ramon JM, Salvans S, Crous X, et al. Effect of Roux-en-Y gastric bypass vs sleeve gastrectomy on glucose and gut hormones: a prospective randomised trial. *J Gastrointest Surg.* 2012;16(6):1116-22. PMID: 22402955
54. Kehagias I, Karamanakos SN, Argentou M, et al. Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the management of patients with BMI < 50 kg/m2. *Obes Surg.* 2011;21(11):1650-6. PMID: 21818647
55. Li JF, Lai DD, Ni B, et al. Comparison of laparoscopic Roux-en-Y gastric bypass with laparoscopic sleeve gastrectomy for morbid obesity or type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Can J Surg.* 2013;56:E158-64. PMID: 24284156
56. Peterli R, Wolnerhanssen BK, Peters T, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. *JAMA.* 2018;319(3):255-65. PMID: 29340679
57. Updated position statement on sleeve gastrectomy as a bariatric procedure. *Surg Obes Relat Dis.* 2012;8(3):e21-6. PMID: 22417852
58. Park CH, Nam SJ, Choi HS, et al. Comparative Efficacy of Bariatric Surgery in the Treatment of Morbid Obesity and Diabetes Mellitus: a Systematic Review and Network Meta-Analysis. *Obes Surg.* 2019;29(7):2180-90. PMID: 31037599
59. Kang JH, Le QA. Effectiveness of bariatric surgical procedures: A systematic review and network meta-analysis of randomized controlled trials. *Medicine.* 2017;96(46):e8632. PMID: 29145284
60. Angrisani L, Lorenzo M, Borrelli V. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 5-year results of a prospective randomized trial. *Surg Obes Relat Dis.* 2007;3(2):127-32; discussion 32-3. PMID: 17331805
61. TEC Assessment 2012. "Laparoscopic Adjustable Gastric Banding In Patients With Body Mass Index Less Than 35 kg/m2 With Weight-Related Comorbidity." BlueCross BlueShield Association Technology Evaluation Center, Vol. 27 Tab TBA.
62. Abbatini F, Rizzello M, Casella G, et al. Long-term effects of laparoscopic sleeve gastrectomy, gastric bypass, and adjustable gastric banding on type 2 diabetes. *Surg Endosc.* 2010;24(5):1005-10. PMID: 19866235

63. TEC Assessment 2007. "Laparoscopic Adjustable Gastric Banding for Morbid Obesity." BlueCross and BlueShield Association Technology Evaluation Center, Vol. 21, Tab 13.
64. Snyder B, Scarborough T, Yu S, et al. Failure of adjustable gastric banding: starting BMI of 46 kg/m2 is a fulcrum of success and failure. *Surg Obes Relat Dis.* 2009;5(3):310-6. PMID: 19136307
65. Angrisani L, Furbetta F, Doldi SB, et al. Results of the Italian multicenter study on 239 super-obese patients treated by adjustable gastric banding. *Obes Surg.* 2002;12(6):846-50. PMID: 12568193
66. Brancatisano A, Wahlroos S, Matthews S, et al. Gastric banding for the treatment of type 2 diabetes mellitus in morbidly obese. *Surg Obes Relat Dis.* 2008;4(3):423-9. PMID: 18226973
67. Christou N, Efthimiou E. Five-year outcomes of laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass in a comprehensive bariatric surgery program in Canada. *Can J Surg.* 2009;52(6):E249-58. PMID: 20011160
68. Cherian PT, Tentzeris V, Sigurdsson A. Variation of outcome in weight loss with band volume adjustments under clinical and radiological control following laparoscopic adjustable gastric banding. *Obes Surg.* 2010;20(1):13-8. PMID: 19841993
69. Cobourn C, Degboe A, Super PA, et al. Safety and effectiveness of LAP-BAND AP System: results of Helping Evaluate Reduction in Obesity (HERO) prospective registry study at 1 year. *J Am Coll Surg.* 2013;217(5):907-18. PMID: 24035447
70. Cottam A, Cottam D, Medlin W, et al. A matched cohort analysis of single anastomosis loop duodenal switch versus Roux-en-Y gastric bypass with 18-month follow-up. *Surg Endosc.* 2015. PMID: 26694182
71. Sanchez-Pernaute A, Rubio MA, Cabrerizo L, et al. Single-anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S) for obese diabetic patients. *Surg Obes Relat Dis.* 2015;11(5):1092-8. PMID: 26048517
72. Sanchez-Pernaute A, Rubio MA, Conde M, et al. Single-anastomosis duodenoileal bypass as a second step after sleeve gastrectomy. *Surg Obes Relat Dis.* 2015;11(2):351-5. PMID: 25543309
73. Lee WJ, Lee KT, Kasama K, et al. Laparoscopic single-anastomosis duodenal-jejunal bypass with sleeve gastrectomy (SADJB-SG): short-term result and comparison with gastric bypass. *Obes Surg.* 2014;24(1):109-13. PMID: 23990452
74. Sanchez-Pernaute A, Rubio MA, Perez Aguirre E, et al. Single-anastomosis duodenoileal bypass with sleeve gastrectomy: metabolic improvement and weight loss in first 100 patients. *Surg Obes Relat Dis.* 2013;9(5):731-5. PMID: 22963820
75. Nakanishi H, Matar RH, Vahibe A, et al. Single Versus Double Anastomosis Duodenal Switch in the Management of Obesity: A Meta-analysis and Systematic Review. *Surg Laparosc Endosc Percutan Tech.* 2022;32(5):595-605. PMID: 36130714
76. Spinos D, Skarentzos K, Esagian SM, et al. The Effectiveness of Single-Anastomosis Duodenoileal Bypass with Sleeve Gastrectomy/One Anastomosis Duodenal Switch (SADI-S/OADS): an Updated Systematic Review. *Obes Surg.* 2021;31(4):1790-800. PMID: 33452998
77. Kallies K, Rogers AM. American Society for Metabolic and Bariatric Surgery updated statement on single-anastomosis duodenal switch. *Surg Obes Relat Dis.* 2020;16(7):825-30. PMID: 32371036
78. Georgiadou D, Sergentanis TN, Nixon A, et al. Efficacy and safety of laparoscopic mini gastric bypass. A systematic review. *Surg Obes Relat Dis.* 2014;10(5):984-91. PMID: 24913595

79. Lee WJ, Yu PJ, Wang W, et al. Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity: a prospective randomized controlled clinical trial. *Ann Surg.* 2005;242(1):20-8. PMID: 15973097
80. Plamper A, Lingohr P, Nadal J, et al. Comparison of mini-gastric bypass with sleeve gastrectomy in a mainly super-obese patient group: first results. *Surg Endosc.* 2017;31(3):1156-62. PMID: 27444823
81. Wang W, Wei PL, Lee YC, et al. Short-term results of laparoscopic mini-gastric bypass. *Obes Surg.* 2005;15(5):648-54. PMID: 15946455
82. Chakhtoura G, Zinzindohoue F, Ghanem Y, et al. Primary results of laparoscopic mini-gastric bypass in a French obesity-surgery specialized university hospital. *Obes Surg.* 2008;18(9):1130-3. PMID: 18566866
83. Noun R, Riachi E, Zeidan S, et al. Mini-gastric bypass by mini-laparotomy: a cost-effective alternative in the laparoscopic era. *Obes Surg.* 2007;17(11):1482-6. PMID: 18219775
84. Johnson WH, Fernanadez AZ, Farrell TM, et al. Surgical revision of loop ("mini") gastric bypass procedure: multicenter review of complications and conversions to Roux-en-Y gastric bypass. *Surg Obes Relat Dis.* 2007;3(1):37-41. PMID: 17196443
85. Dang H, Arias E, Szomstein S, et al. Laparoscopic conversion of distal mini-gastric bypass to proximal Roux-en-Y gastric bypass for malnutrition: case report and review of the literature. *Surg Obes Relat Dis.* 2009;5(3):383-6. PMID: 19356992
86. Hsieh T, Zurita L, Grover H, et al. 10-year outcomes of the vertical transected gastric bypass for obesity: a systematic review. *Obes Surg.* 2014;24(3):456-61. PMID: 24379176
87. Kothari V, Shaligram A, Reynoso J, et al. Impact on perioperative outcomes of concomitant hiatal hernia repair with laparoscopic gastric bypass. *Obes Surg.* 2012;22(10):1607-10. PMID: 22833136
88. Reynoso JF, Goede MR, Tiwari MM, et al. Primary and revisional laparoscopic adjustable gastric band placement in patients with hiatal hernia. *Surg Obes Relat Dis.* 2011;7:290-4. PMID: 21130046
89. Anderson PG, Watson DI. A new surgical technique for the silicone gastric band in the presence of a large hiatus hernia. *Obes Surg.* 1999;9(2):202-4; discussion 04-5. PMID: 10340780
90. Mahawar KK, Carr WR, Jennings N, et al. Simultaneous sleeve gastrectomy and hiatus hernia repair: a systematic review. *Obes Surg.* 2015;25(1):159-66. PMID: 25348434
91. Mills H, Alhindi Y, Idris I, et al. Outcomes of Concurrent Hiatus Hernia Repair with Different Bariatric Surgery Procedures: a Systematic Review and Meta-analysis. *Obes Surg.* 2023;33(12):3755-66. PMID: 37917388
92. Menzo EL, Hinojosa M, Carbonell A, et al. American Society for Metabolic and Bariatric Surgery and American Hernia Society consensus guideline on bariatric surgery and hernia surgery. *Surg Obes Relat Dis.* 2018;14(9):1221-32. PMID: 30154033
93. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. *Surg Obes Relat Dis.* 2022;18(12):1345-56. PMID: 36280539
94. Cottam D, Qureshi FG, Mattar SG, et al. Laparoscopic sleeve gastrectomy as an initial weight-loss procedure for high-risk patients with morbid obesity. *Surg Endosc.* 2006;20(6):859-63. PMID: 16738970
95. Alexandrou A, Felekouras E, Giannopoulos A, et al. What is the actual fate of super-morbid-obese patients who undergo laparoscopic sleeve gastrectomy as the first step of

a two-stage weight-reduction operative strategy? *Obes Surg.* 2012;22(10):1623-8. PMID: 22833137
96. Silecchia G, Rizzello M, Casella G, et al. Two-stage laparoscopic biliopancreatic diversion with duodenal switch as treatment of high-risk super-obese patients: analysis of complications. *Surg Endosc.* 2009;23(5):1032-7. PMID: 18814005
97. Saber AA, Shoar S, Almadani MW, et al. Efficacy of first-time intragastric balloon in weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obes Surg.* 2017;27(2):277-87. PMID: 27465936
98. Moura D, Oliveira J, De Moura EG, et al. Effectiveness of intragastric balloon for obesity: A systematic review and meta-analysis based on randomized control trials. *Surg Obes Relat Dis.* 2016;12(2):420-9. PMID: 26968503
99. Zheng Y, Wang M, He S, et al. Short-term effects of intragastric balloon in association with conservative therapy on weight loss: a meta-analysis. *Journal of translational medicine.* 2015;13:246. PMID: 26219459
100. Weitzner ZN, Phan J, Begashaw MM, et al. Endoscopic therapies for patients with obesity: a systematic review and meta-analysis. *Surg Endosc.* 2023;37(11):8166-77. PMID: 37730854
101. Loo JH, Lim YH, Seah HL, et al. Intragastric Balloon as Bridging Therapy Prior to Bariatric Surgery for Patients with Severe Obesity (BMI ≥ 50 kg/m(2)): a Systematic Review and Meta-analysis. *Obes Surg.* 2022;32(2):489-502. PMID: 34787766
102. Kotinda A, de Moura DTH, Ribeiro IB, et al. Efficacy of Intragastric Balloons for Weight Loss in Overweight and Obese Adults: a Systematic Review and Meta-analysis of Randomized Controlled Trials. *Obes Surg.* 2020;30(7):2743-53. PMID: 32300945
103. Tate CM, Geliebter A. Intragastric balloon treatment for obesity: review of recent studies. *Advances in therapy.* 2017;34(8):1859-75. PMID: 28707286
104. Vargas EJ, Bazerbachi F, Rizk M, et al. Transoral outlet reduction with full thickness endoscopic suturing for weight regain after gastric bypass: a large multicenter international experience and meta-analysis. *Surg Endosc.* 2017. PMID: 28664438
105. Rohde U, Hedback N, Gluud LL, et al. Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: Systematic review and meta-analysis. *Diabetes, obesity & metabolism.* 2015. PMID: 26537317
106. Sullivan S, Stein R, Jonnalagadda S, et al. Aspiration therapy leads to weight loss in obese subjects: a pilot study. *Gastroenterology.* 2013;145(6):1245-52 e1-5. PMID: 24012983
107. Summary of Safety and Effectiveness Data. AspireAssist. June 14, 2016. [cited 12/14/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf15/p150024b.pdf.
108. Eid GM, McCloskey CA, Eagleton JK, et al. StomaphyX vs a sham procedure for revisional surgery to reduce regained weight in Roux-en-Y gastric bypass patients : a randomized clinical trial. *JAMA surgery.* 2014;149:372-9. PMID: 24554030
109. Koehestanie P, de Jonge C, Berends FJ, et al. The effect of the endoscopic duodenal-jejunal bypass liner on obesity and type 2 diabetes mellitus, a multicenter randomized controlled trial. *Ann Surg.* 2014;260(6):984-92. PMID: 25072436
110. Fuller NR, Pearson S, Lau NS, et al. An intragastric balloon in the treatment of obese individuals with metabolic syndrome: a randomized controlled study. *Obesity (Silver Spring).* 2013;21(8):1561-70. PMID: 23512773
111. Ponce J, Quebbemann BB, Patterson EJ. Prospective, randomized, multicenter study evaluating safety and efficacy of intragastric dual-balloon in obesity. *Surg Obes Relat Dis.* 2013;9(2):290-5. PMID: 22951075

112. Farina MG, Baratta R, Nigro A, et al. Intragastric balloon in association with lifestyle and/or pharmacotherapy in the long-term management of obesity. *Obes Surg.* 2012;22(4):565-71. PMID: 21901285
113. De Castro ML, Morales MJ, Del Campo V, et al. Efficacy, safety, and tolerance of two types of intragastric balloons placed in obese subjects: a double-blind comparative study. *Obes Surg.* 2010;20(12):1642-6. PMID: 20390374
114. Catalano MF, Rudic G, Anderson AJ, et al. Weight gain after bariatric surgery as a result of a large gastric stoma: endotherapy with sodium morrhuate may prevent the need for surgical revision. *Gastrointest Endosc.* 2007;66(2):240-5. PMID: 17331511
115. Thompson CC, Slattery J, Bundga ME, et al. Peroral endoscopic reduction of dilated gastrojejunal anastomosis after Roux-en-Y gastric bypass: a possible new option for patients with weight regain. *Surg Endosc.* 2006;20(11):1744-8. PMID: 17024527
116. Ryou M, Mullady DK, Lautz DB, et al. Pilot study evaluating technical feasibility and early outcomes of second-generation endosurgical platform for treatment of weight regain after gastric bypass surgery. *Surg Obes Relat Dis.* 2009;5(4):450-4. PMID: 19632645
117. Rodriguez-Grunert L, Galvao Neto MP, Alamo M, et al. First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. *Surg Obes Relat Dis.* 2008;4(1):55-9. PMID: 18201671
118. Deviere J, Ojeda Valdes G, Cuevas Herrera L, et al. Safety, feasibility and weight loss after transoral gastroplasty: First human multicenter study. *Surg Endosc.* 2008;22(3):589-98. PMID: 17973163
119. Fogel R, De Fogel J, Bonilla Y, et al. Clinical experience of transoral suturing for an endoluminal vertical gastroplasty: 1-year follow-up in 64 patients. *Gastrointest Endosc.* 2008;68(1):51-8. PMID: 18355825
120. Moreno C, Closset J, Dugardeyn S, et al. Transoral gastroplasty is safe, feasible, and induces significant weight loss in morbidly obese patients: results of the second human pilot study. *Endoscopy.* 2008;40(5):406-13. PMID: 18459077
121. Mikami D, Needleman B, Narula V, et al. Natural orifice surgery: initial US experience utilizing the StomaphyX device to reduce gastric pouches after Roux-en-Y gastric bypass. *Surg Endosc.* 2010;24(1):223-8. PMID: 19633885
122. de Jonge C, Rensen SS, Verdam FJ, et al. Endoscopic duodenal-jejunal bypass liner rapidly improves type 2 diabetes. *Obes Surg.* 2013;23(9):1354-60. PMID: 23526068
123. Ryou M, Ryan MB, Thompson CC. Current status of endoluminal bariatric procedures for primary and revision indications. *Gastrointest Endosc Clin N Am.* 2011;21:315-33. PMID: 21569983
124. Espinos JC, Turro R, Mata A, et al. Early experience with the Incisionless Operating Platform (IOP) for the treatment of obesity : the Primary Obesity Surgery Endolumenal (POSE) procedure. *Obes Surg.* 2013;23(9):1375-83. PMID: 23591548
125. Dakin GF, Eid G, Mikami D, et al. Endoluminal revision of gastric bypass for weight regain--a systematic review. *Surg Obes Relat Dis.* 2013;9(3):335-42. PMID: 23561960
126. Mafort TT, Madeira E, Madeira M, et al. Six-month intragastric balloon treatment for obesity improves lung function, body composition, and metabolic syndrome. *Obes Surg.* 2014;24(2):232-40. PMID: 23949905
127. Mion F, Ibrahim M, Marjoux S, et al. Swallowable Obalon(R) gastric balloons as an aid for weight loss: a pilot feasibility study. *Obes Surg.* 2013;23(5):730-3. PMID: 23512445
128. Peker Y, Coskun H, Bozkurt S, et al. Comparison of results of laparoscopic gastric banding and consecutive intragastric balloon application at 18 months: a clinical

prospective study. *J Laparoendosc Adv Surg Tech A.* 2011;21(6):471-5. PMID: 21612448
129. Nikolic M, Mirosevic G, Ljubicic N, et al. Obesity treatment using a Bioenterics intragastric balloon (BIB)--preliminary Croatian results. *Obes Surg.* 2011;21(8):1305-10. PMID: 20352525
130. Forssell H, Noren E. A novel endoscopic weight loss therapy using gastric aspiration: results after 6 months. *Endoscopy.* 2015;47(1):68-71. PMID: 25268305
131. Zorron R, Veltzke-Schlieker W, Adler A, et al. Endoscopic sleeve gastroplasty using Apollo Overstitch as a bridging procedure for superobese and high risk patients. *Endoscopy.* 2018;50(1):81-83. PMID: 29041019
132. Sullivan S, Swain JM, Woodman G, et al. Randomized sham-controlled trial evaluating efficacy and safety of endoscopic gastric plication for primary obesity: The ESSENTIAL trial. *Obesity (Silver Spring).* 2017;25(2):294-301. PMID: 28000425
133. Talebpour M, Sadid D, Talebpour A, et al. Comparison of Short-Term Effectiveness and Postoperative Complications: Laparoscopic Gastric Plication vs Laparoscopic Sleeve Gastrectomy. *Obes Surg.* 2018;28(4):996-1001. PMID: 29043548
134. Ji Y, Wang Y, Zhu J, et al. A systematic review of gastric plication for the treatment of obesity. *Surg Obes Relat Dis.* 2014;10(6):1226-32. PMID: 24582413
135. Talebpour M, Motamedi SM, Talebpour A, et al. Twelve year experience of laparoscopic gastric plication in morbid obesity: development of the technique and patient outcomes. *Ann Surg Innov Res.* 2012;6:7. PMID: 22913751
136. Abdelbaki TN, Huang CK, Ramos A, et al. Gastric plication for morbid obesity: a systematic review. *Obes Surg.* 2012;22(10):1633-9. PMID: 22960951
137. Pattanshetti S, Tai CM, Yen YC, et al. Laparoscopic adjustable gastric banded plication: evolution of procedure and 2-year results. *Obes Surg.* 2013;23(11):1934-8. PMID: 24013809
138. Ahluwalia JS, Kuo HC, Chang PC, et al. Standardized Technique of Laparoscopic Adjustable Gastric Banded Plication with 4-Year Results. *Obes Surg.* 2015;25(9):1756-7. PMID: 26130177
139. Mognol P, Chosidow D, Marmuse JP. Laparoscopic conversion of laparoscopic gastric banding to Roux-en-Y gastric bypass: a review of 70 patients. *Obes Surg.* 2004;14(10):1349-53. PMID: 15603650
140. Brolin RE, Cody RP. Weight loss outcome of revisional bariatric operations varies according to the primary procedure. *Ann Surg.* 2008;248:227-32. PMID: 18650632
141. Bueter M, Thalheimer A, Wierlemann A, et al. Reoperations after gastric banding: replacement or alternative procedures? *Surg Endosc.* 2009;23(2):334-40. PMID: 18443872
142. Fehervari M, Banh S, Varma P, et al. Weight loss specific to indication, remission of diabetes, and short-term complications after sleeve gastrectomy conversion to Roux-en-Y gastric bypass: a systematic review and meta-analysis. *Surg Obes Relat Dis.* 2023;19(4):384-95. PMID: 36581551
143. Mann JP, Jakes AD, Hayden JD, et al. Systematic Review of Definitions of Failure in Revisional Bariatric Surgery. *Obes Surg.* 2014. PMID: 25515500
144. Vitiello A, Berardi G, Peltrini R, et al. One-anastomosis gastric bypass (OAGB) versus Roux-en-Y gastric bypass (RYGB) as revisional procedures after failed laparoscopic sleeve gastrectomy (LSG): systematic review and meta-analysis of comparative studies. *Langenbecks Arch Surg.* 2023;408(1):440. PMID: 37980292
145. Franken RJ, Franken J, Sluiter NR, et al. Efficacy and safety of revisional treatments for weight regain or insufficient weight loss after Roux-en-Y gastric bypass: A systematic

review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2023;24(10):e13607. PMID: 37515352
146. Kermansaravi M, Shahmiri SS, DavarpanahJazi AH, et al. One Anastomosis/Mini-Gastric Bypass (OAGB/MGB) as Revisional Surgery Following Primary Restrictive Bariatric Procedures: a Systematic Review and Meta-Analysis. *Obes Surg.* 2021;31(1):370-83. PMID: 33118133
147. Parmar CD, Gan J, Stier C, et al. One Anastomosis/Mini Gastric Bypass (OAGB-MGB) as revisional bariatric surgery after failed primary adjustable gastric band (LAGB) and sleeve gastrectomy (SG): A systematic review of 1075 patients. *Int J Surg.* 2020;81:32-38. PMID: 32738545
148. Dang JT, Switzer NJ, Wu J, et al. Gastric Band Removal in Revisional Bariatric Surgery, One-Step Versus Two-Step: a Systematic Review and Meta-analysis. *Obes Surg.* 2016;26(4):866-73. PMID: 26843080
149. Sudan R, Nguyen NT, Hutter MM, et al. Morbidity, mortality, and weight loss outcomes after reoperative bariatric surgery in the USA. *J Gastrointest Surg.* 2015;19(1):171-9. PMID: 25186073
150. Brethauer SA, Kothari S, Sudan R, et al. Systematic review on reoperative bariatric surgery: American Society for Metabolic and Bariatric Surgery Revision Task Force. *Surg Obes Relat Dis.* 2014;10(5):952-72. PMID: 24776071
151. Forsell P, Hallerback B, Glise H, et al. Complications following Swedish adjustable gastric banding: a long-term follow-up. *Obes Surg.* 1999;9(1):11-6. PMID: 10065574
152. Lanthaler M, Aigner F, Kinzl J, et al. Long-term results and complications following adjustable gastric banding. *Obes Surg.* 2010;20(8):1078-85. PMID: 20496124
153. Chiapaikeo D, Schultheis M, Protyniak B, et al. Analysis of reoperations after laparoscopic adjustable gastric banding. *JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons.* 2014;18(4). PMID: 25516707
154. Buchwald H, Buchwald JN, McGlennon TW. Systematic review and meta-analysis of medium-term outcomes after banded Roux-en-Y gastric bypass. *Obes Surg.* 2014;24(9):1536-51. PMID: 25001288
155. Gero D, Dayer-Jankechova A, Worreth M, et al. Laparoscopic gastric banding outcomes do not depend on device or technique. long-term results of a prospective randomized study comparing the Lapband(R) and the SAGB(R). *Obes Surg.* 2014;24(1):114-22. PMID: 24068617
156. Arapis K, Chosidow D, Lehmann M, et al. Long-term results of adjustable gastric banding in a cohort of 186 super-obese patients with a BMI>/= 50 kg/m2. *J Visc Surg.* 2012;149:e143-52. PMID: 22386891
157. Perathoner A, Zitt M, Lanthaler M, et al. Long-term follow-up evaluation of revisional gastric bypass after failed adjustable gastric banding. *Surg Endosc.* 2013;27(11):4305-12. PMID: 23807753
158. Cherian PT, Goussous G, Ashori F, et al. Band erosion after laparoscopic gastric banding: a retrospective analysis of 865 patients over 5 years. *Surg Endosc.* 2010;24(8):2031-8. PMID: 20177941
159. Rubenstein RB. Laparoscopic adjustable gastric banding at a U.S. center with up to 3-year follow-up. *Obes Surg.* 2002;12(3):380-4. PMID: 12082892
160. Avriel A, Warner E, Avinoach E, et al. Major respiratory adverse events after laparascopic gastric banding surgery for morbid obesity. *Respir Med.* 2012;106:1192-8. PMID: 22673900

161. Mendes-Castro A, Montenegro J, Cardoso JF, et al. Laparoscopic Adjustable Gastric Band: Complications, Removal and Revision in a Portuguese Highly Differentiated Obesity Treatment Center. *Acta medica portuguesa.* 2015;28(6):735-40. PMID: 26849758
162. Aarts E, Koehestanie P, Dogan K, et al. Revisional surgery after failed gastric banding: results of one-stage conversion to RYGB in 195 patients. *Surg Obes Relat Dis.* 2014;10(6):1077-83. PMID: 25443075
163. Carr WR, Jennings NA, Boyle M, et al. A retrospective comparison of early results of conversion of failed gastric banding to sleeve gastrectomy or gastric bypass. *Surg Obes Relat Dis.* 2015;11(2):379-84. PMID: 25443072
164. Emous M, Apers J, Hoff C, et al. Conversion of failed laparoscopic adjustable gastric banding to Roux-en-Y gastric bypass is safe as a single-step procedure. *Surg Endosc.* 2015;29(8):2217-23. PMID: 25318370
165. Fernando Santos B, Wallaert JB, Trus TL. Band removal and conversion to sleeve or bypass: are they equally safe? *Surg Endosc.* 2014;28(11):3086-91. PMID: 24848153
166. Zhou X, Zeng C. Diabetes remission of bariatric surgery and nonsurgical treatments in type 2 diabetes patients who failure to meet the criteria for surgery: a systematic review and meta-analysis. *BMC Endocr Disord.* 2023;23(1):46. PMID: 36810013
167. Muller-Stich BP, Senft JD, Warschkow R, et al. Surgical versus medical treatment of type 2 diabetes mellitus in nonseverely obese patients: a systematic review and meta-analysis. *Ann Surg.* 2015;261(3):421-9. PMID: 25405560
168. Maglione MA, Gibbons MM, Livhits M, et al. Bariatric Surgery and Nonsurgical Therapy in Adults With Metabolic Conditions and a Body Mass Index of 30.0 to 34.9 kg/m2 [Internet]. 2013; AHRQ Comparative Effectiveness Reviews. Jun. Report No.: 12(13)-EHC139-EF. PMID: 23865093
169. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA.* 2013;309:2240-9. PMID: 23736733
170. Parikh M, Issa R, Vieira D, et al. Role of bariatric surgery as treatment for type 2 diabetes in patients who do not meet current NIH criteria: a systematic review and meta-analysis. *J Am Coll Surg.* 2013;217(3):527-32. PMID: 23890843
171. Ding SA, Simonson DC, Wewalka M, et al. Adjustable Gastric Band Surgery or Medical Management in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *The Journal of clinical endocrinology and metabolism.* 2015;100(7):2546-56. PMID: 25909333
172. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet.* 2015;386(9997):964-73. PMID: 26369473
173. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from the The Obesity Expert Panel, 2013. *Obesity (Silver Spring).* 2014;22 Suppl 2:S5-39. PMID: 24961825
174. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus

Comprehensive Care Plan-2022 Update. *Endocr Pract.* 2022;28(10):923-1049. PMID: 35963508
175. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Obesity (Silver Spring).* 2013;21 Suppl 1:S1-27. PMID: 23529939
176. Mechanick JI, Apovian C, Brethauer S, et al. Clinical Practice Guidelines for the Perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: Co-sponsored by the American Association of Clinical Endocrinologists/American College of Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association and American Society of Anesthesiologists - executive summary.
. *Endocr Pract.* 2019;25(12):1346-59. PMID: 31682518
177. Institute for Clinical Systems Improvement (ICSI). National Guideline Clearinghouse. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. [cited 12/14/2023]. 'Available from:' https://www.guideline.gov/summaries/summary/48544.
178. Wu Z, Gao Z, Qiao Y, et al. Long-Term Results of Bariatric Surgery in Adolescents with at Least 5 Years of Follow-up: a Systematic Review and Meta-Analysis. *Obes Surg.* 2023;33(6):1730-45. PMID: 37115416
179. Washington State Health Technology Assessment: Pediatric Bariatric Surgery, 2007. [cited 12/14/2023]. 'Available from:' https://www.hca.wa.gov/assets/program/pbs_final_evidence_report[1].pdf.
180. Black JA, White B, Viner RM, et al. Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2013;14(8):634-44. PMID: 23577666
181. Washington State Health Technology Assessment: Bariatric Surgery, 2015. [cited 12/14/2023]. 'Available from:' https://www.hca.wa.gov/assets/program/bariatric_final_rpt_040315[1].pdf.
182. Childerhose JE, Tarini BA. Understanding Outcomes in Adolescent Bariatric Surgery. *Pediatrics.* 2015;136(2):e312-4. PMID: 26216327
183. Paulus GF, de Vaan LE, Verdam FJ, et al. Bariatric surgery in morbidly obese adolescents: a systematic review and meta-analysis. *Obes Surg.* 2015;25(5):860-78. PMID: 25697125
184. Pedroso FE, Angriman F, Endo A, et al. Weight loss after bariatric surgery in obese adolescents: a systematic review and meta-analysis. *Surg Obes Relat Dis.* 2017. PMID: 29248351
185. Qi L, Guo Y, Liu CQ, et al. Effects of bariatric surgery on glycemic and lipid metabolism, surgical complication and quality of life in adolescents with obesity: a systematic review and meta-analysis. *Surg Obes Relat Dis.* 2017;13(12):2037-55. PMID: 29079384
186. Shoar S, Mahmoudzadeh H, Naderan M, et al. Long-Term Outcome of Bariatric Surgery in Morbidly Obese Adolescents: a Systematic Review and Meta-Analysis of 950 Patients with a Minimum of 3 years Follow-Up. *Obes Surg.* 2017;27(12):3110-17. PMID: 28573535
187. Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics.* 2023;151(2). PMID: 36622115

188. O'Brien PE, Sawyer SM, Laurie C, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trial. *JAMA.* 2010;303(6):519-26. PMID: 20145228
189. Nadler EP, Youn HA, Ren CJ, et al. An update on 73 US obese pediatric patients treated with laparoscopic adjustable gastric banding: comorbidity resolution and compliance data. *J Pediatr Surg.* 2008;43(1):141-6. PMID: 18206472
190. Nadler EP, Reddy S, Isenalumhe A, et al. Laparoscopic adjustable gastric banding for morbidly obese adolescents affects android fat loss, resolution of comorbidities, and improved metabolic status. *J Am Coll Surg.* 2009;209(5):638-44. PMID: 19854406
191. Holterman AX, Browne A, Tussing L, et al. A prospective trial for laparoscopic adjustable gastric banding in morbidly obese adolescents: an interim report of weight loss, metabolic and quality of life outcomes. *J Pediatr Surg.* 2010;45(1):74-8; discussion 78-9. PMID: 20105583
192. Inge TH, Zeller MH, Jenkins TM, et al. Perioperative outcomes of adolescents undergoing bariatric surgery: the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. *JAMA Pediatr.* 2014;168:47-53. PMID: 24189578
193. Alqahtani AR, Elahmedi M, Abdurabu HY, et al. Ten-Year Outcomes of Children and Adolescents Who Underwent Sleeve Gastrectomy: Weight Loss, Comorbidity Resolution, Adverse Events, and Growth Velocity. *J Am Coll Surg.* 2021;233(6):657-64. PMID: 34563670
194. Lanthaler M, Sieb M, Strasser S, et al. Disappointing mid-term results after laparoscopic gastric banding in young patients. *Surg Obes Relat Dis.* 2009;5(2):218-23. PMID: 18849198
195. Mittermair R, Aigner F, Obermuller S. High complication rate after Swedish adjustable gastric banding in younger patients < or =25 years. *Obes Surg.* 2009;19(4):446-50. PMID: 18998192
196. Summaries for patients. Treating obesity with drugs and surgery: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2005;142:I55. PMID: 15809458
197. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation.* 2013;128(15):1689-712. PMID: 24016455
198. SAGES guideline for clinical application of laparoscopic bariatric surgery. *Surg Endosc.* 2008;22(10):2281-300. PMID: 18791862
199. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism.* 2017;102(3):709-57. PMID: 28359099
200. Fitch A, Fox C, Bauerly K, Gross A, Heim C, Judge-Dietz J, Kaufman T, Krych E, Kumar S, Landin D, Larson J, Leslie D, Martens N, Monaghan-Beery N, Newell T, O'Connor P, Spaniol A, Thomas A, W ebb B. Prevention and management of obesity for children and adolescents. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jul. 94 p. [cited 12/14/2023]. 'Available from:' https://www.guideline.gov/summaries/summary/47102.
201. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128 Suppl 5:S213-56. PMID: 22084329
202. Pratt JSA, Browne A, Browne NT, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obes Relat Dis.* 2018;14(7):882-901. PMID: 30077361

203. Oor JE, Roks DJ, Unlu C, et al. Laparoscopic sleeve gastrectomy and gastroesophageal reflux disease: a systematic review and meta-analysis. *American journal of surgery.* 2016;211(1):250-67. PMID: 26341463
204. Li J, Lai D, Wu D. Laparoscopic Roux-en-Y Gastric Bypass Versus Laparoscopic Sleeve Gastrectomy to Treat Morbid Obesity-Related Comorbidities: a Systematic Review and Meta-analysis. *Obes Surg.* 2016;26(2):429-42. PMID: 26661105
205. Frezza EE, Ikramuddin S, Gourash W, et al. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc.* 2002;16(7):1027-31. PMID: 11984683
206. Smith SC, Edwards CB, Goodman GN. Symptomatic and clinical improvement in morbidly obese patients with gastroesophageal reflux disease following Roux-en-Y gastric bypass. *Obes Surg.* 1997;7(6):479-84. PMID: 9730504
207. Patterson EJ, Davis DG, Khajanchee Y, et al. Comparison of objective outcomes following laparoscopic Nissen fundoplication versus laparoscopic gastric bypass in the morbidly obese with heartburn. *Surg Endosc.* 2003;17(10):1561-5. PMID: 12874685
208. Raftopoulos I, Awais O, Courcoulas AP, et al. Laparoscopic gastric bypass after antireflux surgery for the treatment of gastroesophageal reflux in morbidly obese patients: initial experience. *Obes Surg.* 2004;14(10):1373-80. PMID: 15603654
209. Varela JE, Hinojosa MW, Nguyen NT. Laparoscopic fundoplication compared with laparoscopic gastric bypass in morbidly obese patients with gastroesophageal reflux disease. *Surg Obes Relat Dis.* 2009;5(2):139-43. PMID: 18996768
210. Perry Y, Courcoulas AP, Fernando HC, et al. Laparoscopic Roux-en-Y gastric bypass for recalcitrant gastroesophageal reflux disease in morbidly obese patients. *JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons.* 2004;8(1):19-23. PMID: 14974657
211. Gutschow CA, Collet P, Prenzel K, et al. Long-term results and gastroesophageal reflux in a series of laparoscopic adjustable gastric banding. *J Gastrointest Surg.* 2005;9(7):941-8. PMID: 16137589
212. Peterli R, Borbely Y, Kern B, et al. Early results of the Swiss Multicentre Bypass or Sleeve Study (SM-BOSS): a prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. *Ann Surg.* 2013;258(5):690-4; discussion 95. PMID: 23989054
213. Himpens J, Dobbeleir J, Peeters G. Long-term results of laparoscopic sleeve gastrectomy for obesity. *Ann Surg.* 2010;252(2):319-24. PMID: 20622654
214. Barr AC, Frelich MJ, Bosler ME, et al. GERD and acid reduction medication use following gastric bypass and sleeve gastrectomy. *Surg Endosc.* 2017;31(1):410-15. PMID: 27287901
215. Celio AC, Wu Q, Kasten KR, et al. Comparative effectiveness of Roux-en-Y gastric bypass and sleeve gastrectomy in super obese patients. *Surg Endosc.* 2017;31(1):317-23. PMID: 27287899
216. Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc.* 2010;24(11):2647-69. PMID: 20725747
217. Chakhtoura MT, Nakhoul NN, Shawwa K, et al. Hypovitaminosis D in bariatric surgery: A systematic review of observational studies. *Metabolism: clinical and experimental.* 2016;65(4):574-85. PMID: 26805016
218. Thongprayoon C, Cheungpasitporn W, Vijayvargiya P, et al. The risk of kidney stones following bariatric surgery: a systematic review and meta-analysis. *Renal failure.* 2016;38(3):424-30. PMID: 26803902

219. D'Hoedt A, Vanuytsel T. Dumping syndrome after bariatric surgery: prevalence, pathophysiology and role in weight reduction - a systematic review. *Acta Gastroenterol Belg.* 2023;86(3):417-27. PMID: 37814558
220. Nocca D, Krawczykowsky D, Bomans B, et al. A prospective multicenter study of 163 sleeve gastrectomies: results at 1 and 2 years. *Obes Surg.* 2008;18(5):560-5. PMID: 18317859
221. Lalor PF, Tucker ON, Szomstein S, et al. Complications after laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis.* 2008;4(1):33-8. PMID: 17981515
222. Frezza EE, Reddy S, Gee LL, et al. Complications after sleeve gastrectomy for morbid obesity. *Obes Surg.* 2009;19(6):684-7. PMID: 18923879
223. Himpens J, Dapri G, Cadiere GB. A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: results after 1 and 3 years. *Obes Surg.* 2006;16(11):1450-6. PMID: 17132410
224. Shang E, Hasenberg T, Magdeburg R, et al. First experiences with A circular stapled gastro-jejunostomy by a new transorally introducible stapler system in laparoscopic Roux-en-Y gastric bypass. *Obes Surg.* 2009;19(2):230-6. PMID: 18758872

CODES

NOTE: Code 43843 should not be reported if there is a more specific bariatric surgery code within code range listed below.

Codes	Number	Description
CPT	0813T	Esophagogastroduodenoscopy, flexible, transoral, with volume adjustment of intragastric bariatric balloon
	43290	Esophagogastroduodenoscopy, flexible, transoral; with deployment of intragastric bariatric balloon
	43291	Esophagogastroduodenoscopy, flexible, transoral; with removal of intragastric bariatric balloon(s)
	43631	Gastrectomy, partial, distal; with gastroduodenostomy
	43632	;with gastrojejunostomy
	43633	;with roux-en-Y reconstruction
	43634	;with formation of intestinal pouch
	43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
	43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
	43659	Unlisted laparoscopy procedure, stomach
	43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (gastric band and subcutaneous port components)
	43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only
	43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only
	43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only
	43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components
	43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (ie, sleeve gastrectomy)
	43820	Gastrojejunostomy; without vagotomy

Codes	Number	Description
	43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical banded gastroplasty
	43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical banded gastroplasty
	43845	Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileoileostomy (50 to 100 cm common channel) to limit absorption (biliopancreatic diversion with duodenal switch)
	43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy
	43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption
	43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)
	43860	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction, with or without partial gastrectomy or intestine resection; without vagotomy
	43865	;with vagotomy
	43886	Gastric restrictive procedure, open; revision of subcutaneous port component only
	43887	Gastric restrictive procedure, open; removal of subcutaneous port component only
	43888	Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only
HCPCS	C9784	Gastric restrictive procedure, endoscopic sleeve gastroplasty, with esophagogastroduodenoscopy and intraluminal tube insertion, if performed, including all system and tissue anchoring components
	C9785	Endoscopic outlet reduction, gastric pouch application, with endoscopy and intraluminal tube insertion, if performed, including all system and tissue anchoring components
	S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline

Date of Origin: *January 1996*

Medical Policy Manual Surgery, Policy No. 60

Reduction Mammaplasty

Effective: November 1, 2022

Next Review: July 2023
Last Review: September 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Reduction mammaplasty is the surgical excision of a substantial portion of the breast, including the skin and underlying glandular tissue, until a clinically normal size is obtained.

MEDICAL POLICY CRITERIA

Notes:

- This policy is not applicable when there has been a prior mastectomy for which the Women's Health & Cancer Rights Act applies. The Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants policy (Surgery, Policy No. 40 – see Cross References) may be applicable. Please refer to the Surgery, Policy No. 40 for reconstruction after partial or complete mastectomy.
- This policy is not intended to address treatment of gender dysphoria which is addressed in the Transgender Services medical policy (Medicine, Policy No. 153 – see cross references), which may be applicable.

I. Reduction mammaplasty may be considered **medically necessary** when one or more of the following are met:

A. As a preparatory first stage procedure preceding a nipple-sparing mastectomy,

when the amount of breast tissue removed from each breast is at least the minimum in grams per breast for the patient's body surface area (in meters squared using the Mosteller formula) according to the Schnur Sliding Scale (see Policy Guidelines for body surface area/breast weight table); or

B. When all of the following criteria (1. - 3.) are met:

1. The patient is aged 18 years or older; and
2. The amount of breast tissue removed from each breast, not including fat removed by liposuction, must be at least the minimum in grams per breast for the patient's body surface area* according to the Schnur Sliding Scale (see Policy Guidelines), or, in cases of asymmetry where one breast meets criterion but the other breast does not, the combined weight of the tissue removed from both breasts must total at least twice the Schnur Sliding Scale minimum for the patient's body surface area (the health plan may review medical records to confirm the amount of breast tissue removed during the procedure); and
3. Two or more of the following clinical indications have been present for at least 12 months and have failed to respond to appropriate conservative therapy:
    a. Pain in the upper back, neck, shoulders, and/or arms, with all of the following documented in the medical records by the referring provider:
        i. The pain is of long-standing duration and increasing intensity; and
        ii. The pain has been evaluated to determine that it is not associated with another condition such as arthritis, if applicable; and
        iii. The pain is not relieved by at least three months of conservative therapy such as an appropriate support bra with wide straps, exercises, heat/cold treatments and appropriate non-steroidal anti-inflammatory agents/muscle relaxants.
    b. Shoulder grooving not responding to conservative treatment (e.g., wide-strap or support bra).
    c. Intertrigo between the pendulous breasts and the chest wall persisting despite at least three months of conservative dermatologic treatments (e.g., taking steps to eliminate friction, heat, and maceration by keeping skin cool and dry and where appropriate, antimycotic agents).
    d. Kyphosis documented by x-ray.
    e. Ulnar paresthesia not relieved by at least three months of conservative therapy such as an appropriate support bra with wide straps, range of motion exercises, physical therapy, and appropriate non-steroidal anti-inflammatory agents/muscle relaxants.

II. Reduction mammaplasty is considered **not medically necessary** when Criteria I. is not met.

III. Reduction mammaplasty for gynecomastia is considered **not medically necessary**.

IV. The use of liposuction as an additional procedure with breast reduction surgery is considered **not medically necessary**.

V. The use of liposuction as the sole procedure for breast reduction is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Mosteller formula: body surface area (m^2) = ([height (cm) x weight (kg)] / 3600)^{½} [1]

Click here for link to Body Surface Area Calculator

Schnur Sliding Scale

Body Surface Area (m^2) and Minimum Requirement for Breast Tissue Removal	
Body Surface Area m^2	**Grams per Breast of Minimum Breast Tissue to be Removed**
NOTE: When BSA is < 1.350 minimum is 199 grams	
1.350-1.374	199
1.375-1.399	208
1.400-1.424	218
1.425-1.449	227
1.450-1.474	238
1.475-1.499	249
1.500-1.524	260
1.525-1.549	272
1.550-1.574	284
1.575-1.599	297
1.600-1.624	310
1.625-1.649	324
1.650-1.674	338
1.675-1.699	354
1.700-1.724	370

1.725-1.749	386
1.750-1.774	404
1.775-1.799	422
1.800-1.824	441
1.825-1.849	461
1.850-1.874	482
1.875-1.899	504
1.900-1.924	527
1.925-1.949	550
1.950-1.974	575
1.975-1.999	601
2.000-2.024	628
2.025-2.049	657
2.050-2.074	687
2.075-2.099	717
2.100-2.124	750
2.125-2.149	784
2.150-2.174	819
2.175-2.199	856
2.200-2.224	895
2.225-2.249	935
2.250-2.274	978
2.275-2.299	1022
2.300-2.324	1068
2.325-2.349	1117

2.350-2.374	1167
2.375-2.399	1219
2.400-2.424	1275
2.425-2.449	1333
2.450-2.474	1393
2.475-2.499	1455
2.500-2.524	1522
2.525-2.549	1590
2.550 or greater	1662

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome:

1. Total amount of breast tissue to be removed, include if L/R or bilateral
2. Height and weight
3. Any two of the following detailed in chart notes, history and physical, physical therapy notes, radiologic exams, dermatology treatments notes, and/or any other clinical notes:
    A. Medical records by the referring physician, which include pain in the upper back, neck, shoulders and/or arms with documentation of long standing pain, and detailed notes regarding treatment with at least three months of conservative therapy, and that the pain is not associated with another diagnosis such as arthritis;
    B. Documentation or photograph of shoulder grooving with description of conservative treatment;
    C. Intertrigo despite three months detailed documentation of conservative therapy;
    D. X-ray showing kyphosis;
    E. Ulnar paresthesia despite three months documentation of conservative therapy and outcome with chart notes detailing specific treatment.

CROSS REFERENCES

1. Gender Affirming Interventions for Gender Dysphoria, Medicine, Policy No. 153
2. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
3. Mastectomy as a Treatment of Gynecomastia, Surgery, Policy No. 12.06
4. Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants, Surgery, Policy No. 40
5. Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells, Surgery, Policy No. 182

BACKGROUND

Female breast hypertrophy, or macromastia, is the development of abnormally large breasts in the female. This condition can cause significant clinical manifestations when the excessive breast weight adversely affects the supporting structures of the shoulders, neck and trunk. Macromastia is distinguished from large, normal breasts by the presence of persistent symptoms such as shoulder, neck, or back pain, shoulder grooving, or intertrigo. This condition can be improved and the associated signs and symptoms can be alleviated by reduction mammaplasty surgery.

EVIDENCE SUMMARY

The following literature appraisal is focused on the investigational technique of reduction mammaplasty by liposuction alone. In order to understand the impact on health outcomes of reduction mammaplasty by liposuction alone, prospective clinical trials are needed, comparing liposuction with standard reduction mammaplasty. These comparisons are necessary in order to understand the safety and efficacy of liposuction and to determine whether liposuction offers advantages over conventional surgical procedures with respect to patient satisfaction, complications, durability, and cosmesis.

While there are some published articles concerning the use of liposuction as the sole procedure for breast reduction, none compare the outcomes of liposuction alone to standard excisional reduction mammaplasty.[2-10] Examples of these articles are detailed below:

Moskovitz (2007) conducted a study of liposuction alone for treatment of macromastia in twenty-four African-American women due to their high risk for complex scar formation following standard excision mammaplasty.[8] The mean aspirate was 1075 cc of fat per breast; however, the before and after liposuction pictures indicate that the participants continued to support large breasts. Outcome measures included the SF-36, EuroQol, Multidimensional Body-Self Relations Questionnaire, McGill Pain Questionnaire and Breast-Related Symptoms Questionnaire. Statistical analysis demonstrated a significant improvement in breast-related symptoms and pain. This was a relatively small, non-randomized trial and patients were not blinded to the intervention. Conclusions concerning the effect of liposuction alone on breast-related symptoms in patients with macromastia cannot be made.

Jakubietz (2011) reported the indications and limitations of this procedure compared to conventional surgical excision.[9] Advantages included selective removal of fat, ease of procedure, and the advantages of less invasive procedures such as faster recovery time and reduced scarring. One disadvantage of liposuction alone included the inability to correct shape and ptosis, making aesthetic results optimal only for young patients. In addition, there are concerns about the extent to which subsequent breast imaging may be impaired, and the possible spread of cancer cells. The authors recommended caution when considering use of this technique.

In summary, high quality evidence on the use of liposuction for reduction mammaplasty has not been identified; comparative trials of sufficient size and duration are needed before any conclusions can be made about the use of this technique for breast reduction.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF PLASTIC SURGEONS

In 2011, the American Society of Plastic Surgeons (ASPS) released an evidence-based clinical practice guideline on the use of reduction mammaplasty.[11] Several clinical questions were addressed, including whether women who did not meet standard health insurance criteria for volume of breast resection experience postoperative relief. On the basis of a single study which compared satisfaction outcomes of women who met standard insurance criteria with women who did not meet such criteria, the society concluded that, “resection volume is not correlated to the degree of postoperative symptom relief.” The society recommended extending the option of reduction mammaplasty to this category of patient. However, among women not meeting standard criteria for resection volume, no comparisons were made between surgical and standard conservative treatment, limiting interpretation of the above findings. Additionally, these recommendations did not specifically address the safety and effectiveness of reduction mammaplasty by liposuction.

SUMMARY

Female breast hypertrophy, or macromastia, is the development of abnormally large breasts in the female, which can cause medical problems. There is enough research to show that reduction mammaplasty can improve health outcomes for certain patients with this condition. Therefore, reduction mammaplasty may be considered medically necessary when policy criteria are met. Reduction mammaplasty as treatment for macromastia is considered not medically necessary when policy criteria are not met.

There is not enough research to show that liposuction mammaplasty can improve health outcomes more than traditional mammaplasty techniques. Therefore, reduction mammaplasty by liposuction alone is considered investigational.

Gynecomastia refers to the benign enlargement of the male breast, mainly due to excessive growth of glandular tissue. Reduction mammaplasty (partial removal) for the treatment of gynecomastia is considered not medically necessary as the current standard of care is for the removal of most or all glandular tissue.

REFERENCES

1. Mosteller RD. Simplified calculation of body-surface area. *The New England journal of medicine.* 1987;317(17):1098. PMID: 3657876
2. Courtiss EH. Reduction mammaplasty by suction alone. *Plast Reconstr Surg.* 1993;92(7):1276-84; discussion 85-9. PMID: 8248402
3. Gray LN. Liposuction breast reduction. *Aesthetic Plast Surg.* 1998;22(3):159-62. PMID: 9618179
4. Matarasso A. Suction mammaplasty: the use of suction lipectomy to reduce large breasts. *Plast Reconstr Surg.* 2000;105(7):2604-7; discussion 08-10. PMID: 10845318
5. Sadove R. New observations in liposuction-only breast reduction. *Aesthetic Plast Surg.* 2005;29(1):28-31. PMID: 15759094
6. Habbema L. Breast reduction using liposuction with tumescent local anesthesia and powered cannulas. *Dermatol Surg.* 2009;35(1):41-50; discussion 50-2. PMID: 19076201
7. Abboud MH, Dibo SA. Power-Assisted Liposuction Mammaplasty (PALM): A New Technique for Breast Reduction. *Aesthetic surgery journal / the American Society for Aesthetic Plastic surgery.* 2016;36(1):35-48. PMID: 26208656

8. Moskovitz MJ, Baxt SA, Jain AK, et al. Liposuction breast reduction: a prospective trial in African American women. *Plast Reconstr Surg.* 2007;119(2):718-26; discussion 27-8. PMID: 17230112
9. Jakubietz RG, Jakubietz DF, Gruenert JG, et al. Breast reduction by liposuction in females. *Aesthetic Plast Surg.* 2011;35(3):402-7. PMID: 20976597
10. Auersvald A, Botti C, Botti G, et al. Liporeduction: A Faster and Safer Breast Remodeling Technique. *Plast Reconstr Surg.* 2022;149(3):549-58. PMID: 35196667
11. American Society of Plastic Surgeons. Evidence-based Clinical Practice Guideline: Reduction Mammaplasty. 2011. [cited 08/26/2022]. 'Available from:' http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/Reduction%20Mammaplasty_%20Evidence%20Based%20Guidelines_v5.pdf.
12. Schnur PL, Hoehn JG, Ilstrup DM, et al. Reduction mammaplasty: cosmetic or reconstructive procedure? *Ann Plast Surg.* 1991;27(3):232-7. PMID: 1952749
13. Schnur PL, Schnur DP, Petty PM, et al. Reduction mammaplasty: an outcome study. *Plast Reconstr Surg.* 1997;100(4):875-83. PMID: 9290655

CODES

NOTE: Nipple/areola reconstruction (CPT 19350) is considered an included component of CPT 19318 and not separately allowable.

Codes	Number	Description
CPT	15877	Suction assisted lipectomy; trunk
	19318	Breast reduction
HCPCS	None	

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 74

Vagus Nerve Stimulation

Effective: January 1, 2024

Next Review: April 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vagus nerve stimulation (VNS) involves implantation of an infraclavicular pulse generator that sends weak electric impulses to the left vagus nerve within the carotid sheath in the neck. Transcutaneous (nonimplantable) vagus nerve stimulation has also been proposed as a treatment of a number of conditions.

MEDICAL POLICY CRITERIA

Note: This policy does not apply to vagus nerve **blocking** therapy. See Cross References.

I. Implantable vagus nerve stimulation (VNS) may be considered **medically necessary** as a treatment of medically refractory seizures. Patients must have tried and been unresponsive to or intolerant of at least two antiepileptic drugs.

II. Revision(s) to an existing stimulator may be considered **medically necessary** after the device has been placed.

III. The replacement of all or part of an existing stimulator and/or generator is considered **medically necessary** when the existing stimulator and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

IV. Replacement of all or part of an existing stimulator and/or generator is considered **not medically necessary** when Criterion III. is not met.

V. Implantable VNS is considered **investigational** when Criterion I. is not met and for all other indications, including but not limited to essential tremors.

VI. Transcutaneous and non-implantable vagus nerve stimulation devices are considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Antiepileptic medications given and response

CROSS REFERENCES

1. Gastric Electrical Stimulation; Surgery, Policy No. 111
2. Responsive Neurostimulation, Surgery, Policy No. 216

BACKGROUND

An implanted VNS device delivers mild electronic impulses via two electrodes connected to the generator and wrapped around the vagus nerve. The stimulator may be programmed in advance or may be activated on demand by placing a magnet against the generator implantation site.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this evidence review.

REGULATORY STATUS

Implantable VNS Devices

Several VNS therapy systems by Cyberonics Inc. have pre-market approval (PMA) from the U.S. Food and Drug Administration (FDA) for treatment of refractory partial-onset seizures and chronic or recurrent depression, when certain criteria are met. For example, in 1997, the

NeuroCybernetic Prosthesis (NCP®) system was approved for use in conjunction with drugs or surgery “as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures.” The VNS Therapy™ System was approved in 2005 “for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.” FDA product code: LYJ

Non-implantable VNS Devices

Cerbomed has developed a transcutaneous VNS (t-VNS®) system, NEMOS®, that uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Patients self-administer electric stimulation for several hours a day; no surgical procedure is required. The device has not been FDA approved for use in the US.

electroCore, LLC has developed a non-invasive VNS (gammaCore®) released for use by the FDA in April of 2017. The device is indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck. Product code: PKR

EVIDENCE SUMMARY

VAGUS NERVE STIMULATORS

In order to assess the safety and effectiveness of vagus nerve stimulation (VNS), particularly for indications in which the primary outcomes are subjective (e.g., pain reduction, improved mood, improved functioning), well-designed, randomized controlled trials (RCTs) are necessary. Such trials include double-blinding, appropriate randomization, an appropriate control group (i.e., sham VNS or standard medical treatment), large study populations, adequate follow-up time, and adverse events reporting.

MEDICALLY REFRACTORY SEIZURES

The criteria for VNS for seizures are based on a 1998 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) assessment[1], a 2015 Cochrane review[2] which included the five published double-blind randomized controlled trials (RCTs)[3-5], and numerous case series, retrospective reviews, and other non-randomized studies on adult[6-11], pediatric,[12-19] or mixed[20-25] patient populations. More recently, a 2020 Washington Health Care Authority Health Technology Assessment prepared by the Oregon Health and Science University Center for Evidence-based Policy was published on vagal nerve stimulation for the treatment of epilepsy and depression. All three reviews concluded that VNS reduced seizure frequency in patients with drug resistant partial-onset seizures.

The RCTs were large, well-designed multicenter trials that reported an approximate 25% reduction in partial-onset seizure frequency following three months of VNS. Adverse effects were mild and consisted primarily of hoarseness or voice change during “on” periods of stimulation. The remaining literature is limited to numerous non-randomized trials. Although evidence from non-randomized studies are generally considered unreliable for assessing the safety and effectiveness of VNS, the findings from these numerous studies have consistently shown significantly reduced seizure activity in patients with drug-resistant epilepsy. In addition,

clinical practice guidelines from the American Academy of Neurology stated that "…sufficient evidence exists to rank VNS for epilepsy as effective and safe…"[26] Thus, despite the lack of RCTs in the published clinical evidence, VNS has become a recognized standard of care for treatment in selected patients with medically refractory seizures.

REFRACTORY DEPRESSION

Technology Assessments

The 2020 Washington Health Care Authority Health Technology Assessment discussed above in relation to epilepsy also evaluated the effectiveness of VNS in the treatment of refractory depression.[27] Five studies met inclusion criteria, two of which are RCTs. The RCTs were rated to be at moderate risk of bias, one of the nonrandomized studies was at moderate risk of bias, and the two remaining nonrandomized studies had a high risk of bias. Comparators were low-stimulation VNS, sham VNS, and treatment as usual. Two of the RCTs and one of the nonrandomized studies reported on depression severity. No statistically significant differences were reported in the RCTs. In the nonrandomized study, the reported difference in reduction in depressive symptoms was significantly significant, with a greater reduction in the in the VNS plus treatment as usual group. One RCT each reported that high-stimulation VNS had higher rates of response than low-stimulation VNS and VNS and sham VNS had similar rates of response, and a nonrandomized study reported that VNS with TAU may be associated with higher rates of response than TAU alone. Across studies, no differences were reported in rates of suicide, except for one nonrandomized study that reported that VNS may be associated with higher rates of attempted suicide or self-inflicted injury (very-low-quality of evidence). Harms that were noted to be higher in VNS than sham VNS were voice alteration or hoarseness and cough.

A 2006 BCBSA TEC Assessment[28], evaluated the effectiveness of VNS in the treatment of refractory depression compared with continued medical management. The evidence consisted of one case series, one observational study, and one randomized controlled trial. The assessment found that "overall, the evidence supporting efficacy of VNS is not strong."

The randomized controlled trial (RCT) of 221 patients that compared VNS with a sham control (implanted but inactivated VNS) did not show a statistically significant difference between VNS and continued medical therapy in relieving depression symptoms.[29-31] The trial was short and possibly underpowered to detect a smaller amount of VNS benefit. In addition, the adequacy of blinding was questionable. The observational study included a subset of 205 VNS treated patients from the RCT described above who were followed long-term. A separately recruited control group of 124 patients received ongoing treatment for depression.[29, 32] Although the study findings favored the VNS therapy group, this evidence is considered unreliable due to significant methodological limitations including but not limited to the following: 1) Non-randomized allocation of treatment does not control for possible between-group differences in individual patient characteristics; thus, it cannot be ruled out that these differences, rather than the treatments received, were responsible for the observed outcomes; 2) The lack of a sham study group does not control for the expected placebo effects; 3) The inadequate, non-concurrent comparison group does not permit conclusions on the efficacy of VNS compared with placebo or other treatment options, 4) The differences in sites of care between VNS treated patients and controls may introduce response bias. (Analysis performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness.); and 5)

Differences in concomitant therapy changes cannot be ruled out as an explanation of the observed outcomes.

The case series (Study D-01) was a feasibility study of 60 patients receiving VNS; improvement was reported in depression scores.[33] It is uncertain whether loss to follow-up was addressed adequately in the analysis. In addition, the case series is limited by the lack of an appropriate comparison group.

Systematic Reviews

Bottomley (2020) reported results of a systematic review and meta-analysis of two RCTs (Rush [2005] and Aaronson [2013]), 16 single-arm studies, and four nonrandomized comparative studies of VNS for treatment-resistant depression.[34] The meta-analysis calculated overall pooled effect estimates for VNS and treatment-as-usual groups, respectively, but did not perform quantitative analysis of comparative treatment effects. There was statistically significant heterogeneity. Thus, this meta-analysis provides insufficient evidence to permit comparisons between VNS and the control groups.

In a meta-analysis that included 14 studies, Martin (2012) reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment.[35] However, results from a meta-regression to predict each study's effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity ($p<0.0001$). The authors concluded that current data was insufficient to determine whether VNS is an effective treatment for depression and noted that positive results from uncontrolled studies may be due to placebo effect.

A 2008 systematic review and meta-analysis for VNS of treatment-resistant depression identified no new RCTs since the pivotal RCT described above, which the authors determined to be inconclusive.[36] As noted above, RCTs are considered the appropriate design for studying VNS for any indication. However, this review also included 17 nonrandomized, open studies which found VNS to be associated with a reduction in depressive symptoms. The authors concluded that, while open studies have reported promising results, further clinical trials are needed to study the mechanism of action and cost-effectiveness, and to confirm the efficacy of VNS in treatment-resistant depression.

Randomized Controlled Trials

No randomized controlled trials published after the search dates of the Washington Health Care Authority Health Technology Assessment were identified.

Nonrandomized Studies

Numerous non-randomized studies evaluated the effectiveness of VNS for the treatment of refractory depression.[33, 36-42] It is not possible to reach reliable conclusions from these studies as they fail to control for the biases discussed above.

TREATMENT OF CHRONIC HEART FAILURE

Systematic Reviews

Sant'Anna (2021) conducted a systematic review and meta-analysis on clinical trials comparing VNS with medical therapy for the management of chronic heart failure with reduced

ejection fraction.[43] Four RCTs and three prospective studies met inclusion criteria (n=1,263). Median follow-up was six months (range: 6 to 16 months). Only data from the RCTs were included in the meta-analysis. The certainty of the evidence based on GRADE characteristics was reported as high for all outcomes. The meta-analysis found significant improvements in New York Heart Association functional class, quality of life, six-minute walk test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to sham (Table 1). These studies are limited by a lack of long-term follow-up.

Table 1. Summary of systematic reviews.

Study	Improvement in NYHA functional class	Quality of Life	6-minute walk-test	NT-proBNP levels	Mortality
Sant'Anna (2021)[43]					
Total N	969 (4 RCTs)	450 (3 RCTs)	728 (3 RCTs)	445 (3 RCTs)	1206 (4 RCTs)
Pooled effect (95% CI)	OR, 2.72; (2.07 to 3.57); p<0.0001	MD, -14.18 (-18.09 to -10.28)	MD, 55.46 meters (39.11 to 71.81)	MD, -144.25 (-238.31 to -50.18)	OR, 1.24 (0.82 to 1.89)
I2 (p)	37% (p<0.0001)	49% (p<.0001)	0% (p<0.0001)	65% (p=0.003)	0% (p=0.43)

Randomized Controlled Trials

No RCTs have been published since the search dates of the above SR.

Nonrandomized Studies

In the ANTHEM-HF study (2014), 60 patients with heart failure with reduced ejection fraction were implanted with VNS, randomly assigned to right- or left-sided implantation (n=29 and 31, respectively), and followed for six months.[44] Overall, from baseline to six month follow-up, LV ejection fraction improved by 4.5% (95% confidence interval (CI) 2.4 to 6.6), left ventricular end systolic volume (LVESV) improved by -4.1 mL (95% CI -9.0 to 0.8), LVESD improved by -1.7 mm (95% CI -2.8 to -0.7), heart rate variability improved by 17 ms (95% Ci 6.5 to 28), and six-minute walk distance improved by 56 m (95% CI 37 to 75). Given there was no sham comparator group, it is unclear if the observed improvements may be attributed to VNS or some other confounding factor. A follow-up analysis to ANTHEM-HF by Nearing (2021) evaluated outcomes of VNS at 12, 24, and 36 months.[45] They found that LV ejection fraction improved by 18.7% (p=0.008), 19.3% (p=0.04), and 34.4% (p=0.009) at 12, 24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%; p=0.04). Although this data is promising, a lack of a no-VNS comparator group precludes drawing conclusions based on findings from the uncontrolled studies.

Several small case series describe VNS treatment outcomes in patients with heart failure; however, for the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.[46, 47]

TREATMENT OF UPPER-LIMB IMPAIRMENT DUE TO STROKE

Systematic Reviews

Gao (2023) examined VNS+Rehab for improving motor function, mental health and activities of daily living (ADL) postintervention and at the end of follow-up in patients with a stroke.[48]. Seven RCTs involving 263 (analyzed) participants was included. The effect size of VNS+Rehab over Rehab for motor function was medium postintervention (g=0.432; 95% CI 0.186 to 0.678) and large at the end of follow-up (g=0.840; 95% CI 0.288 to 1.392). No difference was found in the effect of VNS+Rehab over traditional rehabilitation for ADL, mental health or safety outcomes. The results suggest VNS+Rehab showed better motor function outcomes in patients after stroke, while no better than Rehab on mental health or ADL.

Ramos-Castaneda (2022) published a systematic review evaluating VNS on upper limb motor recovery after stroke.[49] Three RCTs by Dawson and Kimberley, which are summarized in the section below, were pooled for the analysis evaluating the role of implanted VNS. Results demonstrated that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score when compared to control (mean difference=2.78; 95% CI, 1.38 to 4.18).

Zhao (2022) published a systematic review and meta-analysis of RCTs evaluating vagus nerve stimulation in conjunction with rehabilitation therapies for restoring upper extremity function following stroke.[50] A total of five RCTs (n=178) met inclusion criteria. A significant effect of VNS compared to the control was identified for the primary outcome of Fugl-Meyer Assessment for Upper Extremity (FMA-UE, MD=3.59; 95% CI 2.55 to 4.63; p<0.01). No significant difference between groups in adverse events associated with the device was identified (RR=1.10; 95% CI 0.92 to 1.32; p=0.29).

Randomized Controlled Trials

Vagus Nerve Stimulation (VNS) paired with rehabilitation delivered by the Vivistim® Paired VNS™ System was approved by the FDA in 2021 to improve motor deficits in chronic ischemic stroke survivors with moderate to severe arm and hand impairment. Liu (2022) described the Vivistim implantation procedure, perioperative management, and complications for chronic stroke survivors enrolled in the pivotal trial.[51] The pivotal, multisite, randomized, triple-blind, sham-controlled trial (VNS-REHAB) enrolled 108 participants. All participants were implanted with the VNS device in an outpatient procedure. Thrombolytic agents were temporarily discontinued during the perioperative period. Participants were discharged within 48 hrs and started rehabilitation therapy approximately 10 days after the procedure. The rate of surgery-related adverse events was lower than previously reported for VNS implantation for epilepsy and depression. One participant had vocal cord paresis that eventually resolved. There were no serious adverse events related to device stimulation. Over 90% of participants were taking antiplatelet drugs (APD) or anticoagulants and no adverse events or serious adverse events were reported as a result of withholding these medications during the perioperative period. This study is the largest, randomized, controlled trial in which a VNS device was implanted in chronic stroke survivors.

Dawson (2021) conducted a randomized controlled trial of VNS in patients with upper limb dysfunction after ischemic stroke.[52] Patients with upper-limb dysfunction after ischemic stroke (n=106) were randomly assigned 1:1 to either VNS plus rehabilitation or rehabilitation with sham stimulation. The Fugl-Meyer Assessment-Upper Extremity score increased by 5 points in the VNS group and 2.4 points in the control group (between-group difference, 2.6; 95% CI 1.0 to 4.2; p=0.0014). Ninety days after in-clinic therapy, a clinically meaningful response was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the

control group (between-group difference, 24%; 95% CI, 6 to 41; p=0.0098). There was one adverse event of vocal cord paresis related to surgery in the control group.

A similar RCT with a smaller patient population was conducted by the same study group in 2016.[53] Twenty-one subjects were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group and +3.0 in the control group (p=0.064). Six patients in the VNS group achieved a clinically meaningful response and four in the control group (p=0.17).

Kimberley (2018) reported results of a randomized, pilot sham-controlled RCT in 17 patients (VNS n=8 and sham VNS, n=9) with arm weakness after ischemic stroke.[54] The mean Fugl-Meyer assessment–upper extremity scores increased by 7.6 with VNS versus 5.3 points with sham at day one (Difference=2.3 points; 95% CI, −1.8 to 6.4; p=0.20) and 9.5 points with VNS versus 3.8 with sham at day 90 (Difference=5.7 points; 95% CI, −1.4 to 11.5; p=0.055). A Fugl-Meyer assessment–upper extremity score change of six points or greater was defined as response; the response rate at day 90 was 88% with VNS versus 33% with sham (p<0.05). There were three serious adverse events related to surgery: wound infection, shortness of breath and dysphagia, and hoarseness because of vocal cord palsy.

Longer-term follow-up studies are needed to evaluate long-term efficacy and safety.

TREATMENT OF TINNITUS

Systematic Review

Stegeman (2021) performed a systematic review of the treatment of tinnitus with vagus nerve stimulation.[55] A total of nine studies were identified, of which five examined transcutaneous VNS and four examined implanted VNS treatment. Two were RCTs, five were cohort studies, and two were case series. Six of the studies used a combined VNS/sound therapy treatment. All included studies had serious risk of bias. Due to heterogeneity in methodology, inclusion criteria, and assessed outcomes, no meta-analysis was completed. Most studies reported a small decrease in tinnitus distress or tinnitus symptom severity.

OTHER INDICATIONS

Nonrandomized Studies

Small case series (n≤40 patients) and one non-randomized comparison study described experiences with VNS in patients with bulimia, anxiety, Alzheimer's disease[56, 57], essential tremor[58], and eating disorders including obesity and food cravings[59]. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited but there are no RCTs. For the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.

NONINVASIVE (TRANSCUTANEOUS) VAGUS NERVE STIMULATORS

Only RCTs and systematic reviews of RCTs will be discussed, as case series are inadequate to determine the effect of the technology.

REFRACTORY EPILEPSY

Wu (2020) reported results of a systematic review and meta-analysis of three RCTs (n=280, range n=60 to 144) of transcutaneous VNS for the treatment of drug-resistant epilepsy.[60] All treatment groups underwent a cymba conchae stimulus at a frequency of 20 to 30-Hz. The control groups received various kinds of sham stimulation at a frequency of 1 HZ, the same frequency stimulation as treatment but at the non-auricular vagus nerve area or no stimulation. Meta-analysis of all three included RCTs found that seizure frequency was significantly reduced with transcutaneous VNS (Mean Difference [MD]=-3.29; 95% CI -6.31 to -0.27). However, meta-analysis of the two RCTs that reported responder rates (undefined) did not find a significant difference between the transcutaneous VNS and control groups (n=238; Odds Ratio [OR]=1.47; 95% CI 0.54 to 4.02]. All three RCTs assessed quality of life using the Quality of Life in Epilepsy Inventory (QOLIE)-31 scale, but found no significant differences between treatment and control groups. Important limitations of the RCTs include imprecision, risk of confounding due to potentially imbalanced use of important nonprotocol interventions (i.e., concomitant antiepileptic drugs), and unacceptable flaws in outcome assessment (i.e., unspecified definition of response, between-group differences in measurement timing, lack of electroencephalography data).

PSYCHIATRIC DISORDERS

Li (2022) published results of an RCT comparing transcutaneous auricular VNS with citalopram for the treatment of major depressive disorder.[61] A total of 107 patients from the outpatient departments of three hospitals in China were randomly assigned to receive t-VNS or citalopram. Treatment was eight weeks of t-VNS, twice per day, plus a four-week follow-up or 12 weeks of citalopram. For the primary outcome of the 17-item Hamilton Depression Rating Scale (HAM-D17) measured every two weeks by trained interviewers blinded to the treatment assignment, although both groups improved significantly, there was no significant group-by-time interaction (95% CI -0.07 to 0.15, p=0.79). There was a significant difference between groups for remission rate at four and six weeks (p=0.007 and p=0.01, respectively), but not at any other time point.

Hein (2013) reported results of two pilot RCTs of a t-VNS device for the treatment of depression, one which included 22 subjects and the other with 15 subjects.[62] In the first study, 11 subjects each were randomized to active or sham t-VNS. At two weeks follow-up, Beck Depression Inventory (BDI) self-rating scores in the active-stimulation group decreased from 27.0 to 14.0 points (p<0.001), while the sham-stimulated patients did not show significant reductions in the BDI (31.0 to 25.8 points). In the second study, seven patients were randomized to active t-VNS and eight patients were randomized to sham t-VNS. In this study, BDI self-rating scores in the active stimulation group decreased from 29.4 to 17.4 points (p<0.05) after two weeks, while the sham-stimulated patients did not show significant change in BDI (28.6 to 25.4 points). The authors do not report direct comparisons in BDI change between the sham- and active-stimulation groups.

Hasan (2015) reported a randomized trial of t-VNS for the treatment of schizophrenia.[63] Twenty patients were assigned either to active t-VNS or to sham treatment for 12 weeks. There was no statistically significant difference in the improvement of schizophrenia status during the observation period.

Shiozawa (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous stimulation of the trigeminal or vagus nerve for psychiatric disorders.[64] They found four studies that addressed t-VNS for psychiatric disorders and included a total of 84

subjects. Three of the four studies evaluated physiologic parameters in healthy patients and one evaluated pharmaco-resistant epilepsy (Stefan, previously described[65]). The authors also include a fifth study in a data table, although not in their text or reference list (Hein, previously described[62]) Overall, the studies included were limited by small size and poor generalizability.

IMPAIRED GLUCOSE TOLERANCE

Huang (2014) reported results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance.[66] The study included 70 patients with impaired glucose tolerance who were randomized to active or sham t-VNS, along with 30 controls who received no t-VNS treatment. After 12 weeks of treatment, patients who received active t-VNS were reported to have significantly lower two-hour glucose tolerance test results than those who received sham t-VNS (7.5 mmol/L vs 8 mmol/L; p=0.004).

TREATMENT OF UPPER-LIMB IMPAIRMENT DUE TO STROKE

Wu (2020) reported results of a pilot randomized sham-controlled trial of 21 patients (nVNS=10 and sham nVNS, n=11) treated with nVNS for upper limb motor function impairment following subacute ischemic stroke.[67] The mean Fugl-Meyer assessment–upper extremity scores increased by 6.90 with nVNS versus 3.18 points with sham after 15 days of intervention (Difference= -3.72 points; 95% CI −5.12 to -2.32; p≤0.001). The improvement in the mean Fugl-Meyer assessment–upper extremity scores remained significantly higher at both the four-week (+7.70 vs. +3.36; p≤0.001) and the 12-week (+7.40 vs. +4.18; p=0.038) follow-ups. There was only one adverse event noted, which was that one patient in the nVNS group developed skin redness at an electrode point of contact.

PAIN

Natelson (2021) reported results of a small RCT with limited follow-up of nVNS for the treatment of pain and migraine in Gulf War Veterans with Gulf War Illness.[68] During the first 10 weeks, the 27 participants were randomized to receive active or sham nVNS, followed by 10 weeks of open-label trial. No significant differences between active and sham nVNS were identified.

Kutlu (2020) reported results of an RCT that compared a home-based exercise treatment program with or without auricular VNS in 60 female patients in Turkey with fibromyalgia syndrome (auricular VNS n=30 and no auricular VNS n=30).[69] The VNS was delivered at Beykoz Public Hospital's Department of Physical Therapy and Rehabilitation in 30-minute sessions on weekdays for four weeks. The home-based exercise program consisted of strengthening, stretching, isometric, and posture exercises that targeted the body and upper and lower extremities. When added to exercise, auricular VNS did not significantly improve mean scores on the Fibromyalgia Impact Questionnaire (37.27 vs. 41.93; p=0.378) or on any 36-Item Short Form Health Survey subscales (e.g., Physical Function: 80.00 vs. 85.00; p=.167). An important limitation of this RCT is the lack of a sham control group.

CLUSTER HEADACHE

Prevention of Cluster Headaches

Gaul (2016, 2017) reported the results of the PREVA study - a randomized open-label study of nVNS as a prophylactic therapy for chronic cluster headache (CH) in patients diagnosed at least one year prior to enrollment.[70, 71] The study was funded by the device manufacturer. In a

two-week baseline period, all 97 participants received only their individualized standard of care (SoC). Patients were then randomized to a four-week period of SoC with nVNS (n=48) or SoC alone, i.e., control (n=49). Four participants from the SoC with nVNS chose to withdraw; one control participant was removed from the study for failing to meet enrollment criteria. In an optional four-week period following, all participants received SoC with nVNS (n=92); 70 completed the optional period (11 controls discontinued from each group).

Efficacy was evaluated by the mean number of CH attacks per week, defined as the number of attacks during the last two weeks of the randomized phase minus the number of attacks during baseline divided by two. Safety and tolerability were assessed in those who were assigned treatment; and the intent-to-treat (ITT) population was those who had more than one efficacy recording in their home diary after randomization.

In the ITT population (n=45 SoC plus nVNS, n=48 in control) authors reported a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI 0.5 to 7.2; p=0.02). However, the proportion of participants receiving SoC plus nVNS in the ITT population from the randomized phase with more than 50% response to treatment was 40.0, and in controls who went on to receive treatment in the extension phase, the proportion was 16.7.

During the randomization phase, 38% participants in the SoC plus nVNS group experienced adverse events (AEs), and 27% of controls experienced AEs. In the extension phase, 25% and 24% experienced AEs, respectively. Overall, the most common AEs for any treatment were CH attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. No serious AEs were considered related to the nVNS device.

The study is limited by a sham placebo control group, which may result in placebo response in the nVNS group. Additionally, the double-blind, study treatment period was less than one month, which limits inference about continued response.

Section Summary

Transcutaneous (or noninvasive) VNS has been investigated for preventing cluster headaches in one RCT. The PREVA study of prevention of cluster headache in patients with chronic cluster headache demonstrated a statistically significant increase in the proportion of patients with a 50% or greater reduction in the mean number of headache attacks and statistically significant reduction in the frequency of attacks for nVNS compared to standard of care with a treatment period of four weeks. There was also an improvement in quality of life as measured by the EQ-5D. However, the study was not blinded.

Treatment of Cluster Headaches

In 2016, Silberstein reported results from the manufacturer funded ACT1 study – a randomized, double-blind, sham-controlled study of nVNS as a treatment for cluster headache (CH).[72] One hundred fifty subjects were randomized to receive sham control or nVNS treatment for less than or equal to one month; completers could enter a three-month nVNS open-label phase. Limitations of this study include that the enrolled population was not reflective of relevant diversity (3.3% Asian, 8% Black, 87.3% white, 1.4% race/ethnicity not reported), a lack of quality of life or functional outcomes, and short follow-up time. In addition, a considerable proportion of patients correctly guessed their treatment allocation after their first treatment, though blinding was found to have improved by the end of the one-month period. The primary end point was response rate, defined as the proportion of subjects who achieved

pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15 to 60 minutes). Subanalyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified.

During the randomized phase of one month, 14 participants discontinued participation from the treatment group, and 8 in the control group discontinued. In the three-month open label period, 17 and 11 discontinued from the treatment and control groups, respectively. Application site reactions and nervous system AEs occurred more frequently with sham treatment than with nVNS in the double-blind phase. Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase.

Intent-to-treat analysis included 133 subjects: 60 nVNS-treated (eCH, n=38; cCH, n=22) and 73 sham-treated (eCH, n=47; cCH, n=26). Authors reported a response in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects. Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham,10.6%; *p*=0.008) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%; *p*=0.48). Sustained response rates were significantly higher with nVNS for the eCH cohort and total population.

In 2018, Goadsby reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks.[73] Ninety-two patients with cluster headaches were randomized to nVNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the nVNS and sham treatment groups. The primary efficacy end point was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between nVNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between nVNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, nVNS demonstrated a 48% response rate compared with 6% response rate for sham-treated (p<0.01). The interaction p-value for the subgroup analysis was statistically significant (p=0.04).

de Coo (2019) combined the data from ACT1 and ACT2 meta-analytically for the two primary outcomes reported in the two studies.[74] The authors reported an interaction between treatment group and cluster headache subtype in the pooled analysis (p<0.05 for both outcomes).

Section Summary

The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. The RCTs reported slightly different outcome measures so that consistencies in magnitude of treatment effects cannot be assessed. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack (27% vs. 15%, p=0.10) and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks (12% vs. 7%, p=0.33). However, in the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2 the proportion of attacks with a pain intensity score of 0 or 1 at 30 minutes was statistically significant overall (43% vs. 28%, p=0.05). The proportion of attacks that were pain-free at 15 minutes was similar in the two treatment groups

overall (14% vs. 12%) but a significant interaction was reported (p=0.04). There was a statistically significantly higher proportion of attacks in the episodic subgroup that were pain-free at 15 minutes in the nVNS group compared to sham (48% vs. 6%, p<0.01). Quality of life and functional outcomes have not been reported. Treatment periods ranged from only two weeks to one month with extended open-label follow-up of up to three months. Studies designed to test the effect of nVNS in the episodic subgroup with longer treatment and follow-up and including quality of life and functional outcomes are needed.

There are few adverse events of nVNS and they are mild and transient.

MIGRAINE

Prevention of Migraine Headaches

Diener (2019) published results of the PREMIUM trial, a phase 3, multicenter, sham-controlled RCT conducted in several European countries. Patients who experienced 5 to 12 migraine days per month were included.[75] The study began with a four-week run-in period during which no treatment was administered; 477 participants entered the run-in. The criteria to remain eligible after run-in were not described in the publication. After run-in, 341 participants were randomized (nVNS, n=169 or sham, n=172) to a 12-week double-blind treatment period followed by a 24-week open-label period of nVNS. Patients administered two 120-second stimulations bilaterally to the neck with gammaCore, three times daily. nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last four weeks (32% vs 25%; p=0.19), reduction in number of migraine days from baseline to the last four weeks (-2.3 vs -1.8; p=0.15), or acute medication days (-1.9 vs -1.4; p=0.11) in the intention-to-treat population. Adverse events were reported in 44% of the nVNS group and 53% of the sham group. The PREMIUM II trial was a multicenter, sham-controlled RCT conducted in several U.S. sites and included patients who experienced 8 to 20 headache days per month with at least 5 of the days being migraine days.[76] The study included a 4-week run-in period during which no treatment was administered (N=336). After the run-in period, 231 patients were randomly assigned to receive nVNS (n = 114) or sham (n = 117) therapy during the double-blind period and were part of the intention to treat (ITT) population (ie, had ≥1 study treatment during the double-blind phase). The COVID-19 pandemic led to an early termination of this trial, therefore, the population was approximately 60% smaller than the statistical target for full power. The modified ITT (mITT) population, which included those who were at least 66% adherent to treatment during the double-blind phase, included 56 patients in the nVNS group and 57 in the sham group. Results showed that in the mITT population, nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12 (mean difference=-0.83 days; p=.2329), nor other outcomes such as mean change in the number of headache days or acute medication days. However, in the mITT population, the percentage of patients with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group (44.87%) than in the sham group (26.81%; p=.048). Furthermore, nVNS was significantly better than sham at decreasing headache impact, as measured by the Headache Impact Test-6 (HIT-6), and at decreasing migraine-related disability, as measured by the Migraine Disability Assessment Scale (MIDAS).

The EVENT trial (Silberstein, 2016) was a feasibility study of prevention with a sample size of 59.[77] It was not powered to detect differences in efficacy outcomes. About twenty percent of participants discontinued treatment after the first two months. The study was supposed to be

blinded, but the sham did not deliver electrical stimulation, which may have compromised the blinding. For the outcome of response, defined as 50% or more reduction in the number of headache days, 10% of the patients in the nVNS group versus 0% in the sham group were responders; statistically testing was not performed.

Section Summary

Three RCTs have evaluated nVNS for prevention of migraine. The EVENT trial was a feasibility study of prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. The PREMIUM trial was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham. With respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last four weeks, reduction in number of migraine days from baseline to the last four weeks or acute medication days. The PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. Results demonstrated that treatment with nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of participants with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. However, interpretation of these findings is limited as it was based on a mITT population of 49% of randomized patients (n= 113 of original 231 participants) due to COVID-19 pandemic-related early termination.

Treatment of Migraine Headaches

The Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS) for the Acute Treatment of Migraine (PRESTO) trial was a multicenter, double-blind, randomized, sham-controlled trial of acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura reported by Tassorelli (2018), Grazzi (2018), and Martelletti (2018).[78-80] The primary efficacy outcome was the proportion of participants who were pain-free without using rescue medication at 120 minutes. There was not a statistically significant difference in the primary outcome (30% vs 20%; p=0.07) although it favored the nVNS group. The nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; p=0.02). PRESTO results did not include quality of life or functional outcomes and the double-blind treatment and follow-up period was 4 weeks. In the additional four weeks of acute nVNS in the open-label period, rates of pain-free response after the first treated attack (28%,) and pain relief (43.4%) were similar to the rates in the double-blind period. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

Section Summary

One RCT has evaluated nVNS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs. 20%; p = 0.07). However, the nVNS group had a higher

proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=0.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was four weeks with an additional four weeks of open-label treatment. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

OTHER INDICATIONS

Small studies of transcutaneous VNS have also been reported for gastrointestinal dysfunction in Parkinson's disease[81], systemic lupus erythematosus[82], cortical arousal and alertness[83], and delayed neurocognitive recovery in elderly patients.[84] Larger studies are needed to know how well transcutaneous VNS works in these populations.

ADVERSE EVENTS

The most commonly reported adverse effects of VNS have been mild and consist primarily of hoarseness of voice during "on" periods of stimulation, transient throat pain, and coughing. More serious adverse events reported include, but are not limited to direct delivery of the current to the nerve due to generator malfunction; modified synchronization between cardiac and respiratory activity affecting the oxygen delivery to tissues; heart block with ventricular standstill; bradyarrhythmias and severe asystolia; and changes in respiration during sleep.[1, 29, 36, 85-88]

PRACTICE GUIDELINE SUMMARY

AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association (APA) (2010, reaffirmed 2015) has level III* recommendations regarding the use of vagus nerve stimulation (VNS) for patients with major depressive disorder.[89] Strategies to address nonresponse during an acute phase of depression include VNS as an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT (electroconvulsive therapy). Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality.

* [III] May be recommended on the basis of individual circumstances (As opposed to level I or II which are recommended with substantial and moderate clinical confidence, respectively.)

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology (AAN) 2013 consensus statement (reaffirmed in 2016 and 2019) states VNS may be considered for seizures in children, for LGS (Lennox-Gastaut-syndrome)- associated seizures, and for improving mood in adults with epilepsy; and VNS may be considered to have improved efficacy over time.[90] These statements are based on Level C evidence, which is defined as, "possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population."

DEPARTMENT OF VETERANS AFFAIRS AND THE DEPARTMENT OF DEFENSE

A 2020 clinical practice guideline from the Department of Veterans Affairs and the Department of Defense (VA/DoD) addressed the primary care management of headache. The guideline included a recommendation with a weak strength of evidence which stated, “We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.”

SUMMARY

Vagus nerve stimulation (VNS) has evolved to be a standard of care as a treatment of medically refractory seizures. Therefore, VNS for medically refractory seizures may be considered medically necessary for patients who have had inadequate response to or are intolerant of at least two antiepileptic drugs.

In certain situations, a stimulator may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing stimulator may be considered medically necessary after the device has been placed.

In certain situations, a stimulator may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient’s medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a stimulator may be considered medically necessary when device replacement Criteria are met.

When a stimulator is in its warranty period or can be repaired or adapted adequately to meet the patient’s medical needs, replacement of the device is considered not medically necessary.

There is not enough research to make conclusions about the benefit of VNS as a treatment for conditions other than medically refractory seizures. Therefore, VNS is considered investigational for all indications other than selected patients with refractory seizures.

There is not enough research to know if or how well transcutaneous and non-implantable vagus nerve stimulators (nVNS) work to treat people with any condition, including but not limited to cluster headache. This does not mean that they do not work, but more research is needed to know. No clinical guidelines based on research recommend these stimulators for people with cluster headache or any other condition. Therefore, transcutaneous and non-implantable vagus nerve stimulators are considered investigational as a treatment for all indications.

REFERENCES

1. TEC Assessment 1998. "Chronic vagus nerve stimulation for the treatment of seizures." BlueCross BlueShield Association Technology Evaluation Center, Vol. 13, Tab 9.
2. Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. *The Cochrane database of systematic reviews.* 2015;4:CD002896. PMID: 25835947
3. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology.* 1998;51(1):48-55. PMID: 9674777

4. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology.* 1995;45(2):224-30. PMID: 7854516
5. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Developmental medicine and child neurology.* 2012;54(9):855-61. PMID: 22540141
6. Morris GL, 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology.* 1999;53(8):1731-5. PMID: 10563620
7. Montavont A, Demarquay G, Ryvlin P, et al. [Long-term efficiency of vagus nerve stimulation (VNS) in non-surgical refractory epilepsies in adolescents and adults]. *Rev Neurol (Paris).* 2007;163(12):1169-77. PMID: 18355464
8. Kostov H, Larsson PG, Roste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? *Acta Neurol Scand Suppl.* 2007;187:55-8. PMID: 17419830
9. Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. *Neurology.* 2002;59(6 Suppl 4):S26-30. PMID: 12270965
10. Lee HO, Koh EJ, Oh YM, et al. Effect of vagus nerve stimulation in post-traumatic epilepsy and failed epilepsy surgery : preliminary report. *J Korean Neurosurg Soc.* 2008;44(4):196-8. PMID: 19096676
11. Cukiert A, Mariani PP, Burattini JA, et al. Vagus nerve stimulation might have a unique effect in reflex eating seizures. *Epilepsia.* 2010;51(2):301-3. PMID: 19780799
12. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *J Pediatr.* 1999;134(5):563-6. PMID: 10228290
13. Hornig GW, Murphy JV, Schallert G, et al. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J.* 1997;90(5):484-8. PMID: 9160063
14. Patwardhan RV, Stong B, Bebin EM, et al. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery.* 2000;47(6):1353-7; discussion 57-8. PMID: 11126906
15. You SJ, Kang HC, Kim HD, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. *J Korean Med Sci.* 2007;22(3):442-5. PMID: 17596651
16. You SJ, Kang HC, Ko TS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *Brain Dev.* 2008;30(3):195-9. PMID: 17825516
17. Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned? *Epilepsy Behav.* 2006;8(1):127-36. PMID: 16376157
18. Rossignol E, Lortie A, Thomas T, et al. Vagus nerve stimulation in pediatric epileptic syndromes. *Seizure.* 2009;18(1):34-7. PMID: 18657451
19. Amar AP, Levy ML, McComb JG, et al. Vagus nerve stimulation for control of intractable seizures in childhood. *Pediatr Neurosurg.* 2001;34(4):218-23. PMID: 11359116
20. Kirse DJ, Werle AH, Murphy JV, et al. Vagus nerve stimulator implantation in children. *Arch Otolaryngol Head Neck Surg.* 2002;128(11):1263-8. PMID: 12431167
21. Mikati MA, Ataya NF, El-Ferezli JC, et al. Quality of life after vagal nerve stimulator insertion. *Epileptic Disord.* 2009;11(1):67-74. PMID: 19286494
22. Kabir SM, Rajaraman C, Rittey C, et al. Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome. *Childs Nerv Syst.* 2009;25(9):1097-100. PMID: 19263056

23. Shahwan A, Bailey C, Maxiner W, et al. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *Epilepsia.* 2009;50(5):1220-8. PMID: 19170732
24. Elliott RE, Carlson C, Kalhorn SP, et al. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery. *Epilepsy Behav.* 2009;16(3):454-60. PMID: 19767244
25. Kuba R, Brazdil M, Kalina M, et al. Vagus nerve stimulation: longitudinal follow-up of patients treated for 5 years. *Seizure.* 2009;18(4):269-74. PMID: 19081273
26. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 1999;53(4):666-9. PMID: 10489023
27. Vagal Nerve Stimulation for Epilepsy and Depression: final evidence report. Center for Evidence-based Policy; Oregon Health & Science University [Internet]. Olympia (WA): Washington State Health Care Authority. [cited 05/05/2023]. 'Available from:' https://www.hca.wa.gov/assets/program/vns-final-rpt-complete-20200520.pdf.
28. TEC Assessment 2006. "Vagus Nerve Stimulation for Treatment-Resistant Depression." BlueCross BlueShield Association Technology Evaluation Center, Vol. 21, Tab 7.
29. U.S. Food and Drug Administration Center for Devices and Radiological Health. Summary of Safety and Effectiveness Data for the Vagus Nerve Stimulation (VNS) Therapy System. [cited 5/11/2022]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf/P970003S050b.pdf.
30. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry.* 2005;58(5):347-54. PMID: 16139580
31. Rudolph, Richard Leslie. “Executive Summary and Discussion of the Vagus Nerve Stimulation (VNS) Therapy Depression Indication Clinical Data (Updated to Include Information from Deficiency Letter Response) Prepared.” (2004). PMID:
32. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry.* 2005;58(5):364-73. PMID: 16139582
33. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology.* 2001;25(5):713-28. PMID: 11682255
34. Bottomley JM, LeReun C, Diamantopoulos A, et al. Vagus nerve stimulation (VNS) therapy in patients with treatment resistant depression: A systematic review and meta-analysis. *Compr Psychiatry.* 2019;98:152156. PMID: 31978785
35. Martin JL, Martin-Sanchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. *Eur Psychiatry.* 2012;27:147-55. PMID: 22137776
36. Daban C, Martinez-Aran A, Cruz N, et al. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *J Affect Disord.* 2008;110(1-2):1-15. PMID: 18374988
37. Sperling W, Reulbach U, Kornhuber J. Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. *Pharmacopsychiatry.* 2009;42(3):85-8. PMID: 19452375
38. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *J Clin Psychopharmacol.* 2010;30(3):273-81. PMID: 20473062

39. Marangell LB, Suppes T, Zboyan HA, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry.* 2008;69(2):183-9. PMID: 18211128
40. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry.* 2000;47(4):276-86. PMID: 10686262
41. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry.* 2002;51(4):280-7. PMID: 11958778
42. Cristancho P, Cristancho MA, Baltuch GH, et al. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. *J Clin Psychiatry.* 2011;72(10):1376-82. PMID: 21295002
43. Sant'Anna LB, Couceiro SLM, Ferreira EA, et al. Vagal Neuromodulation in Chronic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2021;8:766676. PMID: 34901227
44. Premchand RK, Sharma K, Mittal S, et al. autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *Journal of cardiac failure.* 2014;20(11):808-16. PMID: 25187002
45. Nearing BD, Libbus I, Carlson GM, et al. Chronic vagus nerve stimulation is associated with multi-year improvement in intrinsic heart rate recovery and left ventricular ejection fraction in ANTHEM-HF. *Clin Auton Res.* 2021;31(3):453-62. PMID: 33590355
46. De Ferrari GM, Crijns HJ, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J.* 2011;32:847-55. PMID: 21030409
47. Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail.* 2008;10(9):884-91. PMID: 18760668
48. Gao Y, Zhu Y, Lu X, et al. Vagus nerve stimulation paired with rehabilitation for motor function, mental health and activities of daily living after stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2023;94(4):257-66. PMID: 36600569
49. Ramos-Castaneda JA, Barreto-Cortes CF, Losada-Floriano D, et al. Efficacy and Safety of Vagus Nerve Stimulation on Upper Limb Motor Recovery After Stroke. A Systematic Review and Meta-Analysis. *Front Neurol.* 2022;13:889953. PMID: 35847207
50. Zhao K, Yang J, Huang J, et al. Effect of vagus nerve stimulation paired with rehabilitation for upper limb function improvement after stroke: a systematic review and meta-analysis of randomized controlled trials. *Int J Rehabil Res.* 2022;45(2):99-108. PMID: 34839304
51. Liu CY, Russin J, Adelson DP, et al. Vagus nerve stimulation paired with rehabilitation for stroke: Implantation experience from the VNS-REHAB trial. *J Clin Neurosci.* 2022;105:122-28. PMID: 36182812
52. Dawson J, Liu CY, Francisco GE, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet.* 2021;397(10284):1545-53. PMID: 33894832
53. Dawson J, Pierce D, Dixit A, et al. Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Ischemic Stroke. *Stroke; a journal of cerebral circulation.* 2016;47(1):143-50. PMID: 26645257

54. Kimberley TJ, Pierce D, Prudente CN, et al. Vagus Nerve Stimulation Paired With Upper Limb Rehabilitation After Chronic Stroke. *Stroke; a journal of cerebral circulation.* 2018;49(11):2789-92. PMID: 30355189
55. Stegeman I, Velde HM, Robe P, et al. Tinnitus treatment by vagus nerve stimulation: A systematic review. *PLoS One.* 2021;16(3):e0247221. PMID: 33705401
56. Sjogren MJ, Hellstrom PT, Jonsson MA, et al. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. *J Clin Psychiatry.* 2002;63(11):972-80. PMID: 12444809
57. Liu AY, Rajji TK, Blumberger DM, et al. Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2014;22(3):216-40. PMID: 23891366
58. Handforth A, Ondo WG, Tatter S, et al. Vagus nerve stimulation for essential tremor: a pilot efficacy and safety trial. *Neurology.* 2003;61(10):1401-5. PMID: 14638963
59. Bodenlos JS, Kose S, Borckardt JJ, et al. Vagus nerve stimulation acutely alters food craving in adults with depression. *Appetite.* 2007;48(2):145-53. PMID: 17081655
60. Wu K, Wang Z, Zhang Y, et al. Transcutaneous vagus nerve stimulation for the treatment of drug-resistant epilepsy: a meta-analysis and systematic review. *ANZ J Surg.* 2020;90(4):467-71. PMID: 32052569
61. Li S, Rong P, Wang Y, et al. Comparative Effectiveness of Transcutaneous Auricular Vagus Nerve Stimulation vs Citalopram for Major Depressive Disorder: A Randomized Trial. *Neuromodulation.* 2022;25(3):450-60. PMID: 35088753
62. Hein E, Nowak M, Kiess O, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. *J Neural Transm.* 2013;120(5):821-7. PMID: 23117749
63. Hasan A, Wolff-Menzler C, Pfeiffer S, et al. Transcutaneous noninvasive vagus nerve stimulation (tVNS) in the treatment of schizophrenia: a bicentric randomized controlled pilot study. *European archives of psychiatry and clinical neuroscience.* 2015;265(7):589-600. PMID: 26210303
64. Shiozawa P, Silva ME, Carvalho TC, et al. Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: a systematic review. *Arquivos de neuro-psiquiatria.* 2014;72(7):542-7. PMID: 25054988
65. Stefan H, Kreiselmeyer G, Kerling F, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia.* 2012;53(7):e115-8. PMID: 22554199
66. Huang F, Dong J, Kong J, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. *BMC Complement Altern Med.* 2014;14:203. PMID: 24968966
67. Wu D, Ma J, Zhang L, et al. Effect and Safety of Transcutaneous Auricular Vagus Nerve Stimulation on Recovery of Upper Limb Motor Function in Subacute Ischemic Stroke Patients: A Randomized Pilot Study. *Neural Plast.* 2020;2020:8841752. PMID: 32802039
68. Natelson BH, Stegner AJ, Lange G, et al. Vagal nerve stimulation as a possible non-invasive treatment for chronic widespread pain in Gulf Veterans with Gulf War Illness. *Life Sci.* 2021;282:119805. PMID: 34237313
69. Kutlu N, Özden AV, Alptekin HK, et al. The Impact of Auricular Vagus Nerve Stimulation on Pain and Life Quality in Patients with Fibromyalgia Syndrome. *Biomed Res Int.* 2020;2020:8656218. PMID: 32190684

70. Gaul C, Diener HC, Silver N, et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. *Cephalalgia.* 2015. PMID: 26391457
71. Gaul C, Magis D, Liebler E, et al. Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study. *The journal of headache and pain.* 2017;18(1):22. PMID: 28197844
72. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. *Headache.* 2016;56(8):1317-32. PMID: 27593728
73. Goadsby PJ, de Coo IF, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia.* 2018;38(5):959-69. PMID: 29231763
74. de Coo IF, Marin JC, Silberstein SD, et al. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A meta-analysis. *Cephalalgia.* 2019;39(8):967-77. PMID: 31246132
75. Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia.* 2019;39(12):1475-87. PMID: 31522546
76. Najib U, Smith T, Hindiyeh N, et al. Non-invasive vagus nerve stimulation for prevention of migraine: The multicenter, randomized, double-blind, sham-controlled PREMIUM II trial. *Cephalalgia.* 2022;42(7):560-69. PMID: 35001643
77. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology.* 2016;87(5):529-38. PMID: 27412146
78. Martelletti P, Barbanti P, Grazzi L, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: additional findings from the randomized, sham-controlled, double-blind PRESTO trial. *The journal of headache and pain.* 2018;19(1):101. PMID: 30382909
79. Grazzi L, Tassorelli C, de Tommaso M, et al. Practical and clinical utility of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: a post hoc analysis of the randomized, sham-controlled, double-blind PRESTO trial. *The journal of headache and pain.* 2018;19(1):98. PMID: 30340460
80. Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. *Neurology.* 2018;91(4):e364-e73. PMID: 29907608
81. Kaut O, Janocha L, Weismüller TJ, et al. Transcutaneous vagal nerve stimulation improves gastroenteric complaints in Parkinson's disease patients. *NeuroRehabilitation.* 2019;45(4):449-51. PMID: 31868695
82. Aranow C, Atish-Fregoso Y, Lesser M, et al. Transcutaneous auricular vagus nerve stimulation reduces pain and fatigue in patients with systemic lupus erythematosus: a randomised, double-blind, sham-controlled pilot trial. *Ann Rheum Dis.* 2021;80(2):203-08. PMID: 33144299
83. Chen Y, Lu X, Hu L. Transcutaneous Auricular Vagus Nerve Stimulation Facilitates Cortical Arousal and Alertness. *Int J Environ Res Public Health.* 2023;20(2). PMID: 36674156

84. Zhou Q, Yu L, Yin C, et al. Effect of transcutaneous auricular vagus nerve stimulation on delayed neurocognitive recovery in elderly patients. *Aging Clin Exp Res.* 2022;34(10):2421-29. PMID: 35809206
85. Zaaimi B, Grebe R, Berquin P, et al. Vagus nerve stimulation induces changes in respiratory sinus arrhythmia of epileptic children during sleep. *Epilepsia.* 2009;50(11):2473-80. PMID: 19682028
86. Singleton AH, Rosenquist PB, Kimball J, et al. Cardiac rhythm disturbance in a depressed patient after implantation with a vagus nerve stimulator. *J ECT.* 2009;25(3):195-7. PMID: 19384253
87. Iriarte J, Urrestarazu E, Alegre M, et al. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia.* 2009;50(4):928-32. PMID: 19055490
88. Ebben MR, Sethi NK, Conte M, et al. Vagus nerve stimulation, sleep apnea, and CPAP titration. *J Clin Sleep Med.* 2008;4(5):471-3. PMID: 18853706
89. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. [cited 05/05/2023]. 'Available from:' https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.
90. Morris GL, 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81:1453-9. PMID: 23986299

CODES

Codes	Number	Description
CPT	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64568	Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters,

Codes	Number	Description
		responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	95977	;with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1827	Generator, neurostimulator (implantable), non-rechargeable, with implantable stimulation lead and external paired stimulation controller
	E0735	Non-invasive vagus nerve stimulator
	~~K1020~~	~~Non-invasive vagus nerve stimulator~~ (Deleted 01/01/2024)
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

Date of Origin: *February 1998*

Regence

Medical Policy Manual Surgery, Policy No. 84

Deep Brain Stimulation

Effective: May 1, 2025

Next Review: March 2025
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Deep brain stimulation (DBS) involves the stereotactic placement of electrodes into the brain (e.g., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]).

MEDICAL POLICY CRITERIA

Note: The use of spinal cord stimulation as a treatment of chronic pain is addressed in a separate policy (see Cross References section below).

I. When a multidisciplinary evaluation has confirmed both the medical intractability of the patient's symptoms and the potential value of deep brain stimulation (DBS), unilateral or bilateral DBS may be considered **medically necessary** when **both** of the following criteria (A. and B.) are met:

   A. One of the following is met:

      1. The request is for stimulation of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease. Disabling, medically unresponsive tremor defined as tremor causing significant limitation in daily activities AND inadequate symptom

control despite optimal medical management for at least three months before implant.

2. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients with previously levodopa-responsive Parkinson's disease and symptoms such as rigidity, bradykinesia, dystonia or levodopa-induced dyskinesias.

3. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients seven years of age or above with disabling, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis). Disabling, medically unresponsive dystonia defined as dystonia causing significant limitation in daily activities AND inadequate symptom control despite optimal medical management for at least three months before implant.

B. The patient does not have a medical condition that requires repeated MRI, OR if a medical condition requires **repeated MRI,** an **MR-conditional device** is used.

II. Unilateral or bilateral deep brain stimulation revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.

III. Deep brain stimulation is considered **not medically necessary** for essential tremor, Parkinson's disease, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis) when Criterion I. is not met.

IV. Deep brain stimulation is considered **investigational** for all other conditions (see Policy Guidelines).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Deep brain stimulation is considered investigational for indications that do not meet the policy criteria above including but not limited to the following:

- Cerebral Palsy
- Chronic pain (e.g., nociceptive pain; neuropathic pain)
- Cognitive decline/dementia due to Parkinson’s Disease
- Epilepsy/intractable seizures
- Huntington’s disease
- Multiple sclerosis
- Neuropsychiatric applications, including but not limited to the following:
    - Anorexia nervosa
    - Anxiety
    - Bipolar Disorder
    - Depression
    - Obsessive-compulsive disorder
    - Schizophrenia
    - Tourette syndrome
    - Alzheimer’s Disease

- Other movement disorders
- Post-traumatic tremor
- Tardive dyskinesia and tardive dystonia
- Traumatic brain injury (TBI)

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Multidisciplinary evaluations
- Indication for DBS
- Brain region to be stimulated
- Condition that is anticipated to require repeat MRI, if present.
- Name of DBS device

CROSS REFERENCES

1. Spinal Cord and Dorsal Root Ganglion Stimulation, Surgery, Policy No. 45
2. Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin, Surgery, Policy No. 205
3. Responsive Neurostimulation, Surgery, Policy No. 216

BACKGROUND

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later the patient returns to surgery for permanent subcutaneous implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the more severe symptoms. However, the use of bilateral stimulation using two electrode arrays is also used in patients with bilateral, severe symptoms.

After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient's symptoms. This feature may be important for patients with Parkinson's disease, whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of side effects of neurostimulation, such as dysarthria, disequilibrium or involuntary movements.

DBS has been investigated for a variety of indications as discussed below:

- Alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy

  The technique has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor, and tremor associated with Parkinson's disease (PD). More recently, there has been research interest in the use of deep brain stimulation of the globus pallidus or STN as a treatment of other Parkinsonian

symptoms such as rigidity, bradykinesia or akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as "on and off" phenomena, related to the maximum effectiveness of drugs (i.e., the "on" state) and the nadir response during drug troughs (i.e., the "off" state). In addition, levodopa, the most commonly used antiparkinson drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of Parkinson's disease may involve a balance between optimal effects on Parkinson's symptoms vs. the appearance of drug induced dyskinesias. The effect of DBS on both Parkinson's symptoms and drug-induced dyskinesias has also been studied.

- Treatment of primary and secondary dystonia

  Dystonia is defined as a neurological movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. In primary dystonia, dystonia is the only symptom and is unassociated with other pathology. Secondary dystonia is a dystonia brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia. Treatment options for dystonia include oral or injectable medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail.

- Cluster headaches

  Cluster headaches occur as episodic attacks of severe pain lasting from 30 minutes to several hours. The pain is usually unilateral and localized to the eye, temple, forehead, and side of the face. Autonomic symptoms that occur with cluster headaches include ipsilateral facial sweating, flushing, tearing, and rhinorrhea. Cluster headaches occur primarily in men and have been classified as vascular headaches that have been associated with high blood pressure, smoking, and alcohol use. However, the exact pathogenesis of cluster headaches is uncertain. PET scanning and MRI have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal/serotonergic function may also play a role. Treatment of cluster headaches includes pharmacologic interventions for acute episodes and prophylaxis, sphenopalatine ganglion (SPG) blockade and surgical procedures such as percutaneous SPG radiofrequency rhizotomy and gamma knife radiosurgery of the trigeminal nerve.

- Other Neurologic/Psychiatric Conditions

  The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly Tourette syndrome, epilepsy, obsessive-compulsive disorder (OCD), major depressive disorders, bipolar disorder, anorexia, alcohol addiction, and Alzheimer’s disease is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted to neuromodulation through DBS of nodes or targets within neural

circuits involved in these disorders. Currently, a variety of target areas are being studied.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved a number of deep brain stimulation systems for the treatment of essential tremor and tremor due to PD that is not adequately controlled by medication and is causing significant disability. The following DBS devices have been FDA-approved to treat essential tremor and PD-associated tremors under the Premarket Approval Application (PMA) process:

- Master Percept, Percept PC, And Activa® Deep Brain Stimulation Therapy Systems, with SenSight™ DBS accessories, Medtronic, Inc.
- Brio Neurostimulation System, Abbott St. Jude Medical Infinity™ Deep Brain Stimulation (DBS) system, Abbott (formerly St. Jude Medical).
- Vercise Deep Brain Stimulation System, including Vercise™ PC, Vercise Gevia™, and Vercise Genus™, Boston Scientific

The FDA has approved DBS systems for other indications. The Medtronic DBS System for Epilepsy (Medtronic, Inc) was FDA-approved through the PMA process as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Reclaim device (Medtronic, Inc.) was FDA-approved via the Humanitarian Device Exemption (HDE) process for the treatment of severe obsessive-compulsive disorder (OCD).

MR-conditional DBS devices may include the following devices. Please consult company websites for most up-to-date information.

- Medtronic: (*Medtronic DBS systems are MR Conditional and safe in the MR environment as long as certain conditions are met. If the conditions are not met, a significant risk is tissue lesions from component heating, especially at the lead electrodes, resulting in serious and permanent injury including coma, paralysis, or death.)
    - Activa™ RC system
    - Percept™PC neurostimulator
- Boston Scientific (*For the latest version of the safety manual, go to http://www.bostonscientific.com/manuals.)
    - Vercise Gevia™ DBS System

EVIDENCE SUMMARY

The principal outcome for deep brain stimulation (DBS) for any indication is symptom reduction and improved function. Assessment of the safety and efficacy of DBS requires well-designed and well-executed randomized controlled trials (RCTs) comparing DBS with sham or on- versus off- phases to determine the following:

- whether the benefits of DBS outweigh any risks
- whether DBS offers advantages over conventional treatments.

The evidence base is sufficient that deep brain stimulation (DBS) improves the net health outcomes of selected patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients and may be considered medically necessary when criteria are met. Therefore, the evidence for DBS for these indications will not be reviewed in this policy. Below is a brief synopsis of the evidence for Parkinson's disease, essential tremor, or primary dystonias.

SYMTPOMS ASSOCIATED WITH PARKINSON'S DISEASE

Systematic Reviews and Technology Assessments

The policy for PD and tremor was initially based on two BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessments; a 1997 TEC Assessment focused on unilateral deep brain stimulation of the thalamus as a treatment for tremor[1] and a 2001 TEC Assessment focused on the use of deep brain stimulation of the globus pallidus and subthalamic nucleus for a broader range of Parkinson symptoms.[2]

A number of large systematic reviews have been published on the use of DBS for PD and tremor[3-13] confirming the efficacy of DBS in the control of motor signs and improvement of patients' functionality and quality of life.

Randomized Controlled Trials

There have been additional published RCTs of deep brain stimulation for PD, which continue to report overall positive results [14-23]. Some of these trials suggest that subthalamic stimulation was superior to medical therapy in patients with Parkinson's disease and early motor complications, while others did not find significant differences in overall health outcomes for patients. Surgery related adverse effects addressed in these RCTs indicate that the most common adverse effect is infection.

Nonrandomized Studies

Two new DBS systems with directional leads are currently available (approved by the Food and Drug Administration [FDA] in 2016 and 2017). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Published evidence consists of several small observational studies, with sample sizes ranging from 7 to 13.[24-27] The studies showed that patients experienced improved tremor scores and improved quality of life (QOL). Compared with historical data from conventional DBS systems, directional DBS widened the therapeutic window and achieved beneficial effects using lower current level. Comparative, larger studies are needed to support the conclusions from these small studies. Data from a large study of 292 patients are expected in 2018.

PRIMARY DYSTONIA

DBS for the treatment of primary dystonia received FDA approval through the Humanitarian Device Exemption (HDE) process.[28] The HDE approval process is available for those conditions that affect less than 4,000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. As noted in the FDA's analysis of risk and probable benefit, the only other treatment

options for chronic refractory primary dystonias are neurodestructive procedures. DBS provides a reversible alternative. The FDA summary of Safety and Probable Benefit states, “Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and in some cases, progress to a life-threatening stage or constitute a major fixed handicap. When the age of onset of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychological development but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses that may cause permanent disfigurement. Risks associated with DBS for dystonia appear to be similar to the risk associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications Parkinson’s Disease and Essential Tremor), except when used in either child or adolescent patient groups.”

The FDA HDE approval was based on the results of DBS in 201 patients represented in 34 manuscripts. There were three studies that reported at least ten cases. Clinical improvement ranged from 50 to 88%. A total of twenty-one pediatric patients were studied; 81% were older than seven years. Among these patients there was approximately a 60% improvement in clinical scores.

Since the FDA approval, there have been additional published randomized controlled trials of deep brain stimulation for dystonia, which continue to report positive results.[29-31] These trials included one with a long-term follow-up of five years. Two of the trials reported on the serious adverse effects of DBS, the majority of which were related to the implantation procedure. Dysarthria, involuntary movements and depression were common non-serious adverse events reported.[32]

In 2017, Moro published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).[33] Reviewers included studies with at least 10 cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the GPi. There were only two controlled studies, one RCT (described below) and one study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6 to 72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0 to 120) from 24 studies, the mean increase in scores at six months compared with baseline was 23.8 points (95% CI 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95% CI 22.4 to 30.9 points). The mean percentage improvement was 59% at six months and 65% at last follow-up. Fourteen studies reported BFMDRS disability scores (scale range, 0 to 30). Compared with baseline, the mean absolute change in the score was 4.8 points (95% CI 3.1 to 6.6 points) at six months and 6.4 points (95% CI 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44% at six months and 59% at last follow-up. Rodrigues (2019) performed a Cochrane systematic review of RCTs and identified the same two RCTs.[32]

The remaining literature review below will focus on the use of DBS for the investigational indications in this policy.

TARDIVE DYSKINESIA AND TARDIVE DYSTONIA

Systematic Review

Grabel (2023) published a meta-analysis of clinical outcomes of DBS to treat tardive dystonia.[34] Fourteen studies were included that involved 134 patients. Studies were either single case reports or multiple case series. Using a random effects model on the summary mean data for each study yielded an estimated 70.56% overall mean improvement from DBS with high heterogeneity (I^2=93.91%). The authors acknowledge the possibility of positive selection bias due to the inclusion of single case studies. According to the authors no RCTs have been performed that evaluate DBS for TDD.

Tardive dyskinesia and dystonia (TDD) are severe side effects of dopamine-blocking agents, particularly antipsychotics. Little is known about the possible psychiatric complications of DBS in psychiatric patients. The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% (95% CI 71.4% to 83.3%; p<0.000) on the Burke-Fahn-Marsden Dystonia Rating Scale.[35] The data suggest DBS could be effective and relatively safe for patients with treatment-resistant TDD; however, these results should be interpreted with caution, as most of the data are from case reports and small trials.

Mentzel (2015) performed a systematic review to assess the effects and side-effects of deep brain stimulation (DBS) in patients that have developed a severe debilitating treatment-resistant form of TDD.[36] This review included 19 case-reports and small-scale trials without randomization or blinding (n=52 patients). Using the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), the Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptoms Rating Scale (ESRS), the investigators assessed the average improvement in the patients' condition, reporting that improvement as a result of DBS was statistically significant (p<0.00001) on all scales. However, limited conclusions can be drawn from this review on the efficacy and safety of DBS in this population, since there were no randomized controlled trials identified.

Randomized Controlled Trials

Stimulation of the globus pallidus has been examined as a treatment of tardive dyskinesia in a phase II double-blinded (presence and absence of stimulation) multicenter study.[37] The trial was stopped early due to successful treatment (greater than 40% improvement) in the first 10 patients.

Gruber (2018) assessed dystonia/dyskinesia severity using the Burke-Fahn- Marsden-Dystonia-Rating-Scale, BFMDRS at three months between active versus sham DBS.[38] Twenty-five patients were randomized. In the intention-to-treat analyses, the between group difference of dystonia severity was not significant at three months. Adverse events occurred in 10 of the 25 patients; three of the adverse events were serious. The study was originally powered to include 48 patients but only 25 were randomized and analyses may be underpowered.

Nonrandomized Studies

Pouclet-Courtemanche (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with DBS.[39] Patients were assessed after 3, 6, and 12 months after bilateral globus pallidus stimulation. At six months, all patients had experienced greater than 40% reduction in symptoms as measured on the Extrapyramidal Symptoms Rating Scale (ESRS). At 12 months, the mean decrease in ESRS score was 58% (range, 21%

to 81%). An additional small (n=9) case series reported improvement in motor and disability scores.[40]

CEREBRAL PALSY

Koy (2022) published a prospective study aimed at assessing motor and nonmotor outcomes, with a focus on the quality of life (QOL) effects of DBS on pediatric patients with pharmacorefractory dyskinetic cerebral palsy. [41] The multi-site study enrolled 16 patients, age 8 to 18 years for the initial single-arm phase of the study, during which they were treated with DBS that targeted the globus pallidus internus for 12 months. After 12 months of DBS, 14 of the participants entered the second phase of the study; a randomized, double-blind crossover to either DBS for 24 hours followed by sham stimulation for 24 hours, or sham stimulation for 24 hours followed by DBS for 24 hours. The primary endpoint was mean change in the Caregiver Priorities & Child Health Index of Life and Disabilities (CPCHILD) questionnaire from baseline to 12 months. At 12 months the mean change in the CPCHILD score was not statistically significant (p=0.125). Of multiple secondary outcomes, significant results were improvement in Canadian Occupational Performance Measure performance scores from baseline to 12 months (change 1.1 +/- 1.2; [95% CI 0.2 – 1.9] points; p=0.02), and improvement in the Short-Form-36 physical health component noted by both patients and caregivers (patients, change 5.1 +/- 6.2 [95% CI 0.7 – 9.6] points; p= 0.028; caregivers, change 4.6 +/- 7.3 [95% CI 0.5 – 8.6] points; p=0.029). The authors state the statistically significant measures indicate improved performance of activities of daily living and physical health-related QOL for patients and caregivers. Seven other secondary outcome measures of physical health and QOL were not statistically significant. At randomization, there was no significant difference between stimulation modes (ON/OFF) in the BFMDRS-movement scores (p=0.141), or DIS (p=0.513). Limitations of the study include its small number of participants.

Koy (2013) reported data on the therapeutic outcomes of DBS in cerebral palsy.[42] Twenty articles comprising 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was 64.94 ± 25.40 preoperatively and dropped to 50.5 ± 26.77 postoperatively, with a mean improvement of 23.6% (p<0.001) at a median follow-up of 12 months. The mean Burke-Fahn-Marsden Dystonia Rating Scale disability score was 18.54 ± 6.15 preoperatively and 16.83 ± 6.42 postoperatively, with a mean improvement of 9.2% (p<0.001). There was a significant negative correlation between severity of dystonia and clinical outcome (p<0.05). Authors suggest DBS can be an effective treatment option for dyskinetic cerebral palsy. In view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.[43]

EPILEPSY/INTRACTABLE SEIZURES

DBS has been investigated for the treatment of intractable seizures in patients who do not respond to pharmacologic therapy. Approximately one-third of patients with epilepsy do not respond to anti-epileptic drugs and are considered to have drug-resistant epilepsy. Patients with drug-resistant or refractory epilepsy have a higher risk of death as well as a high burden of epilepsy-related disabilities and limitations. To date studies show promise but these early reports of therapeutic success are not confirmed by controlled clinical trials. Questions

regarding the best structures to stimulate, the most effective stimuli, and the contrasting effects of high-frequency and low-frequency stimulation remain unanswered.

Systematic Review

Haneef (2023) published a systematic review and meta-analysis comparing DBS to vagus nerve stimulation (VNS) and responsive neurostimulation (RNS) for generalized drug-resistant epilepsy.[44] Twenty studies, including eight using DBS were included. Mean follow-up time for DBS was 23.1 months and 39.1 months for VNS. RNS data were insufficient for analysis. Seizure reduction was greater for DBS (64.8%) than VNS (48.3%) (p=0.02). Studies addressing both treatments were deemed of moderate heterogeneity. Limitations include that only one DBS study was an RCT.

Skrehot (2023) also published a systematic review and meta-analysis comparing DBS to VNS and RNS for focal epilepsy.[45] The analysis included 24 studies, of which 11 were of DBS. This study also found that DBS was associated with greater seizure reduction than VNS (p<0.01) and that RNS and DBS had similar efficacy at one year follow-up. However, differences in efficacy narrowed by three-year follow-up to non-significant (p = 0.75).

Touma (2022) in collaboration with The International League Against Epilepsy (ILAE) Surgical Therapies Commission published a systematic review and meta-analysis to summarize the available evidence on DBS, vagus nerve stimulation (VNS), and responsive neurostimulation (RNS) in the treatment of drug-resistant epilepsy (DRE).[46] The analysis focused on the efficacy and tolerability of the three therapies for adults. The primary outcome measure was mean percentage decrease in seizure frequency. Thirty studies were included in the review. The majority were VNS studies. DBS was the intervention in only three studies. No study offered a head-to-head comparison of the treatments. Of the three studies involving DBS, one was an RCT, and the other two reported outcomes for the same cohort. The RCT found a significant difference in seizure frequency at 3 months between the intervention group and the control arm (p=0.0017), but the difference in seizure freedom was not statistically significant (relative risk [RR] = 0.3; 95% CI: 0.0, 8.2). Adverse events reported in the RCT include increased risk for depression (p=0.02) and memory impairment (p=0.03) in the intervention arm. However, long-term data showed mean seizure reduction of 69% at five years and 70% at seven years. There was also improvement in quality-of-life scores (QOLIE-31) at five years (p=0.001).

Rheims (2022) published a systematic review and meta-analysis of 28 studies investigating the impact of surgery and neuromodulation for drug-resistant epilepsy on mortality.[47] The authors note that the higher mortality rate in people with drug-resistant epilepsy is primarily due to epilepsy-related deaths. DBS procedure-related deaths specifically in people with drug-resistant epilepsy were not documented. The study cites an overall 0.2% postoperative in-hospital death rate from DBS for movement disorders. The rate of sudden unexpected death in epilepsy (SUDEP) was similar between DBS (2.9/1000 patient years [PY]) and RNS (2.8/1000 PY). The authors were unable to address whether DBS has a protective effect on SUDEP. When seizure freedom is established after surgery, the data suggest reduced mortality and decreased incidence of SUDEP. The available evidence on the potential impact of DBS on mortality from drug-resistant epilepsy is limited so definitive conclusions could not be drawn.

A 2022 systematic review by Vetkas evaluated the effectiveness of DBS of the anterior thalamic nucleus, the centromedian thalamic nucleus, and the hippocampus.[48] A total of 48 articles with 527 patients (sample sizes between 3 and 81) met inclusion criteria. For the

anterior thalamic nucleus, centromedian thalamic nucleus, and hippocampus there were two, two, and three RCTs (including the SANTE trial described below) and 23, 8, and 13 total studies, respectively. There was moderate to high heterogeneity (I^2 69 to 90%) for the anterior thalamic nucleus and the hippocampus and low heterogeneity for the centromedian thalamic nucleus. According to the meta-analysis, the mean seizure reduction after stimulation of the anterior thalamic nucleus, centromedian thalamic nucleus, and hippocampus was 60.8% (95% CI 55.72 to 65.89), 73.4% (95% CI 68.83 to 77.87), and 67.8% (58.14 to 77.46), respectively.

Two systematic reviews published in 2018 on the use of DBS for drug-resistant epilepsy assessed many of the same studies. The larger review, by Li (2018), identified 10 RCTs and 48 uncontrolled studies.[49] The literature search date was not reported. Meta-analyses were not performed. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS was limited due to the small population sizes. The RCT in which DBS targeted the anterior nucleus of the thalamus (Fisher [2010] described below) reported paresthesias (23%), implant site pain (21%), and implant site infection (13%). Reviewers concluded that more robust clinical trials would be needed.

In a 2014 Cochrane review, updated in 2017, the safety, efficacy and tolerability of DBS and cortical stimulation were assessed in patients with refractory epilepsy.[50, 51] The reviews included RCTs comparing DPS to sham stimulation, resective surgery or further treatment with antiepileptic drugs. Of the 10 RCTs identified for inclusion in the 2014 review, three trials were specific to DBS (one anterior thalamic DBS trial, n=109 treatment periods; two centromedian thalamic DBS trials, n=20, 40 treatment periods). The studies added in the 2017 update were a cross-over RCT of bilateral anterior thalamic stimulation (n=4) and a double blind RCT of hippocampal stimulation (n=6) that was not included in the meta-analysis due to missing detailed methodology. The primary outcome measures included the proportion of patients who were disease free and a 50% or greater reduction in seizure frequency after one to three months. The evidence was rated as moderate quality and no statistical or clinically significant differences were reported based upon the primary outcome measures. Authors concluded that there is insufficient evidence upon which to draw conclusions regarding the efficacy and safety of hippocampal DBS or centromedian DBS as a treatment for epilepsy.

Randomized Controlled Trials

Fisher (2010) reported results of a multicenter, RCT of bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE).[52] Fisher randomized patients who had failed at least three antiepileptic drugs to one of two groups, stimulation on or stimulation off. This was a 3-month double blind phase. After this phase, all patients received unblinded stimulation. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on and stimulation off was not significantly different (-42.1% vs. -28.7%, respectively). In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures compared with the control group (-40.4% vs. -14.5%, respectively p=0.0017). During the blinded phase, the stimulation group experienced significantly fewer

seizure-related injuries than patients in the control group (7.4% vs. 25.5%, respectively p=0.01). Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression (8 vs. 1, respectively) or memory problems (7 vs. 1, respectively) as adverse events. Depression symptoms resolved in four of the eight stimulated patients over an average of 76 days (range 14 to 145). There was a progressive reduction in seizure frequency over long-term follow-up. On intention-to-treat analysis, the median change in seizure frequency was -44% at 13 months and -57% at 25 months. By two years, 54% of patients had a seizure reduction of at least 50%, and 14 patients (13%) were seizure-free for at least six months. The most common device-related adverse events were paresthesias in 18.2% of participants, implant site pain in 10.9%, and implant site infection in 9.1%. Eighteen participants (16.4%) withdrew from the study after the implantation because of adverse events. There were five deaths, none of which were considered to be device-related. Although some patients appeared to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was modest.

Troster (2017) assessed neuropsychological adverse events from the SANTE trial during the three-month blinded phase, and at seven-year follow-up during the open-label noncomparative phase.[53] At baseline, there were no differences in depression history between groups. During the three-month blinded phase of the trial, depression was reported in eight (15%) patients from the stimulation group and in one (2%) patient from the no stimulation group (p=0.02). Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (seven in the active group, one in the control group; p=0.03). At seven-year follow-up, after the treatment groups had been combined, there was no statistically significant difference in Profile of Mood State depression score compared with baseline and most cognitive function tests did not improve over baseline measurements.

A seven-year follow-up of SANTE was reported in the FDA SSED.[54] Seventy-three (66% of implanted) patients completed the year seven visit. Reasons for withdrawals from the study after implantation were: death (6), withdrawal of consent (5), investigator decision (3), therapeutic product ineffective (13), implant site infection or pain (6), other adverse event (7) and elective device removal (1). Fifty patients were included in the year 7 analysis of responder rate. Seventy-four percent of the 50 patients were responders (50% or greater reduction in seizure frequency). QOLIE-31 scores (n=67) improved by a mean of 4.9 (SD=11) points at year 7. LSSS scores (n=67) improved by a mean of 18 points (SD=23) at year 7. As the FDA documentation notes, interpretation of the long-term follow-up is limited by several factors: patients were aware they were receiving DBS, only 66% of implanted patients completed the year 7 visit and those who did not do well may be more likely to leave the study, and changes in anti-epileptic drugs were allowed in long-term follow-up.

Cukiert (2017) conducted a double-blind, placebo-controlled randomized trial evaluating outcomes of hippocampal stimulation in 16 patients with refractory temporal lobe epilepsy.[55] Prior to treatment, all patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). All patients underwent DBS device implantation, and were followed for six months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. There was a significant difference in FIAS frequency from the first month

of full stimulation until the end of the blinded phase (p<0.001) and FAS frequency for the same period except for the third month of the blinded phase.

Nonrandomized Studies

Peltola (2023) published long-term follow-up data on anterior nucleus of the thalamus (ANT) DBS therapy for 170 adults with drug resistant epilepsy from the Medtronic Registry for Epilepsy (MORE) registry.[56] MORE is an observational registry that collects prospective and retrospective data on adults with drug-resistant epilepsy being treated in 25 centers across 13 countries. After two years, the median monthly seizure frequency decreased by 33.1% (p<0.0001). A subgroup of 47 patients were followed for five years and had a 55% reduction in median seizure activity. Quality of Life in Epilepsy scores were improved by 2-points overall (p< 0.05), but data were available for only 78 people. Importantly, the most frequently observed adverse events were increased seizure frequency/severity in 16% of participants. Other adverse events were self-reported memory impairment (15%), self-reported depressive mood (15%). Limitations include reliability of self-reported data, non-protocolized visit windows, optional questionnaires and the use of retrospective data.

Kim (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS.[57] Patients' mean age was 31 years, they had had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. Mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year one, 74% at year two and ranged from 62% to 80% through 11 years of follow-up. Complications included one symptomatic intracranial hemorrhage, one infection requiring removal and reimplantation, and two lead disconnections.

Long-term outcomes of the SANTE trial, described above, were reported by Salanova in 2015.[58] The uncontrolled open-label portion of the trial began after three months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the three-year follow-up, and 83 (75%) completed five years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at one year and 69% at five years (p<0.001 for both). During the study, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first several months after implantation. The most frequently reported serious adverse events were implant site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the study and none were considered to be device-related. Depression was reported in 41 (37%) patients over the study; in three cases, this was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the study, half of which had a history of the condition. Although some patients appear to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was overall modest.

TRAUMATIC BRAIN INJURY

Central thalamic deep brain stimulation (CT-DBS) has been investigated as a therapeutic option to improve behavioral functioning in patients with severe traumatic brain injury (TBI)[43]; however, there are no RCTs for this indication.

NEUROPSYCHIATRIC APPLICATIONS

In addition to the areas of research discussed above, DBS is being investigated for the treatment of Tourette syndrome, depression, addiction, alcohol addiction, anorexia, and obsessive compulsive disorder. Evidence remains insufficient to evaluate the efficacy of DBS for these disorders due to small sample sizes and other limitations in the available studies.[59]

Tourette Syndrome

Systematic Reviews

Wehmeyer (2021) conducted a pooled analysis of DBS for treatment-refractory Tourette syndrome.[60] A total of 65 studies with 376 patients were included. The primary outcome was Yale Global Tic Severity Scale (YGTSS) scores, which were significantly reduced at maximum follow-up of median 25 months ($p<0.001$). The median scores decreased from 79.92 points (interquartile range [IQR], 13.25) to 34.69 points (IQR, 20.93) post-surgery, which represented a reduction rate of 56.59%. A majority of patients (69.4%) also experienced symptom reduction of more than 50% at maximum follow-up. In addition, other tic-related outcome measures (modified Rush video-based tic rating scale, YGTSS total tic score) and comorbidities (Yale-Brown Obsessive Compulsive Scale, Becks Depression Inventory), were also significantly reduced after deep brain stimulation.

Baldermann conducted a systematic review that included 57 studies on DBS for Tourette syndrome, four of which were randomized crossover studies. The studies included a total of 156 cases.[61] Twenty-four studies included a single patient each and four had sample sizes of 10 or more (maximum, 18). Half of the patients (n=78) were stimulated in the thalamus and the next most common areas of stimulation were the global pallidus internus anteromedial part (n=44) and postventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was YGTSS scores. In a pooled analysis of within subject pre-post data, there was a median improvement of 53% in the YGTSS, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in the YGTSS and 54% and more than a 50% improvement. In addition, data were pooled from the four crossover RCTs; there were a total of 27 patients receiving DBS and 27 receiving a control intervention. Targets included the thalamus and the globus pallidus. In the pooled analysis, there was a statistically significant between-group difference, favoring DBS (SMD=0.96; 95% CI 0.36 to 1.56). The authors noted that the effect size of 0.96 is considered to be a large effect.

A 2012 systematic review by Pansaon identified 25 published studies, representing data from 69 patients that reported on the efficacy of DBS in the treatment of Tourette syndrome.[62] However, only three studies with methodological quality ratings of fair to poor met the inclusion criteria for evidence-based analysis. The authors recommend that DBS continues to be considered an experimental treatment for severe, medically refractory tics.

Randomized Controlled Trials

Kefalopoulou (2015) reported on double-blind crossover trial that included 15 patients with severe medically refractory Tourette syndrome.[63] They received surgery for bilateral globus pallidus internus DBS and were randomized to the off-position first or the on-position first for three months followed by the opposite position for the next three months. Fifteen patients underwent surgery 14 were randomized and 13 completed assessments after both on- and off-phases. For the 13 study completers, the mean YGTSS scores were 80.7 (SD=12.0) in the off-stimulation phase and 68.3 (SD=18.6) in the on-stimulation phase. Mean difference n

YGTSS scores was 12.4 (95% CI 0.1 to 24.7) which was statistically significant (p=0.048) after Bonferroni correction. There was no between-group difference in YGTSS scores in patients who were randomized to the on-phase first or second. Three serious adverse events were reported, two related to surgery and one related to stimulation. The authors noted that the most effective target for DBS in Tourette syndrome patients needs additional study.

Piedad (2012) analyzed patient and target selection for DBS of Tourette syndrome. The majority of clinical trials for DBS in Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus.[64] Other targets that have been investigated include the subthalamic nucleus, caudate nucleus, globus pallidus internus, and the anterior limb of the internal capsule and nucleus accumbens. The review found no clear consensus in the literature for the best target or for which patients should be treated. Additional study is needed to clarify these issues.

In 2011, Ackermans reported preliminary results of a double-blind crossover trial of thalamic stimulation in six patients with refractory Tourette syndrome.[65] Tic severity during three months of stimulation was significantly lower than during the three months with the stimulator turned off, with a 37% improvement on the Yale Global Tic Severity Scale (mean 25.6 vs. 41.1) and a decrease in tic severity of 49% at one year after surgery compared to preoperative assessments (mean 21.5 vs. 42.2 – both respectively).Secondary outcomes (change in associated behavioral disorder and mood) were not altered by the stimulation. Serious adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances, and reduction of energy levels in all patients. The interim analysis led to the termination of the trial. The authors commented that further RCTs on other targets are urgently needed since the search for the optimal one is still ongoing.

Depression

The role of deep brain stimulation in treatment of other treatment-resistant depression, is also being investigated. Standard treatment modalities for treatment-resistant depression include psychotherapy, medication, and electroconvulsive therapy (ECT). However, even with a number of therapies being available, many patients can still remain symptomatic despite treatment. As an alternative therapy option, there have been multiple trials exploring deep brain stimulation in various cerebral targets for treatment-resistant depression.

Systematic Reviews

Sobstyl (2022) published a systematic review of studies that evaluated deep brain stimulation to the subcallosal cingulate cortex in patients with treatment resistant depression.[66] All study designs were considered but at least five patients were required and follow-up had to be a minimum of 6 months. Among the 14 studies included in the analysis (N=230), mean follow-up was 14 months (range, 6 to 24). Outcomes of interest included response and remission rates at the last follow-up visit. Using raw scores, the response rate at last follow-up was 0.57 (95% CI, 0.44 to 0.69; p=.299; I^2=60.76%) and remission rate was 0.399 (95% CI, 0.2923 to 0.5158; p=.09; I^2=42.80%).

Wu (2021) conducted a meta-analysis of blinded studies that compared deep brain stimulation to control (placebo or sham stimulation).[67] There were 17 studies included, with a total of 233 patients, however, the majority were open-label studies (n=15). Anatomic targets included subcallosal cingulate gyrus (n=8), ventral capsule/ventral striatum (n=2), epidural

prefrontal cortical (n=2), nucleus accumbens (n=1), superior lateral branch of the medial forebrain bundle(n=2), posterior gyrus rectus (n=1) and ventral anterior limb of the interna capsule (n=1). The pooled response rate estimate for the two RCTs was 1.45 (95% CI 0.50 to 4.21) and for the open-label studies it was 0.56 (95% CI 0.43 to 0.69); there was significant heterogeneity (I^2 = 73.6%; p<0.0001). The pooled estimate for remission rate in the open-label studies was 0.32 (95% CI 0.25 to 0.39) with no statistical heterogeneity (I^2 = 30.3%; p=0.127); the pooled estimate for adverse events in the open-label studies was 0.67 (95% CI 0.54 to 0.80) with significant heterogeneity (I^2 =76.8%; p<0.0001).

Hitti (2020) conducted a meta-analysis and meta-regression of blinded studies that compared active deep brain stimulation to sham stimulation (12 trials, 186 patients).[68] Anatomic targets included the ventral anterior limb of the internal capsule, ventral capsule/ventral striatum, subcallosal cingulate, inferior thalamic peduncle, medial forebrain bundle, and lateral habenula. The most common target was the subcallosal cingulate. Meta-analysis showed a modest reduction in depression rating scales (standardized mean difference =-0.75; 95% CI -1.13 to -0.36; p<0.001) with moderate heterogeneity across studies (I^2=59%). Meta-regression did not identify a significant difference between target areas. Adverse events included headache (26% of patients), visual disturbances (21%), worsening depression (16%), sleep disturbance (16%) and anxiety (14%).

In a recent systematic review, the literature was identified and reviewed for research findings related to treatment-resistant BD.[69] Therapeutic trials for treatment-resistant bipolar mania are uncommon and provide few promising leads other than the use of clozapine. Far more pressing challenges are the depressive-dysthymic-dysphoric-mixed phases of BD and long-term prophylaxis. Therapeutic trials for treatment-resistant bipolar depression have assessed various pharmacotherapies, behavioral therapies, and more invasive therapies including electroconvulsive therapy (ECT), transcranial magnetic stimulation, and deep brain stimulation-all of which are promising but limited in effectiveness. Most studies identified in the review were small, involved supplementation of typically complex ongoing treatments, varied in controls, randomization, and blinding, usually involved brief follow-up, and lacked replication. Clearer criteria for defining and predicting treatment resistance in BD are needed, as well as improved trial design with better controls, assessment of specific clinical subgroups, and longer follow-up. Due to significant limitations within literature the effectiveness of DBS for bipolar treatment is not known at this time.

Controlled Trials

Crowell (2019) reported long-term follow-up of a within-subject trial with 28 participants with TRD or bi-polar II disorder who were treated with DBS of the subcallosal cingulate.[70] Patients were included who had depression for at least 12 months with non-response to at least three antidepressant medications, a psychotherapy trial, and electroconvulsive therapy (lifetime). Seventeen of the patients had a one-month sham-controlled period and 11 patients had a one-month open label period before the stimulation was turned on. Eight-year follow-up was available for 14 of the 28 participants. The primary outcome measure was the Illinois Density Index, which assesses the longitudinal area under the curve for behavioral measures; in this study these included response (>50% decrease from baseline) and remission (score <7) on the HAM-D. More than 50% of patients maintained a response and 30% in remission, over the eight years of follow-up. The physician-rated Clinical Global Impressions severity score improved from 6.1 (severely ill) at baseline to less than 3 (mildly ill or better) in this open label trial.

Obsessive-compulsive Disorder

The role of deep brain stimulation in treatment of OCD is also being investigated. This condition can be very debilitating and cause significantly reduced quality of life for patients. Conventional management strategies include cognitive-behavioral therapy, medications, and surgical intervention, however response to treatment may take months, and significant improvement with these therapies is not guaranteed. Deep brain stimulation may be an alternative therapy option for patients with treatment-refractory OCD, and some trials have explored safety and efficacy of this treatment for people with OCD.

Systematic Reviews

Gadot (2022) published a systematic review of the efficacy of deep brain stimulation for treatment-resistant OCD and comorbid depressive symptoms.[71] Studies were included if they reported patient-level data on the effect of deep brain stimulation on the Yale-Brown Obsessive-Compulsive Scale. Thirty-four studies (N=352) were included in the analysis (9 RCTs, 25 nonrandomized trials) and both study types had a low risk of bias. Median follow-up in the included studies was 24 months (IQR, 12 to 32). Outcomes of interest included mean difference and percent reduction in the scale, and responder rate (defined as ≥35% reduction in Yale-Brown Obsessive-Compulsive Scale score). Random effects modeling found that Yale-Brown Obsessive-Compulsive Scale scores decreased by a mean of 47% (14.3 points; p<.01). The response rate at last follow-up was 66% (95% CI, 57% to 74%).

Cruz (2022) conducted a systematic review and meta-analysis of 25 studies published between 2003 and 2020 that assessed the efficacy of DBS for severe and treatment-resistant OCD.[72] Severe OCD was defined as a score of between 24 and 31 on the Yale-Brown Obsessive Compulsive Scale (YBOCS). Treatment resistance was defined as resistance after at least 12 weeks of high-dose selective serotonin reuptake inhibitors (SSRI) therapy and augmentation strategies. Of the 25 studies analyzed, 8 were double-blinded clinical trials, all of which were included in the Raviv (2020) systematic review.[73] The analysis included 303 patients and mean follow-up was 36.98 months. Nearly 45% of the participants were female. Funnel plot was used to assess risk of bias. The meta-analysis found significant improvement in YBOCS scores after DBS (25 studies; SMD=2.39; 95% confidence interval [CI] 1.91-2.87; p<0.0001; $I^{2=}$72%). Analysis restricted to the eight RCTs also demonstrated significant improvement in YBOCS scores but heterogeneity was similar (8 studies; SMD=2.51; 95% CI, 1.80-3.22; p<0.0001; I^2=66%). Subgroup analysis found improved YBOCS scores after DBS with different targets, but could not assess all possible targets. Ventral capsule/ventral striatum (VC/VS) and nucleus accumbens (NAc) were the most frequently used targets (VC/BS, 5 studies; SMD=3.72; 95% CI, 1.25-6.18; p<0.0001; I^2=64%); Nucleus accumbens (NAc) (NAc, 3 studies; SMD=2.14; 95% CI, 1.46-2.81; P=0.003; I^2=89%). The analysis found DBS resulted in improvement in affective symptoms and functioning. Hamilton Depression Rating scores (HAM-D) significantly decreased, indicating clinical improvement (9 studies; SMD=1.19; 95% CI, 0.84-1.54; p<0.0001; I^2=17%). Hamilton Anxiety Rating scores (HAM-A) showed significant improvement (5 studies; SMD=1.00; 95% CI 0.32-1.69; p=0.004; I^2=59%). Global Assessment of Functioning scores also significantly improved after DBS (7 studies; SMD=-3.51; 95% CI, -5.00 - -2.02; p=0.005; I^2=90%). The study strengths include that it independently analyzed the four manifestations of OCD; YBOCS scores, and scores related to affective symptoms and functioning. Limitations include that there was high heterogeneity in most analyses and it was not possible to assess the effectiveness of all of the various DBS targets and modes of delivery. Safety of DBS was not addressed.

Mar-Barrutia (2021) evaluated both the short-term and long-term effects of deep brain stimulation for OCD, and included 29 studies (n=230) for short-term response and 11 studies (n=155) for long-term responses assessment; there were 7 total RCTs included.[74] Mean follow-up duration for the short-term and long-term studies was 1.5 years and 5.3 years, respectively. The authors noted that few studies were graded as low risk of bias, and there was marked heterogeneity among the studies reviewed which makes it difficult for comparison. The primary outcome measured was the YBOCS and the mean changes in scores from pre- to post-treatment were similar in the short-term studies (change from 33.0 to 17.2) and the long-term studies (change from 34.4 to 18.0); however, significantly more patients met criteria for response in the long-term group (70.7%) versus the short-term group (60.6%). There were 26.6% of patients in the long-term group who were classified as non-responders.

A systematic review by Raviv (2020) identified 28 studies that met their criteria on deep brain stimulation for OCD, including nine RCTs, one cohort study, one case-control study, one cross-sectional study, and 16 case series with more than two patients.[73] Only four studies were graded as low risk of bias, and the authors noted that there is no consensus on the optimal target. Striatal targets were the most common and included the anterior limb of the internal capsule, ventral striatum, nucleus accumbens, and caudate nucleus, but there was some discrepancy in nomenclature and overlap in stereotaxic coordinates. Additional targets included the subthalamic nucleus, bed nucleus of stria terminalis, inferior thalamic peduncle, and globus pallidus internus. The majority of studies utilized the Yale-Brown Obsessive Compulsive Scale; a score of 24 or more (of a possible 40) indicates severe illness. Responders were defined as at least 35% reduction in Yale-Brown Obsessive Compulsive Scale score and partial responders as a reduction between 25% and 35%. There was substantial variability in response for each target area, which may be related to the phenotypic diversity within the psychiatric diagnosis.

Vicheva (2020) conducted a systematic review and meta-analysis of the use of DBS for treatment-resistant OCD.[75] Eight studies including 80 patients total met inclusion criteria. There was significant heterogeneity across studies. A meta-analysis of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores found a 38.68% pooled mean reduction. There were five severe surgery-related adverse events (intracerebral hemorrhage in three patients and infection in two patients) and eight severe mood-related serious adverse events (one completed suicide, three suicide attempts in two patients, and suicidal thoughts and depression in four). There were additional mild and transient adverse events.

Kisely conducted a systematic review and meta-analyses pooling study findings evaluating DBS for OCD, including only double-blind RCTs of active versus sham DBS.[76] Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel group RCTs with or without a crossover phase and two were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (three studies), the nucleus accumbens (one study) and the subthalamic nucleus (one study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Y-BOCS. This is a 10-item scale in which higher scores reflect more intense symptoms, and a score of 24 or more (of a possible 40) is considered severe illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline, with a reduction of 25 to 35% or more considered a partial response. Only one of the five studies reported proportion of responders Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS. When data from the

five studies were pooled, there was a statistically significantly greater reduction in the mean Y-BOCS in the active versus sham group (mean difference, -8.49; 95% CI 12.18 to -4.80). The outcome measure, however, does not allow conclusions on whether the difference between groups is clinically meaningful. Trial authors reported 16 serious adverse events including one cerebral hemorrhage and two infections requiring electrode removal. Additionally, nonserious transient adverse events were reported including 13 reports of hypomania, five of increase in depressive or anxious symptoms and six of headaches.

Anorexia Nervosa

Anorexia nervosa is an eating disorder characterized by a chronic course that is refractory to treatment in many patients and has one of the highest mortality rates of any psychiatric disorder. Two systematic reviews and meta-analysis were published in 2022 to evaluate the efficacy of DBS in the treatment of anorexia nervosa. Neither review included RCTs. Karaszewska (2022) sought to estimate the overall effect of DBS in anorexia nervosa by evaluating the evidence of benefit in weight restoration, QOL, and reduction of psychiatric symptoms.[77] The primary outcome was body mass index (BMI) change after DBS. The secondary outcome was combined effect on psychiatric symptoms at the last observation. The meta-analysis included four studies with 56 participants. Only one participant was male. Follow-up periods ranged from 6 to 24 months. Random effects meta-analysis found improvement in BMI after DBS (Hedges's g=1.13; 95% CI=0.80-1.46; Z-value=6.75; p<0.001) without heterogeneity(I^2 =0.00, p=0.901). Meta-analysis also found improvement in combined psychiatric symptom severity at last observation (Hedges's g=0.89; 95% CI=0.57-1.21; Z-value=5.47; p<0.001, I^2=4.29,p=0.371). The most common adverse effect (AE) was pain at the incision site. Less common reported AE's were cutaneous complications, hypomanic symptoms, auto-intoxication, and seizure. The risk of bias was deemed moderate for the primary study outcome of change in BMI, but serious for the secondary outcome measurements. The authors conclude that additional research on DBS therapy for anorexia nervosa is needed, but DBS may be considered an effective "last resort" treatment option for severe treatment-refractory anorexia nervosa.

The goals of the meta-analysis performed by Shaffer (2023) were to assess the efficacy of DBS on longitudinal BMI changes and compare DBS targets with anorexia nervosa.[78] The primary outcome measures were percentage BMI change at 6 and 9-12 months. Eleven studies with 36 participants were included, of whom 94.4% were female. Two of the studies were included in the Karaszewska (2022) review and five were single case studies. The overall mean percentage improvement in BMI was 12.63% at six months (SD 26.72%, n=34; 1.51 [3.28] kg/m^2) and 23.62% at 9-12 months (SD 32.62%, n=25; 2.62 [3.89] kg/m^2]. P-score rankings were calculated for DBS targets based on percentage BMI change at six and 9-12 months. The subcallosal cingulate cortex (SCC) (n=11) had the highest P-score at both time points (6-month: 0.9449, 9-12 month: 0.9771), and the ventral anterior limb of the internal capsule (VALC) (n=4) had the lowest (6-month: 0.0279, 9-12 month: 0.1179). Reported AEs that were considered most likely due to DBS included surgical site infection, pain or headache, seizure, skin ulceration, wound dehiscence or need for revision. Risk of bias in the six studies that included two or more subjects was determined to be small in five studies and fair in one. The authors concluded that there is insufficient evidence that supports DBS as clearly beneficial compared to standard therapy for anorexia nervosa.

In a systematic review by McClelland (2013), two case series and two case reports that applied DBS to anorexic patients were identified and reviewed with mixed results.[79] There are no RCTs investigating DBS for this indication.

Alcohol Addiction

Alcohol dependency can be considered as a chronic mental disorder characterized by frequent relapses even when treated with appropriate medical or psychotherapeutic interventions.

Bach (2023) published an RCT that compared DBS to sham stimulation in 12 male participants with at least a 10-year history of alcohol abuse disorder (AUD) that was treatment resistant.[80] All participants had DBS electrodes surgically placed and then were randomized to have either DBS or sham treatment for six months. Then the study was unblinded and all participants had 12 months of DBS therapy. Nine participants completed the study. The primary outcome measure was time to first alcohol use within six months after randomization. Secondary outcomes were alcohol consumption during the 18-month period after randomization, six subjective measures at 6 and 12 months after randomization, and safety outcomes. The difference between the groups in time to first alcohol use, the primary outcome measure, was not statistically significant (HR = 0.73; 95% CI 0.20-2.62; p=0.625). However, the participants randomized to DBS in the first six months had significantly more abstinent days at six months (p=0.048), a higher mean proportion of abstinent days (p=0.032), and fewer heavy drinking days (p=0.041). The DBS group also reported lower alcohol cravings after six months (p=0.020), but analysis across both groups showed lower alcohol cravings at six months (p=0.014) compared to baseline. Both groups also had significantly higher proportion of abstinent days after 18 months (p=0.004). Further research with larger, more representative groups is needed to understand whether DBS is an effective therapy for alcohol addiction.

A 2012 systematic review by Herremans and Baeken investigated several neuromodulation techniques including deep brain stimulation in the treatment of alcohol addiction.[81] Previous studies investigating these neuromodulation techniques in alcohol addiction remain to date rather limited. Overall, the clinical effects on alcohol addiction were modest. Neuromodulation techniques have only recently been subject to investigation in alcohol addiction and methodological differences between the few studies restrict clear conclusions. Nevertheless, the scarce results encourage further investigation in alcohol addiction.

Alzheimer’s Disease

A 2022 systematic review and meta-analysis by Cheyuo analyzed invasive and non-invasive neuromodulation therapies in the treatment of Alzheimer’s Disease (AD).[82] Six studies were included in the meta-analysis, and of those, four involved DBS. The majority of the participants were in the two studies on non-invasive neuromodulation techniques. Of 242 total participants, 36 were from the four DBS studies. DBS was associated with improved cognitive outcome in people aged 65 years and older (p=0.004), but people younger than 65 years did not report better cognitive outcomes (p=0.65). Non-invasive neuromodulation techniques did not show improved cognitive outcome but were limited by lack of follow-up data. Further research is needed to understand the effect of DBS on cognitive function in people with AD.

OTHER APPLICATIONS

There is interest in applications of DBS beyond that for essential tremors, primary dystonia and Parkinson's disease. Clinical trials are being pursued; however, at this time, FDA approval is limited to the above indications and severe obsessive-compulsive disorder. The following discussion focuses on randomized controlled trials (RCTs) for the investigational indications noted in Policy Guidelines above.

Chronic Pain, Pain Syndromes, and Cluster Headaches

DBS for the treatment of chronic pain was investigated and largely abandoned in the 1980's due to poor results in two trials. With improved technology and surgical techniques there has been a resurgence of interest in DBS for intractable pain. DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has also been investigated as functional studies have suggested cluster headaches have a central hypothalamic pathogenesis. Outcomes and treatment protocols have been heterogenous.

Membrilla (2023) published a systematic review (SR) and meta-analysis of interventions for preventative treatment of refractory chronic cluster headache.[83] Forty-five studies involving 106 participants were included. Of those, ten studies were on DBS, but only one was an RCT. The RCT was the same study included in the Deer (2020) SR described below. The other nine studies were observational and described a variety of DBS stimulation targets. The meta-analysis of the seven studies that reported response data found a pooled response rate of 77.0% (OR 0.770, 95% CI 0.594-0.947, I^2=78.9%, p<0.001). Adverse events included two deaths. One was directly due to the lead implantation procedure that led to cerebral hemorrhage. The authors note the studies showed high heterogeneity, and further research is needed on the safety and efficacy of DBS for chronic cluster headache.

Deer (2020) conducted a systematic review of deep brain stimulation for chronic pain.[84] They identified one RCT from 2017 with 10 patients with post-stroke pain syndrome and one RCT from 2010 with 11 patients who had chronic cluster headaches (described above). Three early case series (1990 to 2017, n=12 to 48) included patients with a variety pain conditions, including phantom limb pain, cancer, brachial plexus injury, failed back surgery, and spinal cord injury. The location of the stimulation was variable. Publication bias was not assessed.

Due to the limited RCTs and small sample sizes, conclusions cannot be reached on the effectiveness of DBS as a treatment of any type of pain, including but not limited to cluster headaches, chronic spinal pain, failed back surgery syndrome, phantom limb pain, facial deafferentation pain, and central or peripheral neuropathic pain.

Morbid Obesity

The study of DBS of the hypothalamus and nucleus accumbens for cluster headache and obsessive-compulsive disorder (OCD) has prompted interest in DBS for obesity and addiction, which are thought to be associated with those brain regions. However, patients with unilateral subthalamic nucleus or globus pallidus internus DBS for PD were found to have gained a mean 4.86 pounds following initiation of DBS.[85] Contreras (2022) performed a systematic review of the literature on DBS for the treatment of refractory obesity.[86] A total of seven studies including 12 patients met inclusion criteria. The incidence of moderate side effects was 33%. Statistical was not possible due to the limited amount of data available in the articles and the small study populations do not permit conclusions on efficacy of DBS for obesity.

Multiple Sclerosis

No randomized controlled trials were found for DBS in the treatment of multiple sclerosis (MS) tremors. Brandmeir (2020) reported a meta-analysis of 13 studies of deep brain stimulation for multiple sclerosis tremor (129 patients received deep brain stimulation and 132 received medical management).[87] Results were compared for tremor severity after deep brain stimulation versus tremor severity at baseline, and were combined across different target areas (ventral intermediate nucleus of the thalamus, ventral oralis nucleus of the thalamus, ventral caudal nucleus of the thalamus, zona incerta) and different levels of evidence. Four studies were rated as level II evidence, but the studies were not randomized and the number of subjects in these studies was small, ranging from 4 to 12. Meta-analysis showed an improvement in the mean tremor score of 2.86 (95% CI 2.03 to 3.70, p<0.001). However, heterogeneity was high, suggesting that meta-analysis is not appropriate, and no distinction was made for the different anatomical targets. There was also evidence of publication bias. The small study populations do not permit conclusions on efficacy of DBS for MS tremors.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY

The 2019 guidelines from American Academy of Neurology (AAN) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics.[88] AAN notes that patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from DBS, but there is no consensus on the optimal brain target. Brain regions that have been stimulated in patients with Tourette Syndrome include the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. AAN concludes that DBS of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

In the 2013 AAN guidelines on the treatment for tardive syndromes (TDS), indicated there is insufficient evidence to support or refute DBS for TDS.[89] This recommendation is based on Level U evidence (evidence is insufficient to support or refute the use of any other treatment over another). The 2011 AAN guideline regarding essential tremor was reaffirmed in 2014 indicating that, “no high quality, long-term studies exist regarding the efficacy and safety of (DBS) for ET.”[90]

The AAN updated its guidelines on the treatment of essential tremor (ET) in 2011.[90] This update did not change the conclusions and recommendations of AAN 2005 practice parameters on DBS for ET.[91] The guidelines stated that bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C, possibly effective), but that there were insufficient data on the risk/benefit ratio of bilateral vs unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

The 2010 guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN.[92] AAN found that DBS of the STN possibly improves sleep quality in patients with advanced PD. However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the STN is not currently used to treat sleep disorders.

AMERICAN PSYCHIATRIC ASSOCIATION

In a 2007 the American Psychiatric Association (APA) published an evidence-based guideline, which was reaffirmed in 2012, on the treatment of patients with obsessive-compulsive disorder.[93] The APA gave their lowest level recommendation for DBS, among a list of other therapies with limited published evidence, for OCD that remains refractory “after first- and second-line treatment and well-supported augmentation strategies have been exhausted.” In the 2010 APA guideline for the treatment of major depression, DBS is listed as a search term in the literature review; however, no recommendations for DBS are mentioned.[94]

CONGRESS OF NEUROLOGICAL SURGEONS

In 2020 the Congress of Neurological Surgeons (CNS) updated the guidelines on DBS for obsessive-compulsive disorder, but the guideline is essentially unchanged since 2014:[95]

1. It is recommended that clinicians utilize bilateral subthalamic nucleus DBS over best medical management for the treatment of patients with medically refractory OCD. (Level I)
2. Clinicians may use bilateral nucleus accumbens or bed nucleus of stria terminalis DBS for the treatment of patients with medically refractory OCD. (Level II)

2018 evidence-based guidelines from the Congress of Neurological Surgeons (CNS) compared the efficacy of bi-lateral deep brain stimulation of the subthalamic nucleus and globus pallidus internus for the treatment of patients with Parkinson disease.[96]

Table 1. Recommendations of the Congress of Neurological Surgeons for DBS for Parkinson Disease

Goal	Most Effective Area of Stimulation (subthalamic nucleus or globus pallidus internus)	Level of Evidence
Improving motor symptoms	subthalamic nucleus or globus pallidus internus are similarly effective	I
Reduction of dopaminergic medication	subthalamic nucleus	I
Treatment of "on" medication dyskinesias	globus pallidus internus if reduction of medication is not anticipated	I
Quality of life	no evidence to recommend one over the other	I
Lessen impact of DBS on cognitive decline	globus pallidus internus	I
Reduce risk of depression	globus pallidus internus	I
Reduce adverse effects	insufficient evidence to recommend one over the other	Insufficient

SUMMARY

There is enough research to show that deep brain stimulation (DBS) improves health outcomes in select patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients. Therefore, DBS, including revision(s) or replacement(s), may be considered medically necessary when policy criteria are met.

Deep brain stimulation (DBS) is not clinically appropriate in patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias when criteria are not met. Therefore, DBS is considered not medically necessary for these indications when criteria are not met.

There is not enough research to determine the safety and effectiveness of deep brain stimulation (DBS) for other conditions. Current practice guidelines do not recommend the use of deep brain stimulation for the treatment of various neurologic and psychiatric disorders. Therefore, DBS is considered investigational for all other indications when policy criteria are not met.

REFERENCES

1. TEC Assessment 1996. "Deep Brain Stimulation for the Thalamus for Tremor." BlueCross BlueShield Association Technology Evaluation Center, Vol. 11, Tab 20.
2. TEC Assessment 2001. "Bilateral Deep Brain Stimulation of the Subthalamic Nucleus or the Globus Pallidus Interns for Treatment of Advanced Parkinson's Disease." BlueCross BlueShield Association Technology Evaluation Center, Vol. 16, Tab 16.
3. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord.* 2006;21 Suppl 14:S290-304. PMID: 16892449
4. Appleby BS, Duggan PS, Regenberg A, et al. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Mov Disord.* 2007;22(12):1722-8. PMID: 17721929
5. Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, et al. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. *Journal of neurology.* 2014. PMID: 24487826
6. Zappia M, Albanese A, Bruno E, et al. Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian Movement Disorders Association. *Journal of neurology.* 2013;260(3):714-40. PMID: 22886006
7. Sako W, Miyazaki Y, Izumi Y, et al. Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation. *J Neurol Neurosurg Psychiatry.* 2014;85:982-6. PMID: 24444854
8. Combs HL, Folley BS, Berry DT, et al. Cognition and Depression Following Deep Brain Stimulation of the Subthalamic Nucleus and Globus Pallidus Pars Internus in Parkinson's Disease: A Meta-Analysis. *Neuropsychol Rev.* 2015;25:439-54. PMID: 26459361
9. Xu F, Ma W, Huang Y, et al. Deep brain stimulation of pallidal versus subthalamic for patients with Parkinson's disease: a meta-analysis of controlled clinical trials. *Neuropsychiatric disease and treatment.* 2016;12:1435-44. PMID: 27382286
10. Tan ZG, Zhou Q, Huang T, et al. Efficacies of globus pallidus stimulation and subthalamic nucleus stimulation for advanced Parkinson's disease: a meta-analysis of randomized controlled trials. *Clinical interventions in aging.* 2016;11:777-86. PMID: 27382262
11. Wang JW, Zhang YQ, Zhang XH, et al. Cognitive and Psychiatric Effects of STN versus GPi Deep Brain Stimulation in Parkinson's Disease: A Meta-Analysis of Randomized Controlled Trials. *PloS one.* 2016;11(6):e0156721. PMID: 27248139

12. Xie CL, Shao B, Chen J, et al. Effects of neurostimulation for advanced Parkinson's disease patients on motor symptoms: A multiple-treatments meta-analysas of randomized controlled trials. *Scientific reports.* 2016;6:25285. PMID: 27142183
13. Lin F, Wu D, Lin C, et al. Pedunculopontine Nucleus Deep Brain Stimulation Improves Gait Disorder in Parkinson's Disease: A Systematic Review and Meta-analysis. *Neurochem Res.* 2020;45(4):709-19. PMID: 31950450
14. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med.* 2013;368(7):610-22. PMID: 23406026
15. Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol.* 2013;12(1):37-44. PMID: 23168021
16. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2006;355(9):896-908. PMID: 16943402
17. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol.* 2008;7(7):605-14. PMID: 18538636
18. Schupbach WM, Maltete D, Houeto JL, et al. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. *Neurology.* 2007;68(4):267-71. PMID: 17151341
19. Schuurman PR, Bosch DA, Merkus MP, et al. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov Disord.* 2008;23(8):1146-53. PMID: 18442104
20. Hariz MI, Krack P, Alesch F, et al. Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6 year follow-up. *J Neurol Neurosurg Psychiatry.* 2008;79(6):694-9. PMID: 17898034
21. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA.* 2009;301(1):63-73. PMID: 19126811
22. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 2010;9(6):581-91. PMID: 20434403
23. Schnitzler A, Mir P, Brodsky MA, et al. Directional Deep Brain Stimulation for Parkinson's Disease: Results of an International Crossover Study With Randomized, Double-Blind Primary Endpoint. *Neuromodulation : journal of the International Neuromodulation Society.* 2022;25(6):817-28. PMID: 34047410
24. Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain : a journal of neurology.* 2014;137(Pt 7):2015-26. PMID: 24844728
25. Steigerwald F, Muller L, Johannes S, et al. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. *Mov Disord.* 2016;31(8):1240-3. PMID: 27241197
26. Rebelo P, Green AL, Aziz TZ, et al. Thalamic Directional Deep Brain Stimulation for tremor: Spend less, get more. *Brain stimulation.* 2018. PMID: 29373260
27. Dembek TA, Reker P, Visser-Vandewalle V, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. *Mov Disord.* 2017;32(10):1380-88. PMID: 28843009

28. FDA Summary of Safety and Probable Benefit: Medtronic Activa Dystonia Therapy. [cited 03/19/2024]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007b.pdf.
29. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med.* 2006;355(19):1978-90. PMID: 17093249
30. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol.* 2014;13(9):875-84. PMID: 25127231
31. Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *Lancet Neurol.* 2012;11(12):1029-38. PMID: 23123071
32. Gruber D, Sudmeyer M, Deuschl G, et al. Neurostimulation in tardive dystonia/dyskinesia: A delayed start, sham stimulation-controlled randomized trial. *Brain stimulation.* 2018;11(6):1368-77. PMID: 30249417
33. Moro E, LeReun C, Krauss JK, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. *Eur J Neurol.* 2017;24(4):552-60. PMID: 28186378
34. Grabel M, Merola A. Pallidal deep brain stimulation for tardive dystonia: meta-analysis of clinical outcomes. *Neurol Sci.* 2023;44(3):827-33. PMID: 36378365
35. Mentzel CL, Tenback DE, Tijssen MA, et al. Efficacy and safety of deep brain stimulation in patients with medication-induced tardive dyskinesia and/or dystonia: a systematic review. *The Journal of clinical psychiatry.* 2012;73(11):1434-8. PMID: 23218160
36. Mentzel CL, Tenback DE, Tijssen MA, et al. [Severe treatment-resistant tardive dystonia: is deep brain stimulation a treatment option]. *Tijdschr Psychiatr.* 2015;57:125-31. PMID: 25669951
37. Damier P, Thobois S, Witjas T, et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. *Arch Gen Psychiatry.* 2007;64(2):170-6. PMID: 17283284
38. Rodrigues FB, Duarte GS, Prescott D, et al. Deep brain stimulation for dystonia. *The Cochrane database of systematic reviews.* 2019;1:CD012405. PMID: 30629283
39. Pouclet-Courtemanche H, Rouaud T, Thobois S, et al. Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia. *Neurology.* 2016;86(7):651-9. PMID: 26791148
40. Gruber D, Trottenberg T, Kivi A, et al. Long-term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology.* 2009;73(1):53-8. PMID: 19564584
41. Koy A, Kühn AA, Huebl J, et al. Quality of Life After Deep Brain Stimulation of Pediatric Patients with Dyskinetic Cerebral Palsy: A Prospective, Single-Arm, Multicenter Study with a Subsequent Randomized Double-Blind Crossover (STIM-CP). *Mov Disord.* 2022;37(4):799-811. PMID: 34967053
42. Koy A, Hellmich M, Pauls KA, et al. Effects of Deep Brain Stimulation in Dyskinetic Cerebral Palsy: A Meta-analysis. *Mov Disord.* 2013. PMID: 23408442
43. Giacino J, Fins JJ, Machado A, et al. Central thalamic deep brain stimulation to promote recovery from chronic posttraumatic minimally conscious state: challenges and opportunities. *Neuromodulation : journal of the International Neuromodulation Society.* 2012;15(4):339-49. PMID: 22624587
44. Haneef Z, Skrehot HC. Neurostimulation in generalized epilepsy: A systematic review and meta-analysis. *Epilepsia.* 2023;64(4):811-20. PMID: 36727550

45. Skrehot HC, Englot DJ, Haneef Z. Neuro-stimulation in focal epilepsy: A systematic review and meta-analysis. *Epilepsy Behav.* 2023;142:109182. PMID: 36972642
46. Touma L, Dansereau B, Chan AY, et al. Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission. *Epilepsia.* 2022;63(6):1314-29. PMID: 35352349
47. Rheims S, Sperling MR, Ryvlin P. Drug-resistant epilepsy and mortality-Why and when do neuromodulation and epilepsy surgery reduce overall mortality. *Epilepsia.* 2022;63(12):3020-36. PMID: 36114753
48. Vetkas A, Fomenko A, Germann J, et al. Deep brain stimulation targets in epilepsy: Systematic review and meta-analysis of anterior and centromedian thalamic nuclei and hippocampus. *Epilepsia.* 2022;63(3):513-24. PMID: 34981509
49. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. *Epilepsia.* 2018;59(2):273-90. PMID: 29218702
50. Sprengers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy. *The Cochrane database of systematic reviews.* 2014;6:CD008497. PMID: 24937707
51. Sprengers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy. *Cochrane Database of Systematic Reviews.* 2017(7). PMID: CD008497
52. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia.* 2010;51(5):899-908. PMID: 20331461
53. Troster AI, Meador KJ, Irwin CP, et al. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. *Seizure.* 2017;45:133-41. PMID: 28061418
54. PMA P960009/S219: FDA Summary of Safety and Effectiveness Data. Medtronic's Deep Brain Stimulator (DBS) System. . [cited 3/19/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S219b.pdf.
55. Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. *Epilepsia.* 2017;58(10):1728-33. PMID: 28744855
56. Peltola J, Colon AJ, Pimentel J, et al. Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Drug-Resistant Epilepsy in the MORE Multicenter Patient Registry. *Neurology.* 2023;100(18):e1852-e65. PMID: 36927882
57. Kim SH, Lim SC, Kim J, et al. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. *Seizure.* 2017;52:154-61. PMID: 29040867
58. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology.* 2015;84(10):1017-25. PMID: 25663221
59. Nuttin B, Wu H, Mayberg H, et al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. *J Neurol Neurosurg Psychiatry.* 2014;85:1003-8. PMID: 24444853
60. Wehmeyer L, Schüller T, Kiess J, et al. Target-Specific Effects of Deep Brain Stimulation for Tourette Syndrome: A Systematic Review and Meta-Analysis. *Front Neurol.* 2021;12:769275. PMID: 34744993
61. Baldermann JC, Schuller T, Huys D, et al. Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis. *Brain stimulation.* 2016;9(2):296-304. PMID: 26827109

62. Steeves T, McKinlay BD, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: behavioural therapy, deep brain stimulation, and transcranial magnetic stimulation. *Canadian journal of psychiatry Revue canadienne de psychiatrie.* 2012;57(3):144-51. PMID: 22398000
63. Kefalopoulou Z, Zrinzo L, Jahanshahi M, et al. Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomised crossover trial. *Lancet Neurol.* 2015;14(6):595-605. PMID: 25882029
64. Piedad JC, Rickards HE, Cavanna AE. What patients with gilles de la tourette syndrome should be treated with deep brain stimulation and what is the best target? *Neurosurgery.* 2012;71(1):173-92. PMID: 22407075
65. Ackermans L, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain : a journal of neurology.* 2011;134(Pt 3):832-44. PMID: 21354977
66. Sobstyl M, Kupryjaniuk A, Prokopienko M, et al. Subcallosal Cingulate Cortex Deep Brain Stimulation for Treatment-Resistant Depression: A Systematic Review. *Front Neurol.* 2022;13:780481. PMID: 35432155
67. Wu Y, Mo J, Sui L, et al. Deep Brain Stimulation in Treatment-Resistant Depression: A Systematic Review and Meta-Analysis on Efficacy and Safety. *Front Neurosci.* 2021;15:655412. PMID: 33867929
68. Hitti FL, Yang AI, Cristancho MA, et al. Deep Brain Stimulation Is Effective for Treatment-Resistant Depression: A Meta-Analysis and Meta-Regression. *J Clin Med.* 2020;9(9). PMID: 32872572
69. Poon SH, Sim K, Sum MY, et al. Evidence-based options for treatment-resistant adult bipolar disorder patients. *Bipolar disorders.* 2012;14(6):573-84. PMID: 22938165
70. Crowell AL, Riva-Posse P, Holtzheimer PE, et al. Long-Term Outcomes of Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression. *The American journal of psychiatry.* 2019;176(11):949-56. PMID: 31581800
71. Gadot R, Najera R, Hirani S, et al. Efficacy of deep brain stimulation for treatment-resistant obsessive-compulsive disorder: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2022. PMID: 36127157
72. Cruz S, Gutiérrez-Rojas L, González-Domenech P, et al. Deep brain stimulation in obsessive-compulsive disorder: Results from meta-analysis. *Psychiatry Res.* 2022;317:114869. PMID: 36240634
73. Raviv N, Staudt MD, Rock AK, et al. A Systematic Review of Deep Brain Stimulation Targets for Obsessive Compulsive Disorder. *Neurosurgery.* 2020;87(6):1098-110. PMID: 32615588
74. Mar-Barrutia L, Real E, Segalás C, et al. Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years. *World J Psychiatry.* 2021;11(9):659-80. PMID: 34631467
75. Vicheva P, Butler M, Shotbolt P. Deep brain stimulation for obsessive-compulsive disorder: A systematic review of randomised controlled trials. *Neuroscience and biobehavioral reviews.* 2020;109:129-38. PMID: 31923474
76. Kisely S, Hall K, Siskind D, et al. Deep brain stimulation for obsessive-compulsive disorder: a systematic review and meta-analysis. *Psychol Med.* 2014;44:3533-42. PMID: 25066053
77. Karaszewska D, Cleintuar P, Oudijn M, et al. Efficacy and safety of deep brain stimulation for treatment-refractory anorexia nervosa: a systematic review and meta-analysis. *Transl Psychiatry.* 2022;12(1):333. PMID: 35970847

78. Shaffer A, Naik A, Bederson M, et al. Efficacy of deep brain stimulation for the treatment of anorexia nervosa: a systematic review and network meta-analysis of patient-level data. *Neurosurg Focus.* 2023;54(2):E5. PMID: 36724522
79. McClelland J, Bozhilova N, Campbell I, et al. A systematic review of the effects of neuromodulation on eating and body weight: evidence from human and animal studies. *European eating disorders review : the journal of the Eating Disorders Association.* 2013;21(6):436-55. PMID: 24155246
80. Bach P, Luderer M, Müller UJ, et al. Deep brain stimulation of the nucleus accumbens in treatment-resistant alcohol use disorder: a double-blind randomized controlled multi-center trial. *Transl Psychiatry.* 2023;13(1):49. PMID: 36755017
81. Herremans SC, Baeken C. The current perspective of neuromodulation techniques in the treatment of alcohol addiction: a systematic review. *Psychiatria Danubina.* 2012;24 Suppl 1:S14-20. PMID: 22945180
82. Cheyuo C, Germann J, Yamamoto K, et al. Connectomic neuromodulation for Alzheimer's disease: A systematic review and meta-analysis of invasive and non-invasive techniques. *Transl Psychiatry.* 2022;12(1):490. PMID: 36411282
83. Membrilla JA, Roa J, Díaz-de-Terán J. Preventive treatment of refractory chronic cluster headache: systematic review and meta-analysis. *Journal of neurology.* 2023;270(2):689-710. PMID: 36310189
84. Deer TR, Falowski S, Arle JE, et al. A Systematic Literature Review of Brain Neurostimulation Therapies for the Treatment of Pain. *Pain medicine (Malden, Mass).* 2020. PMID: 32034418
85. Locke MC, Wu SS, Foote KD, et al. Weight changes in subthalamic nucleus vs globus pallidus internus deep brain stimulation: results from the COMPARE Parkinson disease deep brain stimulation cohort. *Neurosurgery.* 2011;68(5):1233-7; discussion 37-8. PMID: 21273927
86. Contreras López WO, Navarro PA, Crispín S. Effectiveness of Deep Brain Stimulation in Reducing Body Mass Index and Weight: A Systematic Review. *Stereotact Funct Neurosurg.* 2022;100(2):75-85. PMID: 34583359
87. Brandmeir NJ, Murray A, Cheyuo C, et al. Deep Brain Stimulation for Multiple Sclerosis Tremor: A Meta-Analysis. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(4):463-68. PMID: 31755637
88. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92(19):896-906. PMID: 31061208
89. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81:463-9. PMID: 23897874
90. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology.* 2011;77(19):1752-5. PMID: 22013182
91. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2005;64(12):2008-20. PMID: 15972843
92. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice Parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(11):924-31. PMID: 20231670

93. Koran LM, Hanna GL, Hollander E, et al. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *The American journal of psychiatry.* 2007;164(7 Suppl):5-53. PMID: 17849776
94. Alan J. Gelenberg AJ FM, Markowitz jc, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. [cited 03/19/2024]. 'Available from:' https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.
95. Surgeons CoN. Deep Brain Stimulation for Obsessive-Compulsive Disorder. [cited 3/19/2024]. 'Available from:' https://www.cns.org/guidelines/browse-guidelines-detail/deep-brain-stimulation-obsessive-compulsive-disord.
96. Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients With Parkinson's Disease: Executive Summary. *Neurosurgery.* 2018;82(6):753-56. PMID: 29538685

CODES

Codes	Number	Description
CPT	61850	Twist or burr hole(s) for implantation of neurostimulator electrode(s), cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure).
	61867	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
	61868	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	;with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming

Codes	Number	Description
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
	95984	;with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
HCPCS	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Date of Origin: *April 1998*

Regence

Medical Policy Manual Surgery, Policy No. 92

Radiofrequency Ablation (RFA) of Tumors Other than Liver

Effective: January 1, 2024

Next Review: November 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Radiofrequency ablation kills cells using the heat produced by radiofrequency energy delivered into the tumor via a probe.

MEDICAL POLICY CRITERIA

Note: This policy does not address liver tumors (primary or metastatic). See Cross References.

I. Radiofrequency ablation may be considered **medically necessary** to treat tumors when one or more of the following criteria are met:

   A. Localized renal cell carcinoma that is no more than 4 cm in size when one or both of the following criteria are met:

      1. Preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate (GFR) of less than 60 mL/min per m^2) and standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; or

      2. Patient is not considered a surgical candidate.

B. Osteoid osteomas that are unresponsive to initial medical treatment.

C. To palliate pain in patients with osteolytic bone metastases who have failed or are poor candidates for standard treatments (e.g., radiation).

D. Isolated peripheral non-small cell lung cancer (NSCLC) lesion that is no more than 3 cm in size when both of the following criteria are met:

1. Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; and
2. Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

E. Malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when all of the following criteria (1. – 3.) are met:

1. In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status, or the patient is not considered a surgical candidate; and
2. There is no evidence of extrapulmonary metastases; and
3. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

F. Renal angiomyolipomas when one or more of the following criteria are met:

1. Symptomatic lesion (e.g., hemorrhage), or
2. Asymptomatic lesion larger than 4 cm.

G. Benign thyroid nodules when the following criteria are met (1. – 2.):

1. Nodule is symptomatic; and
2. Nodule is confirmed as benign using fine needle aspiration (FNA)

II. Ultrasound-guided radiofrequency ablation (e.g., Acessa™, Sonata®) may be considered **medically necessary** for the treatment of symptomatic uterine fibroids when there are significant clinical manifestations or findings attributable to fibroids, including one or more of the following:

A. Abnormal uterine bleeding

B. Iron-deficiency anemia

C. Dyspareunia

D. Pelvic pain or pressure

E. Urinary or bowel dysfunction

III. Radiofrequency ablation is considered **investigational** as a technique for ablating all other benign or malignant tumors other than liver tumors that do not meet the policy criteria above including but not limited to breast tumors, initial treatment of osteoid osteomas and painful bony metastases, and all primary or metastatic lung (pulmonary) tumors that do not meet medical necessity.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Specific description of the tumor(s) targeted for treatment including the following:
    - Tumor type (primary vs. metastatic; primary tumor type)
    - The location of tumor(s)
    - The number and size(s) of lesion(s) being treated
2. For requests for ultrasound-guided radiofrequency ablation for the treatment of symptomatic uterine fibroids, documentation of significant clinical manifestations or findings attributable to fibroids
3. Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
4. Whether the goal of treatment is curative or palliative
5. Comorbidities and any contraindicated treatments (e.g., surgery; radiation therapy)
6. Prior treatments, if any, and tumor response
7. Documentation of whether this treatment is to preserve organ function

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE), Medicine, Policy No. 140
2. Cryosurgical Ablation of Miscellaneous Solid Tumors, Surgery, Policy No. 132
3. Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation, Surgery, Policy No. 139
4. Microwave Tumor Ablation, Surgery, Policy No. 189
5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204

BACKGROUND

Radiofrequency ablation (RFA) was initially developed to treat inoperable tumors of the liver (see Cross References). Recently, studies have reported on the use of RFA to treat other tumors. For some of these, RFA is being investigated as an alternative to surgery for operable tumors. Well-established local or systemic treatment alternatives are available for each of these malignancies. The hypothesized advantages of RFA for these cancers include improved local control and those common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

Goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain cancerous tumors. The effective volume of RFA depends on the frequency and duration of applied current, local tissue characteristics, and probe configuration (eg, single vs multiple tips). RFA can be performed as an open surgical procedure, laparoscopically or percutaneously, with ultrasound or computed tomography guidance.

Potential complications associated with RFA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during RFA of kidney), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), and secondary tumors (if cells seed during probe removal).

REGULATORY ISSUES

The U.S. Food and Drug Administration (FDA) issued the following statement September 24, 2008 concerning the regulatory status of radiofrequency ablation.[1] "The FDA has cleared RF ablation devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. Some RF ablation devices have been cleared for additional specific treatment indications, including partial or complete ablation of nonresectable liver lesions and palliation of pain associated with metastatic lesions involving bone. The FDA has not cleared any RF ablation devices for the specific treatment indication of partial or complete ablation of lung tumors, citing lack of sufficient clinical data to establish safety and effectiveness for this purpose. The FDA has received reports of death and serious injuries associated with the use of RF ablation devices in the treatment of lung tumors."

In 2012, the Acessa™ System (Acessa Health, formerly Halt Medical) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for percutaneous laparoscopic coagulation and ablation of soft tissue and treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance (K121858). The technology was previously approved in 2010, at which time it was called the Halt 2000GI™ Electrosurgical Radiofrequency Ablation System. In 2014, the ultrasound guidance system received marketing clearance from the FDA (K132744). FDA product code: GEI. In 2018, the third-generation Acessa™ ProVu System® was cleared for marketing by the FDA through the 510(k) process for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. (K181124). FDA product code: HFG.

In 2018, the Sonata® Sonography-Guided Transcervical Fibroid Ablation System (Gynsonics) was cleared for marketing by the FDA through the 510(k) process for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids (K173703). The Sonata system was previously known as Vizablate. FDA product codes: KNF, ITX, and IYO.

EVIDENCE SUMMARY

RENAL CELL CARCINOMA

BACKGROUND

Radical nephrectomy, partial nephrectomy, or nephron-sparing surgery remains the principal treatments of renal cell carcinoma (RCC).

RFA may be considered a treatment option when surgical excision is not an option such as the following:

- When preservation of renal function is necessary (e.g., in patients with marginal renal function, a solitary kidney, bilateral tumors)
- In patients with comorbidities that would render them unfit for surgery.

- In patients at high risk of developing additional renal cancers (as in von Hippel-Lindau disease).

SYSTEMATIC REVIEWS

Green (2023) published a systematic review that evaluated metastasis-directed ablative therapies in extracranial metastatic renal cell carcinoma.[2] 18 prospective and matched-pair case control studies of RFA, cryotherapy, microwave ablation, and stereotactic body radiotherapy (SBRT) in metastatic renal cell carcinoma were included. Most were single-arm studies (n=17), and one study was an RCT. Overall, 570 patients were treated across studies: 56 were treated with cryotherapy (n=2 studies), 90 were treated with RFA (n=2 studies), and 424 (n=14 studies) were treated with SBRT. Study sample sizes ranged from 12 to 69 participants, and mean follow-up occurred at 17.3 months. A median overall survival of 22.7 months was reported in eight studies (five SBRT, two cryotherapy, and one RFA). Median progression-free survival was reported in seven studies (five SBRT, one cryotherapy, and one RFA); the median was 9.3 months (range 3.0 to 22.7 months). The toxicity grade greater than or equal to three ranged from 1.7% to 10%. Due to low sample size, direct comparison of SBRT to ablative studies was not feasible.

Li (2022) conducted a systematic review and meta-analysis to compare the long-term outcomes of RFA to partial nephrectomy for cT1 renal cancer.[3] Seven studies (n=1,635 patients) were included; reviews and case reports were excluded from the review and meta-analysis. Treatment efficacy of RFA was not different than partial nephrectomy in terms of cancer recurrence (OR=1.22, 95% CI, 0.45 to 3.28), progression-free survival (HR=1.26, 95% CI, 0.75 to 2.11), and cancer-specific survival (HR=1.27, 95% CI, 0.41 to 3.95) as well as major complications (OR=1.31, 95% CI, 0.55 to 3.14) ($p>0.05$ for all). RFA was a potential significant risk factor for overall survival (HR=1.76, 95% CI, 1.32 to 2.34, $p<0.001$). The authors did not identify significant heterogeneity or publication bias and concluded that RFA has comparable therapeutic efficacy to partial nephrectomy.

Yanagisawa (2022) published a systematic review (SR) with meta-analysis comparing differential clinical outcomes of partial nephrectomy (PN) versus ablation techniques, including RFA, cryoablation, and microwave ablation, for cT1b and cT1a renal tumors.[4] The review included 27 studies with 13,996 total patients who received either PN or ablation for treatment of their tumors. There were no differences in the percent decline of estimated glomerular filtration rates (eGFR) or in the overall complication rates between PN and ablation therapy for either tumor type. There was no difference in cancer mortality rates between PN and ablation in patients with either cT1a or cT1b tumors. However, compared to ablation, PN was associated with a lower risk of local recurrence in patients with either tumor type (cT1a: pooled risk ratio [RR]; 0.43, 95% confidence intervals [CI]; 0.28-0.66, cT1b: pooled RR; 0.41, 95%CI; 0.23-0.75). A majority of the included studies were retrospective with a significant heterogeneity in methodology.

In their systematic review and meta-analysis, Uhlig (2019) compared oncologic, perioperative, and functional outcomes for PNwith outcomes for various ablative techniques, including RFA and others, for small renal masses (mean diameter=2.53 to 2.84 cm).[5] They identified 47 moderate-quality studies, mostly retrospective, published from 2005 to 2017, including one RCT. A total of 24,077 patients were included, of whom 15,238 received PN and 1,877 received RFA. The network meta-analysis used PN as the reference point. Cancer-specific mortality and local recurrence were calculated as incidence rate ratio. According to the meta-

analysis, for RFA and PN, respectively, cancer-specific mortality was 2.03 and 1.00 (95% CI 0.81 to 5.08), local recurrence was 1.79 and 1.00 (95% CI 1.16 to 2.76), complications OR was 0.89 and 1.00 (95% CI 0.59 to 1.33), and renal function decline (mean difference in glomerular filtration rate) was 6.49 and 0.00 (95% CI 2.87 to 10.10). The overall results indicated that PN had better overall survival (OS) and local control over ablative techniques, but it was not significantly better for cancer-related mortality. In addition, ablation had fewer complications and better renal function outcomes. Across the studies included, patients treated by PN tended to be younger with less comorbidity compared with patients receiving thermal ablation—a consideration when assessing the outcomes for survival and local control.

A 2019 systematic review reported by Favi included a descriptive summary of ablative therapy for renal allograft tumors.[6] The 28 studies that met inclusion criteria assessed RFA (n=78), cryoablation (n=15), MWA (n=3), HIFU (n=3), and irreversible electroporation (n=1) for mainly papillary renal cell carcinoma (RCC) and clear cell RCC. All but two neoplasms were stage T1a N0 M0. In this population, three cases of primary treatment failure, a single case of recurrence, and no cancer-related deaths were reported. Complication rate was mostly below 10% and graft function remained stable in the majority of patients. No meta-analyses were performed and due to the limited sample size the authors were not able to determine a clear benefit of one procedure over the others.

An AHRQ Evidence Report, most recently amended in 2016, included thermal ablation (RFA or cryoablation; surgical or image-guided) as an available management strategies for stage I or II RCC.[7] The report noted that better oncologic outcomes were believed to be achieved with partial or radical nephrectomy; however, these procedures were associated with significantly higher complication rates than thermal ablation or active surveillance.

In 2014 Wang published a meta-analysis of 145 studies published through July 2013 comparing effectiveness and complications of radiofrequency ablation and partial nephrectomy (PN) for treatment of stage T1 renal tumors.[8] The rate of local progression was greater with RFA than laparoscopic/robotic or open partial nephrectomy (4.6%, 1.2%, 1.9%, respectively; $p<0.001$.) RFA had more frequent minor complications than laparoscopic/robotic or open partial nephrectomy (13.8%, 7.5%, 9.5%, respectively; $p<0.001$). However, the rate of major complications was greater with open partial nephrectomy than laparoscopic/robotic partial nephrectomy or RFA (7.9%, 7.9%, 3.1%, respectively, $p<0.001$). Several limitations to this meta-analysis were discussed in the article. These included the limited follow-up duration of the included studies and the unavailability of the original study data. Despite the limitations, the data was sufficient for the authors to conclude that both RFA and PN were viable in terms of short-term outcomes and low complication rates. RFA showed a higher risk of local tumor progression but lower complication rates.

RANDOMIZED CONTROLLED TRIALS

Since the systematic reviews reported above, no additional randomized controlled trials evaluating RFA as a treatment for renal cell carcinoma were identified.

NONRANDOMIZED STUDIES

Published studies have consistently reported fairly high success rates at up to six years follow-up; two to five re-ablation sessions were often necessary to achieve 95% tumor necrosis.[9-32] Numerous case series, while unreliable, consistently suggest that the benefits of RFA outweigh the risks in patients for whom nephrectomy is not possible. Current studies suggest

that physician specialty (i.e., interventional radiology, urology) and experience, and procedure approach (i.e., percutaneous, open, laparoscopic) may impact tumor recurrence and patient survival outcomes, and authors have recommended further study on these variables.

ADVERSE EVENTS

Reported complication rates have been low.[9-31, 33] Complications reported in the literature to date have included the following:

- Perinephric hematomas
- Hemorrhage
- Ureteral strictures
- Percutaneous urinary fistula
- Appendiceal perforation

BREAST TUMORS

BACKGROUND

The standard treatment for breast cancer is surgical excision by lumpectomy or mastectomy. Adjuvant radiation therapy, chemotherapy, and/or hormone therapy may also be used. If treated, fibroadenomas, benign tumors of the breast, are typically surgically excised.

SYSTEMATIC REVIEWS

Xia (2021) conducted a SR and meta-analysis of studies assessing RFA in patients with breast cancer and tumors that were 2 cm or smaller.[34] The primary endpoints of interest were technical success rate, complete ablation rate, and rate of complications. A total of 17 studies were identified, which accounted for 399 patients (401 lesions). Technical success rate ranged from 86.67% to 100% in the included studies; the pooled technical success rate was 99% (95% CI 98% to 100%). After RFA, the majority of patients underwent surgical tumor excision (65.74%, 261/397). The pooled complete ablation rate was 98% (95% CI 97% to 100%). The complication rate in the entire cohort was 6.8%; the most common complications were skin burn (2%), breast inflammation (1.5%), and infections (1%). The pooled complications rate was 2% (95% CI 1% to 4%). Local recurrence was reported in 10 studies (232 cases); there was no local recurrence reported after a median follow-up of 27 months in these patients. The authors noted that prospective studies evaluating the use of RFA alone are needed to validate the place in therapy.

In 2016, Chen reported results from a meta-analysis of clinical trials assessing the effect of RFA for breast cancer.[35] The authors pooled data from fifteen nonrandomized studies that were published between 2001 and 2012. Of the 15 studies, eight studies reported that the tumor size was <2 cm, five studies reported <3 cm, and the remaining two studies reported <5 cm; eleven studies reported complete ablation rate, from which pooled estimates were 89% (95% CI 85 to 93%) of patients receiving RFA achieved a complete ablation. Five studies reported recurrence rate, from which pooled data suggest no local recurrence at a maximum follow-up of 76 months. A statistical test of publication bias showed no potential publication bias (Z=0.78, p=0.436). The analyses were limited by small sample size of the included studies, and heterogeneity in patient selection; the authors conclude large, well-designed studies are necessary.

In 2010, Zhao conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009.[36] Nine of the studies reviewed focused on RFA for small breast tumors ranging in size from 0.5 – 7 cm. Tumor resection was performed immediately after ablation or up to four weeks after RFA. Complete coagulation necrosis rates of 76% to 100% were reported. These studies were limited to feasibility or pilot studies that were difficult to compare due to heterogeneous patient and tumor characteristics and energy sources. In addition, the studies were conducted in the research setting rather than in clinical practice. The authors concluded that RFA for breast cancer tumors was feasible but further studies with longer follow-up on survival, tumor recurrence and cosmetic outcomes are needed.

Similarly, another 2010 review of 17 studies by Soukup reported that RFA for the treatment of breast tumors was feasible and promising.[37] However, while minimal adverse effects and complications occurred with breast RFA, the authors noted that incomplete tumor ablation remained a concern. Additional studies of health outcomes and refinement of the procedure were recommended.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of RFA as a treatment for breast tumors were identified.

NONRANDOMIZED STUDIES

Ito (2018) retrospectively studied the safety and efficacy of percutaneous RFA of breast carcinomas in 386 patients from 10 institutions treated with RFA between 2003 and 2009.[38] Patients were followed for a median of 50 months and ipsilateral breast tumor recurrence was more frequent in patients with initial tumor sizes of 2 cm or more (10% [3/30]) than those with initial tumors 2 cm or less (2.3% [8/355]; p=0.015). Ipsilateral breast tumor recurrence rates five years after RFA were 97%, 94%, and 87% in patients with initial tumor sizes of 1 cm or less, 1.1 to 2.0 cm, and greater than 2 cm, respectively. The authors concluded that RFA was safe for tumors of 2 cm or less. The retrospective design and lack of data on ipsilateral breast tumor recurrence for different types of chemotherapy and endocrine therapy and analyses to ascertain whether adjuvant chemotherapy or endocrine therapy influenced outcomes are the limitations of this study.

The efficacy and safety of using ultrasound-guided RFA for multiple breast fibroadenoma as an alternative to surgical resection were retrospectively analyzed by Li (2016).[39] From 2014 to 2016, 65 patients with 256 nodules were treated with ultrasound-guided RFA and complete ablation was achieved for 251 nodules (98.04%) after the first month of treatment; after the first and third months, tumor volume overall was reduced by 39.06% and 75.99%, respectively. The study reported minimal to no complications such as skin burns, hematoma, or nipple discharge. The retrospective design and short follow-up time limited the conclusions drawn from this study.

The remainder of the published evidence is primarily limited to nonrandomized studies with small numbers of patients.[40-51] These studies preclude conclusions due to methodologic limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.

Systematic reviews, retrospective studies, and observational studies have reported varied and incomplete ablation rates as well as concerns about postablation tumor cell viability. Long-term

improvements in health outcomes have not been demonstrated. Additionally, available studies have not compared RFA with conventional breast-conserving procedures. For small breast tumors, further prospective study, with long-term follow-up, is needed to determine whether RFA can provide local control and survival rates compared with conventional breast-conserving treatment.

LUNG (PULMONARY) TUMORS

BACKGROUND

Surgery is the preferred treatment for primary non-small cell lung carcinoma (NSCLC). Patients with early-stage NSCLC who are not surgical candidates may be candidates for radiation treatment with curative intent. RFA is being investigated as a treatment of small primary lung cancers or lung metastases in patients who are not surgical candidates.

SYSTEMATIC REVIEWS

Laeseke (2023) conducted a systematic review and meta-analysis that compared the efficacy of image guided thermal ablation, including RFA, to SBRT in patients with stage IA NSCLC among studies with at least 40 patients.[52] Comparative and single-arm studies, as well as single treatments from comparative studies were included in the meta-analysis. Studies that enrolled patients with recurrent NSCLC, or that used interventions as salvage treatments, were excluded. Key outcomes of interest were local tumor progression, overall survival, and disease-free survival. 40 image-guided thermal ablation study-arms (n=2,691 patients) and 215 SBRT study-arms (n=54,789 patients) were identified. Local tumor progression was lowest after SBRT at years one and two in single-arm pooled analyses (4% and 9% versus 11% and 18%) and at one year in meta–regressions when compared to ablative therapies (odds ratio [OR]=0.2, 95% CI = 0.07 to 0.63). Microwave ablation patients had the highest disease-free survival of all treatments in single-arm pooled analyses. In meta–regressions at two and three years, disease-free survival was significantly lower for RFA compared to microwave ablation (OR=0.26, 95% CI = 0.12 to 0.58; OR=0.33, 95% CI = 0.16 to 0.66, respectively). Overall survival was similar across treatment types and time points. Older age, male patients, larger tumors, retrospective studies, and non-Asian study region were predictors of worse clinical outcomes. Among high quality studies, stage IA microwave ablation patients had lower local tumor progression, higher overall survival, and generally lower disease-free survival, compared to the main analysis of all NSCLC patients.

Sultan (2023) published a systematic review conducted by the Department of Veterans Affairs to compare the effectiveness of surgery to SBRT, stereotactic ablative radiotherapy (SABR), RFA, cryoablation, microwave ablation, laser ablation, and brachytherapy in patients with early-stage lung cancer.[53] The review authors did not identify any RCTs that examined ablation therapies for stage I lung cancer. RFA, cryoablation, microwave ablation, and laser ablation were assessed in non-randomized comparative studies. RFA was most often studied (k=11). Three retrospective studies compared any type of ablation with SBRT/SABR, and three retrospective studies compared RFA to SBRT/SABR. Ten retrospective studies reported on ablation compared to surgery (n=4 microwave ablation, n=4 RFA, n=2 combined ablation of any type, n=2 SBRT/SABR versus RFA versus surgery). Most of these studies (n=12) had 300 or fewer participants, except for six studies of the National Cancer Database and the Surveillance, Epidemiology and End-Results Database datasets which included 2,000-30,000 participants. All studies included older adults, and most studies did not report on whether participants were medically operable or inoperable. Two studies reported on only medically operable individuals. Due to heterogeneity of patient populations, interventions, and study designs, review authors did not pool data across studies to compare ablative therapies to surgery.

Chan (2021) published a SR and meta-analysis of CT-guided percutaneous ablation for stage I NSCLC.[54] A total of eight studies with 792 patients met inclusion criteria. Statistically significant differences were identified for one- and two-year disease-free survival, favoring surgery OR 2.22, 95% CI 1.14 to 4.34; OR 2.60, 95% CI 1.21 to 5.57 respectively). No statistically significant differences between groups were identified for one- to five-year OS or cancer-specific survival or three- to five-year disease-free survival. According to the subgroup analysis, there was no statistically significant difference in OS between lobectomy and microwave ablation but patients treated with sublobar resection (wedge resection or segmentectomy) had significantly longer one- and two-year OS versus RFA (OR 2.85, 95% CI 1.33 to 6.10; OR 4.54, 95% CI 2.51 to 8.21, respectively).

In a 2013 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review on local nonsurgical therapies for stage I non–small-cell lung cancer (NSCLC), no comparative RFA studies were identified.[55] The AHRQ report found available evidence is insufficient to draw conclusions on the comparative effectiveness of local nonsurgical therapies for NSCLC including RFA.

In a 2013 SR of RFA, surgical excision and stereotactic radiotherapy (SBRT) for colorectal cancer lung metastases, no randomized trials were identified and evidence was also insufficient to draw conclusions on the comparative effectiveness of these therapies.[56]

A 2011 SR also reported low quality evidence consisting of nonrandomized observational case series with no control group. The review included 46 studies with a total of 2,905 ablations in 1,584 patients.[57] The mean tumor size of 2.8 ± 1.0 cm. Local recurrence occurred in 282 cases (12.2%) and ranged from 0% to 64% as reported in 24 studies. Overall survival rates ranged from 25% to 100% with a mean of 59.4% as reported in 21 studies with a mean of 17.7 ± 12.4 months follow-up. The mean cancer-specific survival rate was 82.6% as reported in 24 studies with a range of 55% to 100% with a mean of 17.4 ± 14.1 months follow-up. Mean overall morbidity was 24.6% and most commonly included pneumothorax, pleural effusion and pain. Mortality related to the RFA procedure was 0.21% overall. The authors concluded RFA for the treatment of lung tumors demonstrated promise but that higher quality studies comparing RFA to other local treatment options “are urgently needed.”

In a 2012 review of evidence from 16 studies, Bilal compared RFA to SABR in patients with inoperable early stage non-small cell lung cancer (NSCLC).[58] The authors found overall survival rates for RFA and SABR were similar in patients at one year (68.2 to 95% vs. 81 to 85.7%) and three years (36 to 87.5% vs. 42.7 to 56%). However, survival rates at five years were lower with RFA (20.1 to 27%) than with SABR (47%). Caution must be used in interpreting these findings drawn from comparisons of results from uncontrolled, case series and retrospective reviews.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of RFA as a treatment for pulmonary tumors were identified.

NONRANDOMIZED STUDIES

Current studies consist of small case series, retrospective reviews, or uncontrolled cohort studies which focused primarily on technical feasibility and initial tumor response.[59-91]

One larger nonrandomized case series was published in 2011. Huang prospectively followed 329 consecutive patients treated with RFA for lung tumors.[92] Complications were experienced

by 34.3% (113) patients and was most commonly pneumothorax (19.1%). Overall survival at two and five years was 35.3% and 20.1%, respectively. The risk of local progression was not significantly different in tumors < 4 cm but became significant in tumors > 4 cm.

In 2015 de Baere review of a database from two cancer centers that included all consecutive patients (n=566) with lung metastases treated with RFA.[93] Median follow-up was 35.5 months (range 20 to 53 months) with 235 patients followed for more than two years. During follow-up, 176 patients died, of which 112 had progression of their lung tumor disease. Disease progression was also found in 227 of the 390 patients who were alive at last follow-up. Four-year local efficacy was 89% and lung disease control was 44.1%. Median overall survival was 62 months. Limitations of this study included the lack of a control group, and the lack of consideration of the impact of adjuvant chemotherapy.

Study quality concerns include lack of long-term follow-up, significant interstudy heterogeneity in terms of study design, patient populations and RFA methods used, and non-uniformity of reporting and efficacy scoring criteria. Prospective comparison in an RCT would permit greater certainty for this finding but the studies are consistent with some effect of RFA on lung tumors.

ADVERSE EVENTS

Acute, delayed or recurrent pneumothorax is the most commonly reported complication of lung RFA for primary or metastatic tumors (30 to 56% of treatment sessions).[84, 92, 94-97] Most cases resolved without chest tube placement. Other complications reported in the literature to date are considered uncommon and include, but are not limited to:[96-101] pleural effusion, intrathoracic hemorrhage with or without hemothorax, hemoptysis, pneumonia, pneumonitis, stellate ganglion injury, and brachial plexus injury.

OSTEOID OSTEOMAS

BACKGROUND

Osteiod osteomas (OO) usually heal spontaneously in three to four years and standard initial treatment includes medical management with NSAIDs. Invasive procedures including open surgery, laser photocoagulation, radiofrequency ablation, or core drill excision may be necessary if symptoms cannot be managed with NSAIDs.

SYSTEMATIC REVIEWS

Sangiorgio (2022) published a SR with meta-analysis to evaluate the safety and efficacy of radiofrequency ablation (RFA) versus surgical excision (SE) for the treatment of spinal OO. A total of 31 studies (n=749 patients) were included.[102] The main outcomes were pain before and after intervention, treatments success rate (complete pain relief with no recurrence until the last follow-up) and the number and type of complications. The reported mean treatment success rate was 85.6% (19 studies) for the SE group and 88.6% for the RFA group (18 studies). At last follow-up, the pooled mean difference in pain scores from baseline on a 0–10 scale was 5.8 points in the SE group and 6.7 points in the RFA group. Recurrences were observed in 5.6% of the patients who underwent SE and in 6.7% of the patients treated with RFA. The complication rate was 7.8% in the SE group and 4.4% in the RFA group. The authors conclude that the complication rate was low for both treatments and that RFA is a less invasive procedure which is as a safe and effective option for the treatment of spinal OO.

Lindquester (2020) reported a SR of various thermal ablation techniques for the treatment of OOs.[103] Of the total of 36 studies that met inclusion criteria (n=1798 patients), 32 evaluated RFA, three evaluated cryoablation, and one evaluated microwave ablation. The overall success rate, defined as all ablations minus technical failures, clinical failures, and recurrences, was 91.9% (95% CI 91 to 93%). The rates of technical failure, clinical failure, and recurrence were 0.3%, 2.1%, and 5.6%, respectively. Complications occurred in 2.5% (95% CI 1.9 to 3.3%) of patients.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of RFA as a treatment for osteoid osteomas were identified.

NONRANDOMIZED STUDIES

Numerous nonrandomized uncontrolled case series have consistently suggested that the benefits of RFA outweigh the risks in patients who require treatment due to failed response to nonsurgical treatments.[104-111]

SECTION SUMMARY

Despite the weaknesses in the published clinical evidence, RFA of osteomas has become a standard of care for osteomas that have failed standard treatments. This was based on the lower morbidity and quicker recovery time associated with the procedure compared with open surgery. The risk of osteoma recurrence with RFA is 5 to 10%; recurrent tumors can be retreated with RFA. There are minimal clinical trial data on the risks and benefits of RFA as initial treatment of osteoid tumors. Since most of these tumors heal spontaneously with medical treatment, the necessity of surgical intervention as initial treatment is unclear.

PALLIATION OF PAIN FROM BONE METASTASES

BACKGROUND

External beam irradiation is often the initial palliative therapy for osteolytic bone metastases. However, pain from bone metastases is refractory to radiation therapy in 20% to 30% of patients, while recurrent pain at previously irradiated sites may be ineligible for additional radiation due to risks of normal tissue damage. Other alternatives include hormonal therapy, radiopharmaceuticals such as strontium-89, and bisphosphonates. Less often, surgery or chemotherapy may be used for palliation and intractable pain may require opioid medications. RFA may be considered another alternative for palliating pain from bone metastases.

SYSTEMATIC REVIEWS

Mehta (2020) published a systematic review and meta-analysis of RFA for painful osseous metastases.[112] A total of 14 studies with 426 patients met inclusion criteria. The median pain reduction at a median follow-up of 24 weeks post-RFA was 67% (R^2=-0.66, 95% CI -0.76 to -0.55, I^2=71.24%). Pain scores were not significantly affected by primary tumor type or tumor size.

A systematic review reported by Gennaro (2019) assessed four percutaneous thermal ablation techniques for pain reduction in patients with bone metastases.[113] A total of eleven studies addressing RFA (n=3), MWA (n=1), cryoablation (n=2), and MRgFUS (n=5) were included (total n=364 patients). Mean pain reduction for all techniques combined ranged from 25 to 91%

at four weeks and from 16 to 95% at 12 weeks. There were no complications in the MWA group while the MRgFUS group had the highest complication rate. Overall, the number of minor complications reported ranged from 0 to 59 and the number of significant adverse events ranged from 0 to 4.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of RFA as a treatment for palliation of pain from bone metastases were identified.

NONRANDOMIZED STUDIES

Levy (2020) conducted a global, multicenter, nonrandomized, prospective postmarketing study to evaluate the effectiveness of RFA in patients with painful osteolytic bone metastases.[114] Between October 2017 and March 2019, 134 ablations were performed in 100 patients (68% vs. 32% of the cohort had a single vs. multiple sites treated, respectively). The most common tumor location was thoracic (44%) followed by lumbar (33%). Patient outcomes including pain, pain interference, and quality of life were collected. Forty percent of the cohort did not participate through the six-month follow-up, with two additional discontinuations after six months. The most common reason for discontinuation was death (30 patients), which were all classified as related to the underlying malignancy. The primary endpoint evaluated was pain improvement, from baseline to three months. At baseline, the mean score for worst pain (measured by Brief Pain Inventory) for the entire cohort was 8.2. After RFA, worst pain significantly improved, with mean scores decreasing to 5.6, 4.7, 3.9, 3.7, and 3.5 at three days, one week, one month, three months, and six months, respectively ($p<0.0001$ for all visits). Immediate improvement in pain (≥ 2-point change in worst pain at the treatment site(s) three days after RFA) was achieved by 59% of patients. Four adverse events were reported, of which two resulted in hospitalization for pneumonia and respiratory failure, respectively.

Additional nonrandomized evidence is limited to data from small, poorly designed case series.[115-119] However, though small and uncontrolled, available studies consistently reported significant improvement in pain following RFA in patients who failed or were poor candidates for standard treatments. Clinical trial data is lacking for use of RFA as an alternative to conventional techniques for initial treatment of painful bony metastases.

ANGIOMYOLIPOMA

BACKGROUND

Angiomyolipomas (AMLs) or angiomyolipomata are rare benign tumors that contain blood vessels, smooth muscle, and fat. They are usually associated with the kidneys but may also be in the liver or other locations. They are more frequently seen in patients with tuberous sclerosis complex (TSC). These lesions are usually asymptomatic but may hemorrhage, particularly if large (4 cm or larger). Treatment consists of surveillance as long as the lesion remains small and asymptomatic. Treatment or prevention of hemorrhage may include surgical resection, arterial embolization, or laparoscopic or percutaneous ablation.

PUBLISHED STUDIES

Due to the rare nature of these tumors, there is limited published evidence on the tumor management.[120-125] The current studies have significant methodological limitations including retrospective records review, small size (n=4 to 32), heterogeneity of patients and treatment

modalities, and short-term follow-up. However, the available studies consistently reported low rates of complications and high rates of successful ablation, generally without recurrence at mean follow-up ranging between 9 and 45 months. Some larger tumors (>3.5 cm) required two RFA sessions. Minor complications included transient perinephric hematoma, intercostal nerve transection. A patient in one early study developed a small skin metastasis at the electrode insertion site which was resected and did not recur.

SECTION SUMMARY

Because this is a rare tumor that is often identified incidentally and may not require treatment, it is unlikely that large randomized controlled trials or comparative studies will become available. Due to the risk of potentially life-threatening hemorrhage in large (≥4 cm) AMLs and the low rate of adverse effects, treatment of symptomatic or large lesions may be warranted.

HEAD AND NECK TUMORS

BACKGROUND

Tumors of the head and neck arise in the lip, oral cavity, pharynx, larynx, paranasal sinuses and salivary glands. Treatment depends on the location and extent of the disease.[126] Standard treatment for patients with early-stage disease (stage I or II) is single-modality with surgery or radiation therapy. The two modalities result in similar survival. Combined modality therapy is required for locally advanced disease. In patients with recurrent head and neck cancer, surgical salvage attempts are poor in terms of local control, survival and quality of life, and these recurrent tumors are often untreatable with standard salvage therapies. Palliative chemotherapy or comfort measures may be offered.

SYSTEMATIC REVIEWS RANDOMIZED CONTROLLED TRIALS

No systematic reviews or randomized trials evaluating the safety and effectiveness of RFA for treatment of head and neck tumors were identified.

NONRANDOMIZED STUDIES

Current published evidence is limited to poorly designed case series, feasibility, and retrospective studies that are considered unreliable due to lack of a control group for comparison and lack of randomization to control for bias.[127-131]

In addition to these methodological limitations, prospective case series included small numbers of patients. Small study populations limit the ability to rule out the role of chance as an explanation of study findings.

ADVERSE EVENTS

Complications and adverse events are reported to be uncommon, but are often severe. They are generally related to burning of local soft tissue (e.g., fistula formation).[127-130]

THYROID CANCER

BACKGROUND

Thyroid carcinoma is uncommon, with a lifetime risk of being diagnosed with thyroid carcinoma less than 1%. Thyroid carcinoma occurs two to three times more often in women than men.

The main histological types of thyroid carcinoma include: 1) differentiated (including papillary, follicular, and Hürthle); 2) medullary; 3) anaplastic (aggressive undifferentiated tumor). All anaplastic thyroid carcinomas are considered stage IV and are almost uniformly lethal, however most deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of thyroid carcinoma cases. The treatment of choice for differentiated thyroid carcinoma is surgery followed by radioiodine in selected patients and thyroxine therapy in most patients. There is no effective therapy for anaplastic thyroid carcinoma; most are unresectable, but EBRT may improve local control and provide palliation. Surgical resection is the primary treatment choice for medically unresponsive, symptomatic benign thyroid tumors and thyroid carcinomas. However, techniques for ablation of thyroid tumors (eg, RFA, microwave ablation) are being investigated.

SYSTEMATIC REVIEW

Sun (2022) published a SR to evaluate tumor progression and complications between RFA and thyroidectomy for patients with Papillary thyroid cancer (PTC) or papillary thyroid microcarcinoma (PTMC).[132] Six retrospective, single -center non randomized studies (1708 patients) were included in their analysis (two for PTC and 4 for PTMC). The tumor progression of the RFA group was similar to the surgical groups [odds ratio, 1.31; 95% CI, 0.52-3.29; heterogeneity (I2 statistic), 0%, p = 0.85]. The risk of complication rates was significantly lower in the RFA group than that in the surgical group [odds ratio, 0.18; 95% CI, 0.09-0.35; heterogeneity (I2 statistic), 40%, p = 0.14]. The authors conclude that RFA can achieve a good efficacy and has a lower risk of major complications. The authors indicate that multi-center, large-scale studies with sufficient follow-up (minimum 5 years) analysis are needed.

Cho (2021) reported a systematic review and meta-analysis of five-year outcomes of thermal ablation for papillary thyroid microcarcinoma.[133] A total of three studies (including 207 patients) met inclusion criteria. No local tumor recurrence, lymph node metastasis, distant metastasis or delayed surgery were reported during a mean pooled 67.8-month follow-up. The pooled mean major complication rate was 1.2%, with no reported life-threatening or delayed complications. New tumors in the remaining thyroid gland were successfully treated by repeat thermal ablation in four patients.

Choi (2020) reported a systematic review of thermal ablation techniques for the treatment of primary papillary thyroid microcarcinoma.[134] A total of 11 studies of radiofrequency-, laser-, and microwave-ablation met inclusion criteria. The included 715 patients were pooled for analysis. There was significant between-study heterogeneity for complete disappearance ($p<0.001$, I^2 99%), mean volume reduction ($p<0.001$, I^2 93%), and volume reduction rate ($p <0.001$, I^2 86%). A subgroup analysis showed heterogeneity of the complete disappearance proportion among the treatment modality (I^2 range 95 to 100%). The pooled estimates of complete disappearance, mean volume reduction, and volume reduction rate were 57.6% (95% CI 35.4 to 79.8), 73.5 mm3 (52.4 to 94.6 mm3), and 98.1% (95% CI 96.7 to 99.5), respectively. RFA showed the highest mean volume reduction rate (99.3%), followed by MWA (95.3%) and LA (88.6%; $p<0.001$). The pooled proportions of overall and major complications were 3.2% (95% CI 1.1 to 5.2) and 0.7% (95% CI 0 to 1.5), respectively.

RANDOMIZED CONTROLLED TRIALS

No new RCTs were published since those included in the systematic reviews summarized above.

NONRANDOMIZED STUDIES

Xiao (2021) published a retrospective study of RFA for solitary T1aN0M0 and T1bN0M0 papillary thyroid carcinoma.[135] The overall local tumor progression (LTP) rate was 3.82%. LTP and LTP-free survival rates were not significantly different between those with T1a and T1b disease. One patient with T1b disease developed transient recurrent laryngeal nerve injury. There was an 81.7% rate tumor disappearance in those with T1a disease and 52.7% in those with T1b disease (p<0.001).

Cao (2021) reported a multicenter retrospective study of thermal ablation for the treatment of solitary T1N0M0 papillary thyroid carcinoma.[136] A total of 847 patients were included, of whom 645 underwent MWA and 202 underwent RFA. Statistically significant reductions in tumor size were reported at six, nine, and twelve months (p<0.001). There was complete disappearance of tumors in 68% of T1a patients and 64% of T1b patients (p<0.001). Postablation disease progression occurred in 1.1% of T1a patients and 1.7% of T1b patients (p=0.54). The overall complication rate was 3.4%.

In 2016, Kim reported on a comparative review of 73 patients with recurrent thyroid cancer smaller than 2 cm who had been treated with RFA (n=27) or repeat surgery (n=46).[137] RFA was performed in cases of patient refusal to undergo surgery or poor medical condition. Data were weighted to minimize potential confounders. The three-year recurrence-free survival rates were similar for RFA (92.6%) and surgery (92.2%, p=0.681). Posttreatment hoarseness rate did not differ between the RFA (7.3%) and surgery (9.0%) groups. Posttreatment hypocalcemia occurred only in the surgery group (11.6%).

ADVERSE EVENTS

In 2017, Chung reported results of a systematic review and meta-analysis evaluating the safety of RFA for benign thyroid nodules and recurrent thyroid cancers.[138] Twenty-four studies were included, totalling 2,421 participants and 2,786 thyroid nodules. Overall, 41 major complications and 48 minor complications (as defined by the Society of Interventional Radiology) of RFA were reported, giving a pooled proportion of 2.38% for overall RFA complications (95% CI 1.42% to 3.34%) and 1.35% for major RFA complications (95% CI 0.89% to 1.81%). Subgroup analysis found major complication rates were significantly higher for malignant thyroid nodules than for benign. Major complications included voice change, nodule rupture, permanent hypothyroidism, and brachial plexus injury. Minor complications included pain, hematoma, vomiting, skin burns, and transient thyroiditis.

BENIGN THYROID TUMORS (NODULES)

Thyroid nodules (including multinodal goiter) that have been verified as benign using fine needle aspiration (FNA) may require treatment when they cause symptoms, such as obstruction or compression.

SYSTEMATIC REVIEWS

In 2021, Monpeyssen published a systematic review of RFA for the treatment of benign thyroid nodules.[139] The 17 included studies addressed RFA for the treatment of benign solid (nonfunctioning or autonomous) thyroid nodules with at least 18 months of follow-up. At 12-monhts post-procedure, the volume reduction rate was 67% to 75% from a single procedure

and 93.6% for nodules that received multiple ablations. The 12-month regrowth rate was reported between 0% and 34%.

Cho (2020) reported a systematic review of the efficacy of thermal ablation (RFA and laser ablation) for the treatment of benign thyroid nodules.[140] The analysis demonstrated long-term maintenance (up to 36 months) of volume reduction. Further, RFA was found to be superior to laser ablation. The volume reduction rate for RFA at last follow up was 92.2%, whereas in the laser ablation group, the volume reduction rate peaked at 12 months (52.3%) and was at 43.3% at last follow up.

A 2019 systematic review and meta-analysis was reported by Trimboli on the efficacy of thermal ablation for benign non-functioning solid thyroid nodules.[141] Twelve studies per therapy were identified addressing RFA and laser ablation, with three RCTs on RFA and four on laser ablation. The remainder were prospective and retrospective cohort studies. Overall there was high heterogeneity. Only studies with six months or longer follow-up were included and median follow-up was 12 months. The primary outcome was the volume reduction rate at 6, 12, 24, and 36 months. The volume reduction rate for the RFA group was 68%, 75%, and 87%, respectively, with insufficient 36-month reporting for analysis. The volume reduction rate for the laser ablation group was 48%, 52%, 45%, and 44%, respectively.

In 2014 Fuller reported on a systematic review and meta-analysis of studies on RFA for benign thyroid tumors.[142] Included in the review were nine studies (five observational studies[143-147], four randomized studies[148-151]) totaling 306 treatments. After RFA, statistically significant improvements were reported in nodule size reduction (29.77 mL; 95% CI -13.83 to -5.72), combined symptom improvement and cosmetic scores on the 0 to 6 scale (mean, -2.96; 95% CI -2.66 to -3.25) and withdrawal from methimazole (odds ratio, 40.34; 95% CI 7.78 to 209.09). Twelve adverse events were reported, two of which were considered significant but did not require hospitalization.

RANDOMIZED CONTROLLED TRIALS

No new RCTs were published since those included in the systematic reviews summarized above.

NONRANDOMIZED STUDIES

Kandil (2022) published a prospective, cohort study of benign thyroid nodules (n=233) treated with RFA at two institutions.[152] The median and interquartile range of volume reduction rate (VRR) at 1, 3, 6, and 12 months were 54% [interquartile range (IQR): 36%-73%], 58% (IQR: 37%-80%), 73% (IQR: 51%-90%), and 76% (IQR: 52%-90%), respectively ($p<0.001$). Four patients presented with toxic adenomas and two patients developed temporary hoarseness of voice, but no hematoma or nodular rupture occurred postprocedure. All patients were confirmed euthyroid at 3-month postprocedure follow-up. The authors also report that VRR was significantly related with elastography with stiff and mixed elasticity more likely to have lower VRR than soft nodules. The authors conclude that RFA is a safe and effect treatment option that allows preservation of thyroid function with minimal risk of procedural complications.

ADVERSE EVENTS

See the systematic review above by Chung (2017) that addressed the safety of RFA for benign thyroid nodules and recurrent thyroid cancers and reported significantly higher major complication rates for malignant thyroid nodules than for benign nodules.

CHOLANGIOCARCINOMAS

BACKGROUND

Cholangiocarcinomas are tumors that originate in the bile duct epithelium; 90% are adenocarcinomas. Intrahepatic cholangiocarcinomas (ICC) are located within the hepatic parenchyma and are reviewed under Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204 (see Cross References for a link to the policy). They may also be referred to as peripheral cholangiocarcinomas. Extrahepatic cholangiocarcinomas (ECC) are more common than intrahepatic cholangiocarcinoma and are located within the extrahepatic bile duct. Complete resection with negative margin is potential curative, though recurrence is common and most cases are unresectable due to advanced disease when diagnosed. For unresectable or metastatic cholangiocarcinomas at any location, the primary treatment may include chemotherapy, treatment within a clinical trial, or best supportive care. RFA and other locoregional therapies may be an option. Biliary drainage with biliary stenting may be warranted for unresectable or metastatic extrahepatic disease. Liver transplantation is potentially curative in carefully selected patients with lymph node negative, nondisseminated locally advanced hilar cholangiocarcinomas and otherwise normal biliary and hepatic function or underlying liver disease precluding surgery.

SYSTEMATIC REVIEWS AND RANDOMIZED CONTROLLED TRIALS

No systematic reviews or randomized controlled trials regarding radiofrequency ablation for the treatment of extrahepatic cholangiocarcinomas were identified.

NONRANDOMIZED STUDIES

The evidence for ECC consists of a single short-term case series.[153] This study included 11 patients with hilar ECC. At one-month follow-up after RFA, the reduction in tumor size was 30% in six tumors, 20% in two tumors, and size was unchanged in three tumors. At six months following RFA, the overall size reduction was 35%, with the largest reduction 60%. Overall survival ranged from 10-30 months.

UTERINE FIBROIDS (LEIOMYOMAS OR MYOMAS)

BACKGROUND

Uterine fibroids, also known as leiomyomas or myomas, are benign smooth muscle tumors of the uterus occurring in women during their reproductive years. They frequently occur in multiples, and the tumor location within the uterus is often used to describe the fibroids (intramural, submucosal, subserosal, or cervical myomas). Surgery, including hysterectomy and various myomectomy procedures, is considered the criterion standard treatment for symptom resolution. There has been long-standing research interest in developing minimally invasive alternatives for treating uterine fibroids, including procedures that retain the uterus and allow for future childbearing. Various techniques to induce myolysis have also been studied including Nd:YAG lasers, bipolar electrodes, cryomyolysis, and radiofrequency

ablation. With these techniques, an energy source is used to create areas of necrosis within uterine fibroids, reducing their volume and thus relieving symptoms.

SYSTEMATIC REVIEWS

Polin (2022) published a SR of pregnancy outcomes after radiofrequency ablation (RFA) of uterine myomas.[154] Ten publications were included in the review. There were 50 pregnancies reported among 923 RFA patients: 40 pregnancies after 559 laparoscopic RFAs and 10 pregnancies after 364 transcervical RFAs. Most patients had between 1 and 3 myomas ablated, and myomas size ranged from <2 cm to 12.5 cm. The authors reported two complications of the 44 deliveries (placenta previa and delayed postpartum hemorrhage). There were no cases of uterine rupture, uterine window, or invasive placentation and no fetal complications. The spontaneous abortion rate (12%) was comparable with the general obstetric population. The authors conclude that hat radiofrequency myoma ablation may offer a safe and effective alternative to existing treatments for women who desire future fertility.

Morris (2022) completed a SR evaluating the associations between minimally invasive approaches to fibroid treatment and quality of life (QoL) or fibroid-associated symptoms.[155] A total of 37 studies were included (26 evaluating individual approaches and 11 comparative studies of minimally invasive approaches and surgical interventions). Radiofrequency ablation and ultrasound-guided sclerotherapy (USGS) significantly improved overall QoL. The authors conclude that outcomes among minimally invasive approaches were similar, presenting patients with numerous non-surgical options for fibroid treatment.

Zhang (2022) published a SR evaluating the efficacy of uterine-preserving, minimally invasive treatment modalities in reducing fibroid-related bleeding.[156] Eighty-four studies were included in the review (10 RCTs and 74 observational studies). Fifteen studies demonstrated significantly reduced bleeding severity after radiofrequency ablation (RFA). The authors conclude that additional research is needed to determine best practices and that long-term evidence is limited in current literature.

Arnreiter and Oppelt reported on the safety and efficacy of transcervical ultrasound-guided RFA using the Sonata system in a 2021 systematic review.[157] A total of 10 studies met inclusion criteria, all of which were rated as fair quality on the Newcastle Ottawa Scale (NOS). The reported reduction in total and perfused myoma volume was 63.2% and 64.5%. Clinically meaningful reduction in menstrual blood loss after 12 months was achieved in 87.2% of patients. Symptom Severity Scores dropped by 28.8 ± 19.3, 23.3 ± 23.7, and 23.7 ± 19.4 points at three, six, and twelve months and Health-Related Quality of Life Scores increased to 77.5 ± 22.0, 82.8 ± 19.0, and 83.3 ± 20.5 points. The reintervention rate at an average of 64 months post-ablation was 11.8%. Time to return to activities of daily life was 2.9 ± 2.5 days. There were three reported pregnancies following ablation, all of which were without complications.

Berman (2020) conducted a retrospective review of pregnancy delivery and safety after laparoscopic RFA of uterine fibroids.[158] The review included results from two RCTs, six cohort studies, and commercial cases (total N=28) that evaluated rates of spontaneous abortion, preterm delivery, postpartum hemorrhage, placental abnormalities, intrauterine growth restriction, and rates of cesarean delivery. Thirty pregnancies resulted in 26 full-term births (86.7%), with an equal distribution of vaginal and cesarean deliveries, and the spontaneous abortion rate (13.3%) was within the range for the general population. There were no cases of preterm delivery, uterine rupture, placental abruption, placenta accreta, or intrauterine growth

restriction. One patient experienced severe postpartum hemorrhage. More rigorous prospective studies evaluating pregnancy outcomes after laparoscopic RFA are needed.

Bradley (2019) published a systematic review and meta-analysis of RFA for the treatment of uterine fibroids.[159] A total of 32 articles representing 20 studies of percutaneous laparoscopic (19 articles; Accessa device; n=461 patients), transvaginal (8 articles; n=579 patients), and transcervical RFA (5 articles; Sonata device; n=214 patients) met inclusion criteria. The number of patients ranged from 11 to 153 and the mean follow-up ranged from in-hospital to 64 months. Study quality was rated as good or fair for 19 of 20 studies. A meta-analysis was conducted of 1,283 patients at the 12-month follow-up. The weighted mean time to discharge was 8.2 hours (95% CI 6.3 to 10.0 hours) and the weighted mean time to normal activities was 5.2 days (95% CI 3.3 to 7.1 days). There was a decrease in fibroid volume of 66%, an increase in health-related quality of life by 39 points, and a decrease in symptom severity score of 42 points (all $p<0.001$ versus baseline). The annual cumulative rates of reintervention due to fibroid-related symptoms were 4.2%, 8.2%, and 11.5% at one, two, and three years, respectively. Complication reporting within the included studies was highly inconsistent and inadequate and therefore was not reported in this systematic review. However, the authors noted that no serious procedural complications such as death or iatrogenic injury to the bowel, bladder, or ureter were reported in any study. There were no statistically significant differences across RFA approaches for reintervention rates or fibroid volume reduction, but procedure time was significantly different (all pairwise comparisons $p\leq0.002$), with laparoscopic being longest (73 minutes) followed by transcervical (44 minutes) and transvaginal (24 minutes).

A systematic review and meta-analysis by Sandberg (2018) evaluated the risk of reintervention for hysterectomy and QOL after uterine-sparing interventions for fibroids.[160] Risk of reintervention at 12 months was 0.3% for radiofrequency volumetric thermal ablation (RFVTA) compared with 3.6% for UAE and 1.1% for myomectomy. Symptom severity and QOL scores were similar for the three treatments. Only one RFVTA study was identified on reintervention risk at 36 months; none was identified on reintervention risk at 60 months.

A systematic review by Havryliuk (2017) that did not separate outcomes by the length of follow-up found a reintervention rate of 5.2% after RFVTA (four studies, 12- to 36-month follow-up) compared to 4.2% after myomectomy (six studies, 12- to 52-month follow-up).[161] There was no significant difference in complication rates between RFVTA (6.3%) and myomectomy (7.9%). The length of stay after myomectomy was two days (range 0.5 to 6.0). No data were provided on length of stay after RFVTA.

Lin (2018) conducted a meta-analysis of improvement in symptom severity, QOL, and reintervention after laparoscopic radiofrequency ablation.[162] The review included one RCT and seven non-comparative trials. The recurrence risk at a weighted mean follow-up of 24.65 months (range, 3 to 36 months) was 4.4%. Improvements in symptoms and QOL were maintained out to 24 months in three studies and out to 36 months in one study. No studies were identified that had follow-up longer than 36 months.

RANDOMIZED CONTROLLED TRIALS

Rattray (2018) and Yu (2022) published three- and 12-month outcomes of a RCT comparing laparoscopic radiofrequency ablation (Lap-RFA) and myomectomy for patients with symptomatic uterine leiomyomas (ULs).[163, 164] Patients (n=57) were randomized to either laparoscopic RFA (n=30) or myomectomy (n=27). There was a significant improvement in UL symptoms at 3 and 12 months after the procedure within each treatment group, and these

improvements were similar between treatment groups. At 3 and 12 months after the procedure, the percentages of patients who were hospitalized in the LAP-RFA group were 74% and 49% lower than those of patients in the laparoscopic myomectomy group, respectively, with the 3-month difference being statistically significant. The authors conclude that LAP-RFA has lower healthcare resource use overall, including lower postprocedure hospitalization rate and shorter length of stay. Both studies reported 1 (<1%) serious adverse event within 30 days of the procedure. No efficacy outcomes were reported. The authors conclude that the results suggest that LAP-RFA is a safe, effective, uterine-sparing alternative to laparoscopic myomectomy in the treatment of ULs.

In Germany in 2014, Brucker published a single-center manufacturer-sponsored randomized controlled trial (RCT) comparing radiofrequency volumetric thermal ablation (RFVTA) with the Acessa system to laparoscopic myomectomy.[165] The trial included 51 premenopausal women at least 18 years old with symptomatic uterine fibroids less than 10 cm in any diameter and a uterine size of less than 17 weeks of gestation. Pregnancy and lactation were exclusion criteria. Prior to randomization, all women underwent laparoscopic ultrasound mapping. Data on 50 of the 51 women were analyzed. The primary study outcome, mean (SD) time to hospital discharge, was 10.0 (5.5) hours in the RFVTA group and 29.9 (14.2) hours in the myomectomy group. The criterion for noninferiority (no more than 10% longer hospital stay with RFVTA than laparoscopic myomectomy) was met at a significance level of $p<0.001$. All patients in the myomectomy group were hospitalized overnight; although not explicitly stated, this appeared to be the standard procedure at the study hospital. In the Acessa group, there was one unplanned hospitalization due to unexplained vertigo and four hospitalizations as standard procedure because the patients also underwent adhesiolysis.

Secondary outcomes of the RCT were reported in a 2015 publication by Hahn [166] (12-month outcomes) and a 2016 publication by Kramer [167] (24-month outcomes). Analysis was per protocol and 43 (84%) of 51 randomized participants were available for both the 12- and 24-month analyses. Each publication reported on 12 symptoms: heavy menstrual bleeding, increased abdominal gait, dyspareunia, pelvic discomfort/pain, dysmenorrhea, urinary frequency, urinary retention, sleep disturbance, backache, localized pain, and “other symptoms” (not specified). At 12 months, no participants reported four of the symptoms (dyspareunia, urinary retention, sleep disturbance, uterine pain) and there were no statistically significant between-group differences in the frequency of any of the remaining eight symptoms (at the $p<0.05$ level). The most commonly reported symptom at 12 months (heavy menstrual bleeding) occurred in seven (33%) of women in the RFVTA group and two (9%) of women in the laparoscopic myomectomy group ($p=0.069$) after controlling for baseline bleeding. At 24 months, no participants reported urinary retention or “other” symptoms, and there were no statistically significant between-group differences in any of the 10 reported symptoms. The most commonly reported symptom at 24 months (dysmenorrhea) occurred in eight (38%) in the RFVTA group and in seven (32%) in the laparoscopic myomectomy group ($p=0.67$). Patients were also assessed using several validated questionnaires (eg, the Uterine Fibroid Symptom and Quality of Life). There were no statistically significant between-group differences at 12 or 24 months on these validated questionnaires. In addition, the authors described pregnancy outcomes. Three patients in the RFVTA group conceived and all delivered a healthy neonate; the number of women who desired to become pregnant was not reported. Limitations of the 12- and 24-month analyses included lack of intention-to-treat analysis and failure to describe secondary study hypotheses and statistical analyses clearly. The RCT was relatively small in size and thus may have been underpowered to detect clinically meaningful

differences in secondary outcomes, so these results do not rule out potential differences between treatments.

NONRANDOMIZED STUDIES

Shifrin (2021) conducted a subgroup analysis of patients with submucous (type 1, 2, or 2-5) or large fibroids (> 5 cm) from patients in the FAST-EU and SONATA clinical trials.[168] In total, 72.5% of the 534 treated fibroids were not amenable to hysteroscopic resection because they were intramural, transmural, or subserous. At 3 month follow-up, 86% of women with only submucous fibroids and 81% of women with large fibroids experienced bleeding reduction. At 12 month follow-up, a reduction in menstrual bleeding was found in 92% to 96% of women with submucous fibroids and 86% to 100% of women with large fibroids (although fibroids >5 cm was an exclusion in SONATA, 2.5% (n=11) of patients were in this category). Improvement in the SSS, HR-QoL, and EQ-5D were also noted in these subgroups. Rates of surgical reintervention for women with submucous fibroids was less than 3.7%.

Yüce (2020) reported on 35 patients treated with percutaneous RFA.[169] The fibroid volume was reduced significantly compared to baseline at 3, 6, and 12 months ($p<0.001$), and Visual Analogue Scores were significantly reduced at 6 and 12 months ($p<0.01$).

A prospective observational study by Rey (2019) assessed the effectiveness of transvaginal ultrasound-guided RFA of myomas (TRFAM) in reducing tumor volume and eliminating metrorrhagia associated with myomas.[170] The study included 205 women with symptomatic type II/III uterine submucosal or intramural cavity-distorting myomas undergoing RFA. The preoperative mean standard deviation (SD) volume of the myomas was 122.4 (182.5) cm3 (95% CI 82.1 to 162.8). Mean myoma volume decreased significantly at one (85.2 [147.9] cm3; p=0.001), three (67.3 [138.0] cm3; p=0.001), six (59.3 [135.3] cm3; p=0.001, and 12 months (49.6 [121.4] cm3; p=0.001). At 12 months, the mean volume reduction was 60% compared with preoperative volume. All patients returned to normal menstruation at a mean follow-up of three months and 12 months. Of the 205 patients, 201 (98.04%) were satisfied with the procedure. The investigators conceded that a larger population with a longer follow-up is needed, but their study suggests that transvaginal ultrasound-guided RFA of myomas TRFAM is effective and safe for treating select patients with metrorrhagia secondary to myomas.

A large retrospective case series was published by Yin in 2015.[171] The study was conducted in China and used Chinese gynecologic radiofrequency ablation devices. It included 1216 consecutive patients treated at a single hospital over a 10-year period. All fibroids were less than 6 cm in size and mean diameter was 4.5 cm (range, 3.1 to 6.0 cm). Mean follow-up time was 36.5 months. Among the 476 premenopausal women, the mean reduction in myoma diameter was 2.7 cm at six months, 2.4 cm at 12 months, and 2.2 cm at 24 months. Among the 740 peri- or postmenopausal women, mean reduction was 3.3 cm at six months, 2.3 cm at 12 months, and 2.3 cm at 24 months. Myoma diameter was significantly lower at each of these time-points posttreatment compared with pretreatment. In the premenopausal subgroup, the proportion of women with dysmenorrhea decreased from 43.7% at baseline to 7.6% at 12 months and to 6.7% at 24 months; rates were significantly lower after treatment.

In 2013, Chudnoff published a prospective industry-funded multicenter study.[172] It included 135 premenopausal women at least 25 years old with symptomatic uterine fibroids, a uterine size of 14 weeks of gestation or less, and six or fewer treatable fibroids, with no single fibroid larger than 7 cm. In addition, women desired to preserve their uteri but not to have children in the future. RFVTA was conducted using the Acessa system. According to the study protocol,

most fibroids less than 1 cm in diameter were not treated. The primary efficacy outcomes were change in the volume of menstrual bleeding and the surgical reintervention rate after 12 months. A total of 127 (94%) of 135 women completed the study. From baseline to 12 months, 53 (42%) of 127 women (95% confidence interval, 32% to 49%) experienced at least a 50% reduction in the volume of menstrual bleeding. Most women (104/127 [82%]) experienced a decrease in menstrual bleeding at 12 months. Only one woman underwent a surgical reintervention through 12 months (this woman had been lost to follow-up and was not included in the other efficacy analyses). Three-year outcomes were reported by Berman in 2014.[173] A total of 104 (77%) of the 135 women who participated in the study were evaluable at three years. Fourteen underwent reintervention over the three years to treat uterine fibroid symptoms. Eleven women had hysterectomies, two had myomectomies, and one had uterine artery embolization. Bleeding outcomes were not reported at three years, but the authors stated that quality-of-life variables improved from baseline to 36 months and that most of the improvement in quality of life occurred within three months of the procedure.

MISCELLANEOUS TUMORS

BACKGROUND

The standard treatment of miscellaneous tumors depends on the type, location, and extent of the cancer. A large number of phase II or III clinical trials involving the use of RFA in the treatment of primary or metastatic cancers are underway.[174]

SYSTEMATIC REVIEWS

Tang (2022) published a SR evaluating the safety and efficacy of RFA, microwave ablation (MWA), and laser ablation (LA) for the treatment of cervical metastatic lymph nodes (CMLNs) of papillary thyroid carcinoma (PTC). A total of 17 studies were included (312 patients and 559 CMLNs).[175] The pooled proportions of VRR, complete disappearance and recurrence of CMLNs were 91.28% [95% confidence interval (CI): 86.60-95.97%], 67.9% [95% CI: 53.1-81.1%] and 7.8% [95%CI: 3.0-14.1%], respectively. The pooled proportions of overall and major complications were 2.9% [95%CI: 0.3-7.1%] and 0.3% [95%CI: 0-1.9%], respectively. The VRR of MWA was the highest (97.97%), followed by RFA (95.57%) and LA (84.46%) ($p<0.001$).The authors conclude that thermal ablations were safe and effective for the treatment of CMLNs of PTC. Each treatment had significant heterogeneity in VRR.

Nadeem (2021) published a SR of RFA for adrenal tumors. A total of 15 studies including 292 patients were included. No comparative results were reported. Overall, cumulative technical success, primary technique efficacy, and secondary technique efficacy rates were 99%, 95.1% and 100%, respectively. Local progression rates at three, six, and 12 months were 20.3%, 26.3%, and 29.3%, respectively, and overall survival rates at six, 12, and 18 months were 81.8%, 59.6%, and 62.9%. The intraprocedural complication rate was 30.2%.

Imperatore (2020) and Dhaliwal (2020) performed SR of RFA of pancreatic neuroendocrine tumors and unresectable pancreatic ductal adenocarcinoma (PDAC), respectively.[176, 177] Zhang (2020) published a systematic review of various ultrasound-guided ablation techniques for the treatment of solid pancreatic tumors.[178] Additionally, a systematic review by Rombouts (2015) examined studies of ablative therapies, including RFA, in patients with locally advanced pancreatic cancer.[179] No RCTs were identified in any of these systematic reviews, and conclusions are limited by the sparse evidence available on RFA in this setting.

Thomson (2019) published a SR on non-surgical treatments for Morton's neuroma.[180] A total of 22 studies, addressing nine non-operative treatment modalities, met inclusion criteria. In addition to RFA, treatment modalities included corticosteroid injection, alcohol injection, extra-corporeal shockwave therapy (ESWT), cryoablation, capsaicin injection, Botulinum toxin, orthosis and YAG laser therapy. All showed statistically significant improvements, but the pain-relieving results for alcohol injection were only short-term and orthotics, capsaicin injections, cryoablation, Botulinum toxin, RFA and ESWT had limitations to their application.

The remainder of the current published evidence on RFA for other tumors is limited to unreliable data from small case series and retrospective reviews. Evidence from these studies is considered unreliable due to methodological limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.[127, 143, 144, 181-196]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for thyroid carcinoma (v..2023) indicate that local therapies such as RFA may be considered for locoregional recurrence of thyroid carcinoma-papillary carcinoma in select individuals with limited burden nodal disease. Additionally, local therapies, including RFA, can be considered in those with metastatic disease.[197]

NCCN guidelines for colon cancer (v.3.2023) indicate that for metastases, "ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection."[198] The guidelines also state that "ablative techniques can also be considered [in patients whose primary colon tumor was resected for cure when metastatic lung tumors are] unresectable and amenable to complete ablation" (category 2A)."

NCCN guidelines for kidney cancer (v.1.2024) indicate "thermal ablation (e.g., cryosurgery, radiofrequency ablation) is an option for the management of individuals with clinical stage T1 renal lesions." Thermal ablation is an option for masses <3 cm, but it may also be an option for larger masses in select individuals. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications.[199] RFA is also an option for relapse or Stage IV and in select patients (e.g., elderly patients, others) with competing health risks.

NCCN guidelines for the treatment of non-small cell lung cancer (v.4.2023) state: "For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation and cryotherapy. Image-guided thermal ablation (cryotherapy, microwave, radiofrequency) may be an option for selected patients who will not be receiving SABR or definitive RT"[200]

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology (ACR) Appropriateness Criteria® (updated in 2021) consider RFA to be an alternative to partial nephrectomy for small (<4 cm) RCC tumors.[201]

The 2014 ACR Appropriateness Criteria on early-stage NSCLC that current evidence from a number of retrospective series involving varied patient populations reported a wide range of responses to RFA, ranging from 38% to 93%.[202] Primary tumor relapse rate after RFA ranged from 8% to 43% and two-year cancer-specific survival after RFA ranged from 57% to 93%,

with three-year OS of 15% to 46%. Predictors of complete response included smaller tumor size metastases, and ablation zone four times the tumor diameter. The document quoted the 2012 ACCP/STS guidelines[203] summarized below.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians (ACCP) guidelines on the treatment of stage I and II NSCLC indicate RFA has been used effectively in clinical stage 1 NSCLC. Therefore, in medically inoperable patients, peripheral NSCLC tumors less than 3 cm may be treated with RFA.[204]

The ACCP also joined with the Society of Thoracic Surgeons (STS) to develop consensus guidelines on the treatment of high-risk patients with stage I NSCLC.[203] These consensus guidelines indicate RFA is an alternative treatment option in patients who are not surgical candidates due to severe medical comorbidity.

AMERICAN THYROID ASSOCIATION

The 2021 American Thyroid Association (ATA) Guidelines for Management of Patients With Anaplastic Thyroid Cancer state that local therapy (including RFA) is a reasonable option for oligo-progressive metastases “to postpone the need to change otherwise beneficial systemic therapy.”[205]

AMERICAN UROLOGICAL ASSOCIATION

The 2017 American Urological Association (AUA) Guidelines state that “Physicians should consider TA [thermal ablation] as an alternate approach for the management of cT1a renal masses <3 cm in size.” and “Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation.” Both are rated as “Conditional Recommendation; Evidence Level Grade C.”[206] The guidelines were updated in 2021 and recommendations are generally consistent with the 2017 guideline.[207] The 2021 AUA guideline explicitly states that RFA and cryoablation may be offered as options to patients who elect thermal ablation.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin #96 (now #228), *Management of Symptomatic Uterine Leiomyomas* states “Laparoscopic radiofrequency ablation can be considered as a minimally invasive treatment option for the management of symptomatic leiomyomas in patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes.”[208]

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical published clinical practice guidelines (updated in 2016)for the diagnosis and management of thyroid nodules provides the following recommendations:[209] “Consider laser or radiofrequency ablation for the treatment of solid or complex thyroid nodules that progressively enlarge, are symptomatic or cause cosmetic concern [BEL 2, GRADE C]. Repeat FNA for cytologic confirmation before thermal ablation treatment [BEL 3, GRADE B].” BEL2 indicates a level of evidence that includes RCTs with limited body of data and well-conducted prospective cohort studies and meta-analyses of

cohort studies and BEL3 indicates a level of evidence that includes methodologically flawed clinical trials and observational studies.

SOCIETY OF INTERVENTIONAL RADIOLOGY

The Society of Interventional Radiology (2020) published a position statement on the role of percutaneous ablation in renal cell carcinoma.[210] The relevant recommendations are as follows: In patients with small renal tumors (stage T1a), percutaneous thermal ablation is a safe and effective treatment with fewer complications than nephrectomy and acceptable long-term oncological and survival outcomes. In selected patients with suspected T1a renal cell carcinoma, percutaneous thermal ablation should be offered over active surveillance. (Level of Evidence: C; Strength of Recommendation: Moderate)"

In high-risk patients with T1b renal cell carcinoma who are not surgical candidates, percutaneous thermal ablation may be an appropriate treatment option; however, further research in this area is required. (Level of Evidence: D; Strength of Recommendation: Weak)"

Radiofrequency ablation, cryoablation, and microwave ablation are all appropriate modalities for thermal ablation, and method of ablation should be left to the discretion of the operating physician. (Level of Evidence: D; Strength of Recommendation: Weak)"

SUMMARY

RENAL CELL CARCINOMA

Although there are currently no high-quality studies of radiofrequency ablation (RFA) of renal cell carcinoma (RCC), the overall body of published evidence suggests RFA may be beneficial in the short- to mid-term for small (4 cm or smaller), localized RCCs in patients who are not considered candidates for partial or complete surgical removal of the kidney. Therefore, RFA may be medically necessary for small RCCs in patients who are not surgical candidates or when preservation of kidney function is necessary, such as in patients with only one kidney.

Surgical excision is the preferred treatment for renal cell carcinoma (RCC) in patients who are considered to be healthy enough for surgery. There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective as surgical excision for treatment of RCC tumors. Therefore, RFA is considered investigational for treatment of RCC tumors for which surgical resection is an option.

BREAST TUMORS

There is insufficient evidence to determine the effectiveness of radiofrequency ablation for treatment of benign or malignant breast masses. Therefore, this treatment is considered investigational for the treatment of these tumors.

LUNG TUMORS

Surgical resection is the treatment of choice for primary non-small cell lung cancer (NSCLC) or metastatic tumors in the lung. For those patients who are unable to tolerate surgery, radiofrequency ablation (RFA) may be a treatment option in certain cases. While available studies are limited by study design, accumulating evidence suggests that RFA may be

similar to surgery in survival rates, and rates of procedure-related complications and mortality. Therefore, in patients with NSCLC or metastatic tumors in the lung who are ineligible for surgical treatment, RFA may be medically necessary when the policy criteria are met. There is not enough evidence to show that radiofrequency ablation (RFA) is effective as alternative treatments when criteria are not met. Therefore, RFA is considered investigational when the policy criteria are not met.

OSTEOID OSTEOMAS

Although the published evidence is limited to studies of lower methodological quality, radiofrequency ablation (RFA) of osteomas has become a standard of care based on expert opinion that the potential benefits of RFA outweigh risks in patients with osteoid tumors who have failed nonsurgical treatments. Therefore, RFA may be medically necessary for select patients when policy criteria are met.

The current preferred treatment of osteoid osteomas is non-surgical medical treatment. There is insufficient evidence to determine the effectiveness of radiofrequency ablation (RFA) for initial (first-line) treatment of osteoid tumors. RFA is, therefore, considered investigational as initial treatment of these tumors in patients who have not undergone standard medical management.

ANGIOMYOLIPOMAS

The current published evidence on radiofrequency ablation (RFA) of angiomyolipomas (AMLs) is limited to studies of lower methodological quality. However, because these tumors are rare, it is unlikely that evidence from large comparative studies will become available. Given the potential for life-threatening hemorrhage from large AMLs (4 cm or larger), and the consistent reports that the potential benefits of treatment outweigh any risks, RFA may be medical necessary to treat symptomatic or large asymptomatic AMLs. There is not enough evidence to show that radiofrequency ablation (RFA) is effective as alternative treatments when criteria are not met. Therefore, RFA of asymptomatic AMLs smaller than 4 cm is considered investigational.

PALLIATION OF PAIN FOR BONE METASTASES

The current evidence for radiofrequency ablation (RFA) for treatment of painful metastatic tumors in the bone is limited to studies of lower methodological quality; however, these studies have consistently reported significant improvement in pain following RFA in patients who have failed or are poor candidates for standard treatments. In light of this evidence, the unlikelihood of randomized controlled trials in these patients, and the lack of treatment options, the potential benefits of RFA appear to outweigh risks. Therefore, RFA may be medically necessary in patients with painful metastatic bone lesions who have failed or are poor candidates for standard treatments.

Because of the lack of data on the effectiveness of radiofrequency ablation (RFA) for initial (first-line) treatment of painful bony metastases, this indication is considered investigational.

HEAD AND NECK CANCERS

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of tumors of the head and neck. Therefore, RFA is considered investigational for the treatment of head and neck cancers.

THYROID TUMORS

Radiofrequency ablation (RFA) appears to be a safe alternative to more invasive surgical treatment for benign thyroid tumors. In addition, clinical guidelines based on evidence recommend this treatment. Therefore, RFA may be considered medically necessary for the treatment of benign thyroid tumors (nodules) when criteria are met.

There is not enough evidence to show that radiofrequency ablation (RFA) is safe and effective for benign thyroid tumors that do not meet the criteria. Therefore, RFA is considered investigational for the treatment of benign thyroid tumors (nodules) when criteria are not met.

While radiofrequency ablation (RFA) has been shown to reduce the size of malignant thyroid tumors and improve clinical symptoms, complications can be common. The available evidence is insufficient to determine whether any beneficial effects of RFA outweigh the risks. Therefore, RFA for the treatment of malignant thyroid tumors is considered investigational.

UTERINE FIBROIDS

There is enough research to show that radiofrequency ablation (RFA) may improve health outcomes for people with uterine fibroids. Additionally, clinical guidelines based on evidence from the American College of Obstetricians and Gynecologists (ACOG) recommend this treatment option. Therefore, RFA may be considered medically necessary for treating uterine fibroids when criteria are met.

There is not enough research to show that radiofrequency ablation (RFA) improves health outcomes for people with uterine fibroids when policy criteria are not met. Therefore, RFA is considered investigational for the treatment of uterine fibroids when policy criteria are not met.

MISCELLANEOUS TUMORS

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of other tumors. Therefore, RFA is considered investigational for all other tumors.

REFERENCES

1. FDA Public Health Notification: Radiofrequency Ablation of Lung Tumors - Clarification of Regulatory Status. 2008. [cited 11/13/2023]. 'Available from:' http://wayback.archive-it.org/7993/20170111190507/http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061985.htm.
2. Green H, Taylor A, Khoo V. Beyond the Knife in Renal Cell Carcinoma: A Systematic Review-To Ablate or Not to Ablate? *Cancers (Basel).* 2023;15(13). PMID: 37444565

3. Li L, Zhu J, Shao H, et al. Long-term outcomes of radiofrequency ablation vs. partial nephrectomy for cT1 renal cancer: A meta-analysis and systematic review. *Front Surg.* 2022;9:1012897. PMID: 36684152
4. Yanagisawa T, Mori K, Kawada T, et al. Differential efficacy of ablation therapy versus partial nephrectomy between clinical T1a and T1b renal tumors: A systematic review and meta-analysis. *Urol Oncol.* 2022;40(7):315-30. PMID: 35562311
5. Uhlig J, Strauss A, Rücker G, et al. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. *European radiology.* 2019;29(3):1293-307. PMID: 30255245
6. Favi E, Raison N, Ambrogi F, et al. Systematic review of ablative therapy for the treatment of renal allograft neoplasms. *World J Clin Cases.* 2019;7(17):2487-504. PMID: 31559284
7. Pierorazio PM, Johnson MH, Patel HD, et al. 2016. PMID: 27010048
8. Wang S QC, Peng Z, et al. Radiofrequency ablation versus partial nephrectomy for the treatment of clinical stage 1 renal masses: a systematic review and meta-analysis. *Chin Med J (Engl).* 2014;127(13):2497-503. PMID: 24985591
9. Memarsadeghi M, Schmook T, Remzi M, et al. Percutaneous radiofrequency ablation of renal tumors: midterm results in 16 patients. *Eur J Radiol.* 2006;59(2):183-9. PMID: 16725292
10. Gupta A, Raman JD, Leveillee RJ, et al. General anesthesia and contrast-enhanced computed tomography to optimize renal percutaneous radiofrequency ablation: multi-institutional intermediate-term results. *J Endourol.* 2009;23(7):1099-105. PMID: 19530948
11. Long L, Park S. Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty. *J Endourol.* 2009;23(3):421-6. PMID: 19260799
12. Mylona S, Kokkinaki A, Pomoni M, et al. Percutaneous radiofrequency ablation of renal cell carcinomas in patients with solitary kidney: 6 years experience. *Eur J Radiol.* 2009;69(2):351-6. PMID: 18313248
13. Carey RI, Leveillee RJ. First prize: direct real-time temperature monitoring for laparoscopic and CT-guided radiofrequency ablation of renal tumors between 3 and 5 cm. *J Endourol.* 2007;21(8):807-13. PMID: 17867933
14. Ahrar K, Matin S, Wood CG, et al. Percutaneous radiofrequency ablation of renal tumors: technique, complications, and outcomes. *J Vasc Interv Radiol.* 2005;16(5):679-88. PMID: 15872323
15. Boss A, Clasen S, Kuczyk M, et al. Magnetic resonance-guided percutaneous radiofrequency ablation of renal cell carcinomas: a pilot clinical study. *Invest Radiol.* 2005;40(9):583-90. PMID: 16118551
16. Chiou YY, Hwang JI, Chou YH, et al. Percutaneous radiofrequency ablation of renal cell carcinoma. *J Chin Med Assoc.* 2005;68(5):221-5. PMID: 15909727
17. Gervais DA, McGovern FJ, Arellano RS, et al. Radiofrequency ablation of renal cell carcinoma: part 1, Indications, results, and role in patient management over a 6-year period and ablation of 100 tumors. *AJR Am J Roentgenol.* 2005;185(1):64-71. PMID: 15972400
18. Mahnken AH, Rohde D, Brkovic D, et al. Percutaneous radiofrequency ablation of renal cell carcinoma: preliminary results. *Acta Radiol.* 2005;46(2):208-14. PMID: 15902899
19. Matsumoto ED, Johnson DB, Ogan K, et al. Short-term efficacy of temperature-based radiofrequency ablation of small renal tumors. *Urology.* 2005;65(5):877-81. PMID: 15882715

20. McDougal WS, Gervais DA, McGovern FJ, et al. Long-term followup of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. *J Urol.* 2005;174(1):61-3. PMID: 15947578
21. Merkle EM, Nour SG, Lewin JS. MR imaging follow-up after percutaneous radiofrequency ablation of renal cell carcinoma: findings in 18 patients during first 6 months. *Radiology.* 2005;235(3):1065-71. PMID: 15914485
22. Varkarakis IM, Allaf ME, Inagaki T, et al. Percutaneous radio frequency ablation of renal masses: results at a 2-year mean followup. *J Urol.* 2005;174(2):456-60; discussion 60. PMID: 16006864
23. Weizer AZ, Raj GV, O'Connell M, et al. Complications after percutaneous radiofrequency ablation of renal tumors. *Urology.* 2005;66(6):1176-80. PMID: 16360436
24. Aron M, Gill IS. Minimally invasive nephron-sparing surgery (MINSS) for renal tumours. Part II: probe ablative therapy. *European urology.* 2007;51(2):348-57. PMID: 17084513
25. Mouraviev V, Joniau S, Van Poppel H, et al. Current status of minimally invasive ablative techniques in the treatment of small renal tumours. *European urology.* 2007;51(2):328-36. PMID: 17069964
26. Wingo MS, Leveillee RJ. Central and deep renal tumors can be effectively ablated: radiofrequency ablation outcomes with fiberoptic peripheral temperature monitoring. *J Endourol.* 2008;22(6):1261-7. PMID: 18484892
27. Zagoria RJ, Traver MA, Werle DM, et al. Oncologic efficacy of CT-guided percutaneous radiofrequency ablation of renal cell carcinomas. *AJR Am J Roentgenol.* 2007;189(2):429-36. PMID: 17646471
28. Breen DJ, Rutherford EE, Stedman B, et al. Management of renal tumors by image-guided radiofrequency ablation: experience in 105 tumors. *Cardiovasc Intervent Radiol.* 2007;30(5):936-42. PMID: 17573550
29. Abdellaoui A, Watkinson AF. Radiofrequency ablation of renal tumors. *Future Oncol.* 2008;4(1):103-11. PMID: 18241005
30. Stern JM, Svatek R, Park S, et al. Intermediate comparison of partial nephrectomy and radiofrequency ablation for clinical T1a renal tumours. *BJU international.* 2007;100(2):287-90. PMID: 17617136
31. Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass : a meta-analysis. *Cancer.* 2008;113(10):2671-80. PMID: 18816624
32. Iannuccilli JD, Dupuy DE, Beland MD, et al. Effectiveness and safety of computed tomography-guided radiofrequency ablation of renal cancer: a 14-year single institution experience in 203 patients. *Eur Radiol.* 2016;26(6):1656-64. PMID: 26373755
33. Boone J, Bex A, Prevoo W. Percutaneous radiofrequency ablation of a small renal mass complicated by appendiceal perforation. *Cardiovasc Intervent Radiol.* 2012;35(3):695-9. PMID: 22011782
34. Xia LY, Hu QL, Xu WY. Efficacy and Safety of Radiofrequency Ablation for Breast Cancer Smaller Than 2 cm: A Systematic Review and Meta-Analysis. *Front Oncol.* 2021;11:651646. PMID: 34012918
35. Chen J, Zhang C, Li F, et al. A meta-analysis of clinical trials assessing the effect of radiofrequency ablation for breast cancer. *OncoTargets and therapy.* 2016;9:1759-66. PMID: 27042126
36. Zhao Z, Wu F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. *Eur J Surg Oncol.* 2010;36(12):1149-55. PMID: 20889281
37. Soukup B, Bismohun S, Reefy S, et al. The evolving role of radiofrequency ablation therapy of breast lesions. *Anticancer research.* 2010;30(9):3693-7. PMID: 20944155

38. Ito T, Oura S, Nagamine S, et al. Radiofrequency Ablation of Breast Cancer: A Retrospective Study. *Clinical breast cancer.* 2018;18(4):e495-e500. PMID: 29079443
39. Li P, Xiao-Yin T, Cui D, et al. Evaluation of the safety and efficacy of percutaneous radiofrequency ablation for treating multiple breast fibroadenoma. *Journal of cancer research and therapeutics.* 2016;12(Supplement):C138-c42. PMID: 28230006
40. Kontos M, Felekouras E, Fentiman IS. Radiofrequency ablation in the treatment of primary breast cancer: no surgical redundancies yet. *Int J Clin Pract.* 2008;62(5):816-20. PMID: 18412934
41. Singletary SE. Breast cancer surgery for the 21st century: the continuing evolution of minimally invasive treatments. *Minerva Chir.* 2006;61(4):333-52. PMID: 17122766
42. Noguchi M. Radiofrequency ablation therapy for small breast cancer. *Semin Ultrasound CT MR.* 2009;30(2):105-12. PMID: 19358441
43. van der Ploeg IM, van Esser S, van den Bosch MA, et al. Radiofrequency ablation for breast cancer: a review of the literature. *Eur J Surg Oncol.* 2007;33(6):673-7. PMID: 17369003
44. Noguchi M. Is radiofrequency ablation treatment for small breast cancer ready for "prime time"? *Breast Cancer Res Treat.* 2007;106(3):307-14. PMID: 17972173
45. van Esser S, van den Bosch MA, van Diest PJ, et al. Minimally invasive ablative therapies for invasive breast carcinomas: an overview of current literature. *World J Surg.* 2007;31(12):2284-92. PMID: 17957404
46. Imoto S, Wada N, Sakemura N, et al. Feasibility study on radiofrequency ablation followed by partial mastectomy for stage I breast cancer patients. *Breast.* 2009;18(2):130-4. PMID: 19324550
47. Garbay JR, Mathieu MC, Lamuraglia M, et al. Radiofrequency thermal ablation of breast cancer local recurrence: a phase II clinical trial. *Ann Surg Oncol.* 2008;15(11):3222-6. PMID: 18709415
48. Athanassiou E, Sioutopoulou D, Vamvakopoulos N, et al. The fat content of small primary breast cancer interferes with radiofrequency-induced thermal ablation. *Eur Surg Res.* 2009;42(1):54-8. PMID: 18987475
49. Kinoshita T, Iwamoto E, Tsuda H, et al. Radiofrequency ablation as local therapy for early breast carcinomas. *Breast Cancer.* 2011;18(1):10-7. PMID: 20072824
50. Klimberg VS, Ochoa D, Henry-Tillman R, et al. Long-term results of phase II ablation after breast lumpectomy added to extend intraoperative margins (ABLATE l) trial. *Journal of the American College of Surgeons.* 2014;218(4):741-9. PMID: 24655863
51. Rubio IT, Landolfi S, Molla M, et al. Breast-conservative surgery followed by radiofrequency ablation of margins decreases the need for a second surgical procedure for close or positive margins. *Clinical breast cancer.* 2014;14(5):346-51. PMID: 24703804
52. Laeseke P, Ng C, Ferko N, et al. Stereotactic body radiation therapy and thermal ablation for treatment of NSCLC: A systematic literature review and meta-analysis. *Lung Cancer.* 2023;182:107259. PMID: 37321074
53. Sultan S, Ullman K, Ester E, et al. VA Evidence-based Synthesis Program Reports. Non-surgical Therapies for Early-stage Non-small Cell Lung Cancer: A Systematic Review. Washington (DC): Department of Veterans Affairs (US), 2023.
54. Chan MV, Huo YR, Cao C, et al. Survival outcomes for surgical resection versus CT-guided percutaneous ablation for stage I non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. *Eur Radiol.* 2021;31(7):5421-33. PMID: 33449192

55. Ratko TA, Vats V, Brock J, et al. Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non-Small-Cell Lung Cancer. *AHRQ Comparative Effectiveness Reviews.* 2013. PMID: 23865091
56. Schlijper RC, Grutters JP, Houben R, et al. What to choose as radical local treatment for lung metastases from colo-rectal cancer: surgery or radiofrequency ablation? *Cancer treatment reviews.* 2014;40(1):60-7. PMID: 23768754
57. Chan VO, McDermott S, Malone DE, et al. Percutaneous radiofrequency ablation of lung tumors: evaluation of the literature using evidence-based techniques. *Journal of thoracic imaging.* 2011;26(1):18-26. PMID: 20829720
58. Bilal H, Mahmood S, Rajashanker B, et al. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interactive cardiovascular and thoracic surgery.* 2012;15(2):258-65. PMID: 22581864
59. Akeboshi M, Yamakado K, Nakatsuka A, et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. *J Vasc Interv Radiol.* 2004;15(5):463-70. PMID: 15126656
60. Belfiore G, Moggio G, Tedeschi E, et al. CT-guided radiofrequency ablation: a potential complementary therapy for patients with unresectable primary lung cancer--a preliminary report of 33 patients. *AJR Am J Roentgenol.* 2004;183(4):1003-11. PMID: 15385294
61. Gadaleta C, Catino A, Ranieri G, et al. Radiofrequency thermal ablation of 69 lung neoplasms. *J Chemother.* 2004;16 Suppl 5:86-9. PMID: 15675488
62. Jin GY, Lee JM, Lee YC, et al. Primary and secondary lung malignancies treated with percutaneous radiofrequency ablation: evaluation with follow-up helical CT. *AJR Am J Roentgenol.* 2004;183(4):1013-20. PMID: 15385295
63. Kang S, Luo R, Liao W, et al. Single group study to evaluate the feasibility and complications of radiofrequency ablation and usefulness of post treatment position emission tomography in lung tumours. *World J Surg Oncol.* 2004;2:30. PMID: 15350201
64. King J, Glenn D, Clark W, et al. Percutaneous radiofrequency ablation of pulmonary metastases in patients with colorectal cancer. *The British journal of surgery.* 2004;91(2):217-23. PMID: 14760671
65. Lee JM, Jin GY, Goldberg SN, et al. Percutaneous radiofrequency ablation for inoperable non-small cell lung cancer and metastases: preliminary report. *Radiology.* 2004;230(1):125-34. PMID: 14645875
66. Steinke K, Glenn D, King J, et al. Percutaneous imaging-guided radiofrequency ablation in patients with colorectal pulmonary metastases: 1-year follow-up. *Ann Surg Oncol.* 2004;11(2):207-12. PMID: 14761926
67. Yasui K, Kanazawa S, Sano Y, et al. Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology.* 2004;231(3):850-7. PMID: 15105453
68. Bojarski JD, Dupuy DE, Mayo-Smith WW. CT imaging findings of pulmonary neoplasms after treatment with radiofrequency ablation: results in 32 tumors. *AJR Am J Roentgenol.* 2005;185(2):466-71. PMID: 16037522
69. Fernando HC, De Hoyos A, Landreneau RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. *J Thorac Cardiovasc Surg.* 2005;129(3):639-44. PMID: 15746749
70. Nguyen CL, Scott WJ, Young NA, et al. Radiofrequency ablation of primary lung cancer: results from an ablate and resect pilot study. *Chest.* 2005;128(5):3507-11. PMID: 16304306

71. VanSonnenberg E, Shankar S, Morrison PR, et al. Radiofrequency ablation of thoracic lesions: part 2, initial clinical experience--technical and multidisciplinary considerations in 30 patients. *AJR Am J Roentgenol.* 2005;184(2):381-90. PMID: 15671350
72. Simon CJ, Dupuy DE, DiPetrillo TA, et al. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology.* 2007;243(1):268-75. PMID: 17392258
73. Ambrogi MC, Lucchi M, Dini P, et al. Percutaneous radiofrequency ablation of lung tumours: results in the mid-term. *Eur J Cardiothorac Surg.* 2006;30(1):177-83. PMID: 16723242
74. de Baere T, Palussiere J, Auperin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology.* 2006;240(2):587-96. PMID: 16864679
75. Yamakado K, Hase S, Matsuoka T, et al. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. *J Vasc Interv Radiol.* 2007;18(3):393-8. PMID: 17377185
76. Zhu JC, Yan TD, Morris DL. A systematic review of radiofrequency ablation for lung tumors. *Ann Surg Oncol.* 2008;15(6):1765-74. PMID: 18368456
77. Yan TD, King J, Sjarif A, et al. Treatment failure after percutaneous radiofrequency ablation for nonsurgical candidates with pulmonary metastases from colorectal carcinoma. *Ann Surg Oncol.* 2007;14(5):1718-26. PMID: 17285398
78. Haasbeek CJ, Senan S, Smit EF, et al. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. *Oncologist.* 2008;13(3):309-19. PMID: 18378542
79. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2007;2(7 Suppl 3):S94-100. PMID: 17603311
80. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol.* 2008;9(7):621-8. PMID: 18565793
81. Zhu JC, Yan TD, Glenn D, et al. Radiofrequency ablation of lung tumors: feasibility and safety. *Ann Thorac Surg.* 2009;87(4):1023-8. PMID: 19324122
82. Pennathur A, Abbas G, Gooding WE, et al. Image-guided radiofrequency ablation of lung neoplasm in 100 consecutive patients by a thoracic surgical service. *Ann Thorac Surg.* 2009;88(5):1601-6; discussion 07-8. PMID: 19853119
83. Beland MD, Wasser EJ, Mayo-Smith WW, et al. Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation. *Radiology.* 2010;254(1):301-7. PMID: 20032160
84. Lanuti M, Sharma A, Digumarthy SR, et al. Radiofrequency ablation for treatment of medically inoperable stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2009;137(1):160-6. PMID: 19154919
85. Yamakado K, Inoue Y, Takao M, et al. Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. *Oncol Rep.* 2009;22(4):885-91. PMID: 19724869
86. Soga N, Yamakado K, Gohara H, et al. Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. *BJU international.* 2009;104(6):790-4. PMID: 19338555
87. Zemlyak A, Moore WH, Bilfinger TV. Comparison of survival after sublobar resections and ablative therapies for stage I non-small cell lung cancer. *Journal of the American College of Surgeons.* 2010;211(1):68-72. PMID: 20610251

88. Lee H, Jin GY, Han YM, et al. Comparison of survival rate in primary non-small-cell lung cancer among elderly patients treated with radiofrequency ablation, surgery, or chemotherapy. *Cardiovasc Intervent Radiol.* 2012;35(2):343-50. PMID: 21626257
89. Ambrogi MC, Fanucchi O, Cioni R, et al. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2011;6(12):2044-51. PMID: 22052222
90. von Meyenfeldt EM, Prevoo W, Peyrot D, et al. Local progression after radiofrequency ablation for pulmonary metastases. *Cancer.* 2011;117(16):3781-7. PMID: 21319158
91. Ochiai S, Yamakado K, Kodama H, et al. Comparison of therapeutic results from radiofrequency ablation and stereotactic body radiotherapy in solitary lung tumors measuring 5 cm or smaller. *International journal of clinical oncology.* 2015;20(3):499-507. PMID: 25130494
92. Huang L, Han Y, Zhao J, et al. Is radiofrequency thermal ablation a safe and effective procedure in the treatment of pulmonary malignancies? *Eur J Cardiothorac Surg.* 2011;39(3):348-51. PMID: 20663679
93. de Baere T, Auperin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. *Ann Oncol.* 2015;26:987-91. PMID: 25688058
94. Yoshimatsu R, Yamagami T, Terayama K, et al. Delayed and recurrent pneumothorax after radiofrequency ablation of lung tumors. *Chest.* 2009;135(4):1002-9. PMID: 19017870
95. Hiraki T, Tajiri N, Mimura H, et al. Pneumothorax, pleural effusion, and chest tube placement after radiofrequency ablation of lung tumors: incidence and risk factors. *Radiology.* 2006;241(1):275-83. PMID: 16908680
96. Sano Y, Kanazawa S, Gobara H, et al. Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: a large single-center experience. *Cancer.* 2007;109(7):1397-405. PMID: 17315166
97. Okuma T, Matsuoka T, Yamamoto A, et al. Frequency and risk factors of various complications after computed tomography-guided radiofrequency ablation of lung tumors. *Cardiovasc Intervent Radiol.* 2008;31(1):122-30. PMID: 17985181
98. Hiraki T, Mimura H, Gobara H, et al. Two cases of needle-tract seeding after percutaneous radiofrequency ablation for lung cancer. *J Vasc Interv Radiol.* 2009;20(3):415-8. PMID: 19167247
99. Nomura M, Yamakado K, Nomoto Y, et al. Complications after lung radiofrequency ablation: risk factors for lung inflammation. *Br J Radiol.* 2008;81(963):244-9. PMID: 18208852
100. Hiraki T, Gobara H, Kato K, et al. Bronchiolitis obliterans organizing pneumonia after radiofrequency ablation of lung cancer: report of three cases. *J Vasc Interv Radiol.* 2012;23(1):126-30. PMID: 22221477
101. Palussiere J, Cannella M, Gomez F, et al. Stellate ganglion injury after percutaneous radiofrequency ablation of a lung tumor. *Cardiovasc Intervent Radiol.* 2011;34(4):873-6. PMID: 21153414
102. Sangiorgio A, Oldrini LM, Candrian C, et al. Radiofrequency ablation is as safe and effective as surgical excision for spinal osteoid osteoma: a systematic review and meta-analysis. *Eur Spine J.* 2022. PMID: 36214895
103. Lindquester WS, Crowley J, Hawkins CM. Percutaneous thermal ablation for treatment of osteoid osteoma: a systematic review and analysis. *Skeletal Radiol.* 2020;49(9):1403-11. PMID: 32270226

104. Rosenthal DI, Hornicek FJ, Torriani M, et al. Osteoid osteoma: percutaneous treatment with radiofrequency energy. *Radiology.* 2003;229(1):171-5. PMID: 12944597
105. Cioni R, Armillotta N, Bargellini I, et al. CT-guided radiofrequency ablation of osteoid osteoma: long-term results. *Eur Radiol.* 2004;14(7):1203-8. PMID: 15014976
106. Martel J, Bueno A, Ortiz E. Percutaneous radiofrequency treatment of osteoid osteoma using cool-tip electrodes. *Eur J Radiol.* 2005;56(3):403-8. PMID: 15964164
107. Ghanem I. The management of osteoid osteoma: updates and controversies. *Curr Opin Pediatr.* 2006;18(1):36-41. PMID: 16470160
108. Papagelopoulos PJ, Mavrogenis AF, Kyriakopoulos CK, et al. Radiofrequency ablation of intra-articular osteoid osteoma of the hip. *J Int Med Res.* 2006;34(5):537-44. PMID: 17133784
109. Rimondi E, Mavrogenis AF, Rossi G, et al. Radiofrequency ablation for non-spinal osteoid osteomas in 557 patients. *Eur Radiol.* 2012;22(1):181-8. PMID: 21842430
110. Knudsen M, Riishede A, Lucke A, et al. Computed tomography-guided radiofrequency ablation is a safe and effective treatment of osteoid osteoma located outside the spine. *Danish medical journal.* 2015;62(5). PMID: 26050823
111. Lassalle L, Campagna R, Corcos G, et al. Therapeutic outcome of CT-guided radiofrequency ablation in patients with osteoid osteoma. *Skeletal Radiol.* 2017;46(7):949-56. PMID: 28429047
112. Mehta TI, Heiberger C, Kazi S, et al. Effectiveness of Radiofrequency Ablation in the Treatment of Painful Osseous Metastases: A Correlation Meta-Analysis with Machine Learning Cluster Identification. *J Vasc Interv Radiol.* 2020;31(11):1753-62. PMID: 33012648
113. Gennaro N, Sconfienza LM, Ambrogi F, et al. Thermal ablation to relieve pain from metastatic bone disease: a systematic review. *Skeletal radiology.* 2019;48(8):1161-69. PMID: 30627778
114. Levy J, Hopkins T, Morris J, et al. Radiofrequency Ablation for the Palliative Treatment of Bone Metastases: Outcomes from the Multicenter OsteoCool Tumor Ablation Post-Market Study (OPuS One Study) in 100 Patients. *J Vasc Interv Radiol.* 2020;31(11):1745-52. PMID: 33129427
115. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(2):300-6. PMID: 14722039
116. Kojima H, Tanigawa N, Kariya S, et al. Clinical assessment of percutaneous radiofrequency ablation for painful metastatic bone tumors. *Cardiovasc Intervent Radiol.* 2006;29(6):1022-6. PMID: 16988875
117. Proschek D, Kurth A, Proschek P, et al. Prospective pilot-study of combined bipolar radiofrequency ablation and application of bone cement in bone metastases. *Anticancer research.* 2009;29(7):2787-92. PMID: 19596962
118. Thanos L, Mylona S, Galani P, et al. Radiofrequency ablation of osseous metastases for the palliation of pain. *Skeletal Radiol.* 2008;37(3):189-94. PMID: 18030464
119. Gronemeyer DH, Schirp S, Gevargez A. Image-guided radiofrequency ablation of spinal tumors: preliminary experience with an expandable array electrode. *Cancer J.* 2002;8(1):33-9. PMID: 11898806
120. Tan YK, Best SL, Olweny E, et al. Radiofrequency ablation of incidental benign small renal mass: outcomes and follow-up protocol. *Urology.* 2012;79:827-30. PMID: 22309782

121. Castle SM, Gorbatiy V, Ekwenna O, et al. Radiofrequency ablation (RFA) therapy for renal angiomyolipoma (AML): an alternative to angio-embolization and nephron-sparing surgery. *BJU international.* 2012;109(3):384-7. PMID: 22176671
122. Chang Z, Zhang JM, Ying JQ, et al. Characteristics and treatment strategy of hepatic angiomyolipoma: a series of 94 patients collected from four institutions. *J Gastrointestin Liver Dis.* 2011;20:65-9. PMID: 21451800
123. Sooriakumaran P, Gibbs P, Coughlin G, et al. Angiomyolipomata: challenges, solutions, and future prospects based on over 100 cases treated. *BJU international.* 2010;105:101-6. PMID: 19493268
124. Gregory SM, Anderson CJ, Patel U. Radiofrequency ablation of large renal angiomyolipoma: median-term follow-up. *Cardiovasc Intervent Radiol.* 2013;36(3):682-9. PMID: 23354958
125. Mayo-Smith WW, Dupuy DE, Parikh PM, et al. Imaging-guided percutaneous radiofrequency ablation of solid renal masses: techniques and outcomes of 38 treatment sessions in 32 consecutive patients. *AJR Am J Roentgenol.* 2003;180(6):1503-8. PMID: 12760909
126. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Head and Neck Cancer v.1.2024. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck_blocks.pdf.
127. Owen RP, Silver CE, Ravikumar TS, et al. Techniques for radiofrequency ablation of head and neck tumors. *Arch Otolaryngol Head Neck Surg.* 2004;130(1):52-6. PMID: 14732768
128. Brook AL, Gold MM, Miller TS, et al. CT-guided radiofrequency ablation in the palliative treatment of recurrent advanced head and neck malignancies. *J Vasc Interv Radiol.* 2008;19(5):725-35. PMID: 18440462
129. Carney AS, Timms MS, Marnane CN, et al. Radiofrequency coblation for the resection of head and neck malignancies. *Otolaryngol Head Neck Surg.* 2008;138(1):81-5. PMID: 18164998
130. Liukko T, Makitie AA, Markkola A, et al. Radiofrequency induced thermotherapy: an alternative palliative treatment modality in head and neck cancer. *Eur Arch Otorhinolaryngol.* 2006;263(6):532-6. PMID: 16565858
131. Owen RP, Khan SA, Negassa A, et al. Radiofrequency ablation of advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2011;137(5):493-8. PMID: 21576561
132. Sun YD, Zhang H, Zhu HT, et al. A systematic review and meta-analysis comparing tumor progression and complications between radiofrequency ablation and thyroidectomy for papillary thyroid carcinoma. *Front Oncol.* 2022;12:994728. PMID: 36530996
133. Cho SJ, Baek SM, Na DG, et al. Five-year follow-up results of thermal ablation for low-risk papillary thyroid microcarcinomas: systematic review and meta-analysis. *Eur Radiol.* 2021;31(9):6446-56. PMID: 33713168
134. Choi Y, Jung SL. Efficacy and Safety of Thermal Ablation Techniques for the Treatment of Primary Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-Analysis. *Thyroid.* 2020;30(5):720-31. PMID: 31801432
135. Xiao J, Zhang Y, Yan L, et al. Ultrasonography-guided radiofrequency ablation for solitary T1aN0M0 and T1bN0M0 papillary thyroid carcinoma: a retrospective comparative study. *Eur J Endocrinol.* 2021;186(1):105-13. PMID: 34757942
136. Cao XJ, Wang SR, Che Y, et al. Efficacy and Safety of Thermal Ablation for Treatment of Solitary T1N0M0 Papillary Thyroid Carcinoma: A Multicenter Retrospective Study. *Radiology.* 2021;300(1):209-16. PMID: 33904775

137. Kim JH, Yoo WS, Park YJ, et al. Efficacy and safety of radiofrequency ablation for treatment of locally recurrent thyroid cancers smaller than 2 cm. *Radiology.* 2015;276(3):909-18. PMID: 25848897
138. Chung SR, Suh CH, Baek JH, et al. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2017;33(8):920-30. PMID: 28565997
139. Monpeyssen H, Alamri A, Ben Hamou A. Long-Term Results of Ultrasound-Guided Radiofrequency Ablation of Benign Thyroid Nodules: State of the Art and Future Perspectives-A Systematic Review. *Front Endocrinol (Lausanne).* 2021;12:622996. PMID: 34122328
140. Cho SJ, Baek JH, Chung SR, et al. Long-Term Results of Thermal Ablation of Benign Thyroid Nodules: A Systematic Review and Meta-Analysis. *Endocrinol Metab (Seoul).* 2020;35(2):339-50. PMID: 32615718
141. Trimboli P, Castellana M, Sconfienza LM, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. *Endocrine.* 2019:10.1007/s12020-019-02019-3. PMID: 31327158
142. Fuller CW NS, Lohia S, et al. Radiofrequency ablation for treatment of benign thyroid nodules: systematic review. *Laryngoscope.* 2014;124(1):346-53. PMID: 24122763
143. Deandrea M, Limone P, Basso E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. *Ultrasound Med Biol.* 2008;34(5):784-91. PMID: 18207307
144. Spiezia S, Garberoglio R, Milone F, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. *Thyroid.* 2009;19(3):219-25. PMID: 19265492
145. Kim YS, Rhim H, Tae K, et al. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. *Thyroid.* 2006;16(4):361-7. PMID: 16646682
146. Kim DW. Sonography-guided ethanol ablation of a remnant solid component after radio-frequency ablation of benign solid thyroid nodules: a preliminary study. *AJNR Am J Neuroradiol.* 2012;33:1139-43. PMID: 22268084
147. Jang SW, Baek JH, Kim JK, et al. How to manage the patients with unsatisfactory results after ethanol ablation for thyroid nodules: role of radiofrequency ablation. *Eur J Radiol.* 2012;81:905-10. PMID: 21388767
148. Baek JH, Lee JH, Sung JY, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. *Radiology.* 2012;262(1):335-42. PMID: 21998044
149. Huh JY, Baek JH, Choi H, et al. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. *Radiology.* 2012;263(3):909-16. PMID: 22438360
150. Faggiano A, Ramundo V, Assanti AP, et al. Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. *J Clin Endocrinol Metab.* 2012;97:4439-45. PMID: 23019349
151. Sung JY, Baek JH, Kim KS, et al. Single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. *Radiology.* 2013;269:293-300. PMID: 23616630
152. Kandil E, Omar M, Aboueisha M, et al. Efficacy and Safety of Radiofrequency Ablation of Thyroid Nodules: A Multi-institutional Prospective Cohort Study. *Ann Surg.* 2022;276(4):589-96. PMID: 35837903

153. Fan WJ, Wu PH, Zhang L, et al. Radiofrequency ablation as a treatment for hilar cholangiocarcinoma. *World J Gastroenterol.* 2008;14(28):4540-5. PMID: 18680236
154. Polin M, Hur HC. Radiofrequency Ablation of Uterine Myomas and Pregnancy Outcomes: An Updated Review of the Literature. *Journal of minimally invasive gynecology.* 2022;29(6):709-15. PMID: 35123041
155. Morris JM, Liang A, Fleckenstein K, et al. A Systematic Review of Minimally Invasive Approaches to Uterine Fibroid Treatment for Improving Quality of Life and Fibroid-Associated Symptoms. *Reproductive sciences (Thousand Oaks, Calif).* 2022. PMID: 36401073
156. Zhang J, Go VA, Blanck JF, et al. A Systematic Review of Minimally Invasive Treatments for Uterine Fibroid-Related Bleeding. *Reproductive sciences (Thousand Oaks, Calif).* 2022;29(10):2786-809. PMID: 34480321
157. Arnreiter C, Oppelt P. A Systematic Review of the Treatment of Uterine Myomas Using Transcervical Ultrasound-Guided Radiofrequency Ablation with the Sonata System. *Journal of minimally invasive gynecology.* 2021;28(8):1462-69. PMID: 33892184
158. Berman JM, Shashoua A, Olson C, et al. Case Series of Reproductive Outcomes after Laparoscopic Radiofrequency Ablation of Symptomatic Myomas. *Journal of minimally invasive gynecology.* 2020;27(3):639-45. PMID: 31238151
159. Bradley LD, Pasic RP, Miller LE. Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies. *J Laparoendosc Adv Surg Tech A.* 2019;29(12):1507-17. PMID: 31702440
160. Sandberg EM, Tummers FHMP, Cohen SL, et al. Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis. *Fertil Steril.* 2018;109(4):698-707.e1. PMID: 29653718
161. Havryliuk Y, Setton R, Carlow JJ, et al. Symptomatic Fibroid Management: Systematic Review of the Literature. *JSLS.* 2017;21(3):e2017.00041. PMID: 28951653
162. Lin L, Ma H, Wang J, et al. Quality of Life, Adverse Events, and Reintervention Outcomes after Laparoscopic Radiofrequency Ablation for Symptomatic Uterine Fibroids: A Meta-Analysis. *Journal of minimally invasive gynecology.* 2019;26(3):409-16. PMID: 30253997
163. Rattray DD, Weins L, Regush LC, et al. Clinical outcomes and health care utilization pre- and post-laparoscopic radiofrequency ablation of symptomatic fibroids and laparoscopic myomectomy: a randomized trial of uterine-sparing techniques (TRUST) in Canada. *Clinicoecon Outcomes Res.* 2018;10:201-12. PMID: 29670382
164. Yu S, Bhagavath B, Shobeiri SA, et al. Clinical and Patient Reported Outcomes of Pre- and Postsurgical Treatment of Symptomatic Uterine Leiomyomas: A 12-Month Follow-up Review of TRUST, a Surgical Randomized Clinical Trial Comparing Laparoscopic Radiofrequency Ablation and Myomectomy. *Journal of minimally invasive gynecology.* 2022;29(6):726-37. PMID: 35085837
165. Brucker SY, Hahn M, Kraemer D, et al. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2014;125(3):261-5. PMID: 24698202
166. Hahn M, Brucker S, Kraemer D, et al. Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: long-term follow-up from a randomized trial. *Geburtshilfe und Frauenheilkunde.* 2015;75(5):442-49. PMID: 26097247
167. Kramer B, Hahn M, Taran FA, et al. Interim analysis of a randomized controlled trial comparing laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids with laparoscopic myomectomy. *International journal of gynaecology and obstetrics: the*

official organ of the International Federation of Gynaecology and Obstetrics. 2016;133(2):206-11. PMID: 26892690
168. Shifrin G, Engelhardt M, Gee P, et al. Transcervical fibroid ablation with the Sonata™ system for treatment of submucous and large uterine fibroids. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2021;155(1):79-85. PMID: 33544889
169. Yüce G, Tayarer A, Keskin HL, et al. Ultrasound guided percutaneous radiofrequency thermal ablation of symptomatic uterine fibroids - results from a single center and 52 weeks of follow up. *Ginekol Pol.* 2020;91(8):447-52. PMID: 32902841
170. Rey VE, Labrador R, Falcon M, et al. Transvaginal Radiofrequency Ablation of Myomas: Technique, Outcomes, and Complications. *J Laparoendosc Adv Surg Tech A.* 2019;29(1):24-28. PMID: 30198831
171. Yin G, Chen M, Yang S, et al. Treatment of uterine myomas by radiofrequency thermal ablation: a 10-year retrospective cohort study. *Reproductive sciences (Thousand Oaks, Calif).* 2015;22(5):609-14. PMID: 25355802
172. Chudnoff SG, Berman JM, Levine DJ, et al. Outpatient procedure for the treatment and relief of symptomatic uterine myomas. *Obstetrics and gynecology.* 2013;121(5):1075-82. PMID: 23635746
173. Berman JM, Guido RS, Garza Leal JG, et al. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. *Journal of minimally invasive gynecology.* 2014;21(5):767-74. PMID: 24613404
174. ClinicalTrials.gov website; Radiofrequency Ablation. [cited 11/14/2023]. 'Available from:' http://www.clinicaltrials.gov/ct2/results?term=%22radiofrequency+ablation%22.
175. Tang W, Tang X, Jiang D, et al. Safety and efficacy of thermal ablation for cervical metastatic lymph nodes in papillary thyroid carcinoma: A systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2022;13:967044. PMID: 36072932
176. Dhaliwal A, Kolli S, Dhindsa BS, et al. Efficacy of EUS-RFA in pancreatic tumors: Is it ready for prime time? A systematic review and meta-analysis. *Endosc Int Open.* 2020;8(10):E1243-e51. PMID: 33015325
177. Imperatore N, de Nucci G, Mandelli ED, et al. Endoscopic ultrasound-guided radiofrequency ablation of pancreatic neuroendocrine tumors: a systematic review of the literature. *Endosc Int Open.* 2020;8(12):E1759-e64. PMID: 33269308
178. Zhang L, Tan S, Huang S, et al. The safety and efficacy of endoscopic ultrasound-guided ablation therapy for solid pancreatic tumors: a systematic review. *Scand J Gastroenterol.* 2020;55(9):1121-31. PMID: 32730715
179. Rombouts SJ, Vogel JA, van Santvoort HC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. *The British journal of surgery.* 2015;102(3):182-93. PMID: 25524417
180. Thomson L, Aujla RS, Divall P, et al. Non-surgical treatments for Morton's neuroma: A systematic review. *Foot Ankle Surg.* 2019:S1268-7731(19)30179-1. PMID: 31718949
181. Mayo-Smith WW, Dupuy DE. Adrenal neoplasms: CT-guided radiofrequency ablation--preliminary results. *Radiology.* 2004;231(1):225-30. PMID: 14990812
182. Nair RT, vanSonnenberg E, Shankar S, et al. Visceral and soft-tissue tumors: radiofrequency and alcohol ablation for pain relief--initial experience. *Radiology.* 2008;248(3):1067-76. PMID: 18710995
183. Locklin JK, Mannes A, Berger A, et al. Palliation of soft tissue cancer pain with radiofrequency ablation. *J Support Oncol.* 2004;2(5):439-45. PMID: 15524075

184. Arima K, Yamakado K, Suzuki R, et al. Image-guided radiofrequency ablation for adrenocortical adenoma with Cushing syndrome: outcomes after mean follow-up of 33 months. *Urology.* 2007;70(3):407-11. PMID: 17905083
185. Wood BJ, Abraham J, Hvizda JL, et al. Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. *Cancer.* 2003;97(3):554-60. PMID: 12548596
186. Spiliotis JD, Datsis AC, Michalopoulos NV, et al. Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. *Langenbecks Arch Surg.* 2007;392(1):55-60. PMID: 17089173
187. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(8):978-86. PMID: 17350947
188. Rosenthal DI. Radiofrequency treatment. *Orthop Clin North Am.* 2006;37(3):475-84, viii. PMID: 16846772
189. Rybak LD, Rosenthal DI, Wittig JC. Chondroblastoma: radiofrequency ablation--alternative to surgical resection in selected cases. *Radiology.* 2009;251(2):599-604. PMID: 19304917
190. Vavra P, Dostalik J, Zacharoulis D, et al. Endoscopic radiofrequency ablation in colorectal cancer: initial clinical results of a new bipolar radiofrequency ablation device. *Dis Colon Rectum.* 2009;52(2):355-8. PMID: 19279436
191. Kameyama S, Murakami H, Masuda H, et al. Minimally invasive magnetic resonance imaging-guided stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas. *Neurosurgery.* 2009;65(3):438-49; discussion 49. PMID: 19687687
192. Zou YP, Li WM, Zheng F, et al. Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. *World J Gastroenterol.* 2010;16(40):5104-10. PMID: 20976848
193. Gunjur A, Duong C, Ball D, et al. Surgical and ablative therapies for the management of adrenal 'oligometastases' - A systematic review. *Cancer treatment reviews.* 2014;40(7):838-46. PMID: 24791623
194. Xie C, Jeys L, James SL. Radiofrequency ablation of chondroblastoma: long-term clinical and imaging outcomes. *Eur Radiol.* 2015;25(4):1127-34. PMID: 25432292
195. Kondajji AM, Evans A, Lum M, et al. A systematic review of stereotactic radiofrequency ablation for hypothalamic hamartomas. *J Neurol Sci.* 2021;424:117428. PMID: 33813160
196. Guo RQ, Li YM, Li XG. Comparison of the radiofrequency ablation versus laparoscopic adrenalectomy for aldosterone-producing adenoma: a meta-analysis of perioperative outcomes and safety. *Updates Surg.* 2021;73(4):1477-85. PMID: 34165729
197. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Thyroid Carcinoma. v.4.2023. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/thyroid_blocks.pdf.
198. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon cancer. v.3.2023. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/colon_blocks.pdf.
199. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Kidney Cancer v.1.2024. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf.
200. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. v.4.2023. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf.

201. Purysko AS, Nikolaidis P, Khatri G, et al. ACR Appropriateness Criteria® Post-Treatment Follow-up and Active Surveillance of Clinically Localized Renal Cell Carcinoma: 2021 Update. *Journal of the American College of Radiology : JACR.* 2022;19(5s):S156-s74. PMID: 35550799
202. Videtic GM, Chang JY, Chetty IJ, et al. ACR appropriateness Criteria(R) early-stage non-small-cell lung cancer. *Am J Clin Oncol.* 2014;37:201-7. PMID: 25180631
203. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest.* 2012;142:1620-35. PMID: 23208335
204. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e278S-313S. PMID: 23649443
205. Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. *Thyroid.* 2021;31(3):337-86. PMID: 33728999
206. Campbell S, Uzzo RG, Allaf ME, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. *The Journal of urology.* 2017;198(3):520-29. PMID: 28479239
207. Campbell SC, Clark PE, Chang SS, et al. Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-Up: AUA Guideline: Part I. *J Urol.* 2021;206(2):199-208. PMID: 34115547
208. Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin Summary, Number 228. *Obstetrics and gynecology.* 2021;137(6):1131-33. PMID: 34011880
209. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules - 2016 Update. *Endocr Pract.* 2016;22(5):622-39. PMID: 27167915
210. Morris CS, Baerlocher MO, Dariushnia SR, et al. Society of Interventional Radiology Position Statement on the Role of Percutaneous Ablation in Renal Cell Carcinoma: Endorsed by the Canadian Association for Interventional Radiology and the Society of Interventional Oncology. *J Vasc Interv Radiol.* 2020;31(2):189-94.e3. PMID: 31917025

CODES

Codes	Number	Description
CPT	20982	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; radiofrequency
	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; radiofrequency
	50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed

Codes	Number	Description
	58580	Transcervical ablation of uterine fibroid(s), including intraoperative ultrasound guidance and monitoring, radiofrequency
	50592	Ablation, one or more renal tumor(s), percutaneous, unilateral, radiofrequency
	58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency
	60699	Unlisted procedure, endocrine system
	~~0404T~~	~~Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency~~ (Deleted 01/01/2024)
HCPCS	None	

Date of Origin: *December 1998*

Regence

Medical Policy Manual Surgery, Policy No. 104

Varicose Vein Treatment

Effective: December 1, 2023

Next Review: March 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Varicose veins are dilated, tortuous veins that may cause pain or skin ulcers; however, the majority of treatment is done for cosmetic reasons. Invasive treatment may include surgical removal and/or destruction using lasers, heat, or injection of sclerosing solution.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy. In addition, when there is a contract denial for treatment of varicose veins, the denial not only includes treatment but also the associated venous imaging studies (i.e. CPT 93970 or 93971) for treatment planning.
- This policy addresses treatment of the superficial system veins of the lower extremity (e.g., great and small saphenous veins, saphenous tributaries, varicose veins and associated lower extremity perforator veins), upper extremity varices, and vulvar varices.
- Embolization, ablation, and sclerotherapy of the ovarian, internal iliac, or gonadal veins for treatment of pelvic congestion syndrome or varicoceles are addressed separately (see Cross References below).

- This policy uses the nomenclature great saphenous vein and small saphenous vein. Great saphenous veins are also known as long saphenous veins (CPT nomenclature) or greater saphenous veins. Small saphenous veins are also known as short saphenous veins (CPT nomenclature) or lesser saphenous veins.

I. **ALL** of the following **general criteria** (see List of Information Needed for Review) must be met for varicose vein treatment to be considered for coverage:

A. One or more of the following indications must be documented:

1. Functional impairment, attributed to varicose veins, which limits performance of instrumental activities of daily living (ADLs). Instrumental ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning. Clinical records **must specifically document** ALL of the following:

a. The specific instrumental ADL that is impaired; and

b. A description of how performance of the instrumental ADL is limited; and

c. Progress notes must document patient compliance with medically supervised conservative therapy, including the current use for a minimum of 3 months of compression (minimum 15 mmHg) stockings and the patient's response; or

2. Venous imaging study documented recurrent attacks of superficial phlebitis; or

3. Recurrent or persistent hemorrhage from ruptured varix, which does not include bleeding caused by scratching or shaving; or

4. Documentation of ulceration from venous stasis where incompetent varices are a significant contributing factor; and

B. A complete venous imaging study in the superficial system veins (e.g., great and small saphenous veins, perforator veins, and saphenous tributaries) is performed including documentation of the diameter of the vein and the reflux in seconds measured at multiple levels in the thigh and calf.

II. Procedures

A. Endovenous ablation

1. Endovenous radiofrequency, laser ablation, or endovenous glue or adhesive of incompetent great or small saphenous veins may be considered **medically necessary** when ALL of the following Criteria (a.-d.) are met:

a. Criterion I. above is met.

b. Documentation by venous imaging study of minimum vein diameter measurements for:

i. Great saphenous vein diameter 5.5 mm or greater (not at or closely adjacent to the saphenofemoral junction)

ii. Small saphenous vein diameter is 4 mm or greater (not at or closely adjacent to the saphenopopliteal junction); and

c. Incompetence exceeding 0.5 seconds; and

d. Clinical documentation that all incompetent segments of the same vein will be treated in the same session and with the same modality.

B. Ligation/stripping and phlebectomy (i.e., stab, hook, transilluminated powered)

1. Ligation/stripping and phlebectomy of incompetent superficial system veins (including the great and small saphenous veins and saphenous tributaries including accessory saphenous veins) and varicose veins may be considered **medically necessary** when ALL of the following Criteria (a.-d.) are met:

a. Criterion I. above is met; and

b. The incompetent superficial veins proximal to the vein to be treated either have been treated or are being treated concurrently; and

c. Documentation by venous imaging study of minimum vein diameter of 4mm or greater (not at or closely adjacent to the saphenofemoral junction or saphenopopliteal junction); and

d. Incompetence exceeding 0.5 seconds.

C. Sclerotherapy

1. Sclerotherapy (liquid, foam, or microfoam) of the following superficial system veins: great saphenous vein below the knee, small saphenous vein, and saphenous tributaries including accessory saphenous veins, and other varicose veins may be considered **medically necessary** when ALL of the following Criteria (a.-c.) are met:

a. Criterion I. above is met; and

b. Documentation by venous imaging study of minimum vein diameter of 4mm or greater (not at or closely adjacent to the saphenofemoral junction or saphenopopliteal junction); and

c. The incompetent superficial veins proximal to the vein to be treated either have been treated or are being treated concurrently.

2. Venous imaging study guidance (see Policy Guidelines) may be considered **medically necessary** for liquid, foam, or microfoam sclerotherapy of the great saphenous vein below the knee, small saphenous vein, accessory saphenous veins and saphenous tributaries**.**

III. Treatment sessions (see List of Information Needed for Review): When applicable medical necessity criteria detailed above are met, either initial or subsequent treatment may be considered **medically necessary** when performed within either of the following numbers of treatment sessions:

A. One treatment session; or

B. Two treatment sessions of bilateral veins (a separate session for each of the right and left legs).

IV. Varicose vein treatment is considered **not medically necessary** when Criterion I. is not met.

V. If Criterion II.A.1. is not met, endovenous radiofrequency, laser ablation, or endovenous glue or adhesive of incompetent great or small saphenous veins is considered **not medically necessary.**

VI. Endovenous ablation is considered **investigational** for ALL of the following:

A. Cryoablation of any vein; and

B. Radiofrequency, endovenous glue or adhesive, or laser ablation of veins other than the great or small saphenous veins, including but not limited to the following:

1. accessory saphenous veins
2. branch tributaries
3. perforator veins; and

C. Ablation of any other veins (e.g., vulvar varices); and

D. Mechanochemical ablation of any vein; and

E. Microwave ablation of any vein; and

F. Steam injection ablation of any vein.

VII. If Criterion II.B.1. is not met, ligation/stripping or phlebectomy (including perforator veins) is considered **not medically necessary.**

VIII. If Criterion II.C.1. is not met, sclerotherapy is considered **not medically necessary.**

IX. Sclerotherapy is considered **investigational** for ALL of the following:

A. Vulvar, including labial and buttock varices; and

B. Upper extremity varices; and

C. Great saphenous vein from the saphenous femoral junction (SFJ) to knee; and

D. Perforator veins

X. Sclerotherapy of small (less than 4 mm in diameter) superficial veins, including but not limited to reticular veins and/or telangiectasias (spider veins) is considered **cosmetic.**

XI. Venous imaging study guidance is considered **not medically necessary** for sclerotherapy of all other superficial system veins**.**

XII. Separate sessions for ablation of segments of a continuous vein are considered **not medically necessary** (See Policy Guidelines).

XIII. Treatment sessions not meeting Criterion III. above are considered **not medically necessary**.

XIV. Follow-up venous imaging studies performed within 6 months following the most recent ipsilateral treatment, in the absence of complications, are considered **not medically necessary**, including but not limited to routine confirmation studies

following endovenous ablation. Focused venous imaging studies to confirm ablation or rule out deep vein thrombosis or endovenous heat-induced thrombosis are considered a component of and incidental to the procedure or follow-up evaluation.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History of present illness and physical examination.
- Impact on activities of daily living (including the specific ADL) impaired, how it impacts performance, and what is done to alleviate it. Conservative therapy treatment plan (including units of compression stocking strength documented in mmHg and timeframe) with documented results and evidence of medical supervision.
    - Note: Impact on ADLs and conservative therapy plan are not required when there are documented recurrent attacks of superficial phlebitis, recurrent or persistent hemorrhage from ruptured varix, which does not include bleeding caused by scratching or shaving, and/or ulceration from venous stasis where incompetent varices are a significant contributing factor)
- Complete venous imaging studies including vein names with measurements of seconds of reflux and average vein diameters not including focal dilations (i.e. valve).
    - Not at or closely adjacent to the saphenofemoral junction refers to the **measurement in the mid to distal thigh** where the ablation most commonly is being done.
    - Not at or closely adjacent to the saphenofemoral junction refers to the **measurement in the mid-calf** where the ablation most commonly is being done.
- Documentation of ulceration from venous stasis where incompetent varices are a significant contributing factor which may include photographs.
- Procedures requested:
    - Specific procedures to be performed
    - Specific veins to be treated
    - Number of treatment session(s) being requested
    - If bilateral endovenous ablation is requested, document whether a bilateral or two unilateral sessions are being requested
    - Specify the veins to be treated in each session
    - For ablations, specify how all incompetent segments of the same vein are to be treated

ADDITIONAL INFORMATION

- Additional Venous Imaging Studies
    - For additional treatment sessions after previous varicose vein procedures, additional imaging is only required when the previous imaging did not identify the veins requested in the additional treatment session(s). Additional imaging is not required when an initial request was denied (for criteria not related to imaging)

and the member is seeking subsequent approval. Initial imaging will be considered adequate unless there is a relevant intervening venous procedure(s), in which case new imaging studies may be requested.

- Conservative Therapy
  - Compression stockings should be worn daily while the patient is out of bed. *Unna boot* or *compression wrap* may be utilized in lieu of compression stockings when there is documentation of an open venous stasis ulcer of the leg to be treated. For additional treatment requests after initial treatment, there must have been 3 months of conservative therapy after the most recent varicose vein procedure which has not successfully treated the patient's symptoms.
- Treatment Sessions
  - Each treatment session should address as much abnormality as is appropriate and reasonable and may include more than one vein and/or modality.
  - Endovenous laser or radiofrequency ablation of the entire incompetent saphenous vein usually can be accomplished in a single treatment session. Although additional procedures, including ligation or sclerotherapy, performed in the same treatment session on the same ablated saphenous vein are considered included components of the ablation procedure, procedures on other saphenous venous systems may be distinct procedural services.

CROSS REFERENCES

1. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
2. Ovarian Internal Iliac, and Gonadal Vein Embolization as a Treatment of Pelvic Congestion Syndrome, Surgery, Policy No.147

BACKGROUND

The venous system of the lower extremities consists of the superficial system (e.g., great and small saphenous veins and accessory or tributary veins that travel in parallel with the great and small saphenous veins) and the deep system (e.g., popliteal and femoral veins). These two parallel systems are interconnected via perforator veins and at the saphenofemoral and the saphenopopliteal junctions.

One-way valves are present within all veins to direct the return of blood up the lower limb. Larger varicose veins, many protruding above the surface of the skin, typically are related to valve incompetence. As the venous pressure in the deep system is generally greater than that of the superficial system, valve incompetence leads to increased hydrostatic pressure transmitted to the unsupported superficial vein system. Backflow (venous reflux) with pooling of blood ultimately results in varicosities. In addition, clusters of varicosities may appear related to incompetent perforating veins, such as Hunter and Dodd, located in the mid- and distal thigh, respectively and/or associated with incompetence at the saphenofemoral junction. In some instances, the valvular incompetence may be isolated to a perforator vein, such as the Boyd perforating vein located in the anteromedial calf. These varicosities are often not associated with saphenous vein incompetence since the perforating veins in the lower part of the leg do not communicate directly with the saphenous vein.

Although many varicose veins are asymptomatic, when present, symptoms include itching, burning, heaviness, fatigue, and pain. In addition, chronic venous insufficiency secondary to venous reflux can lead to peripheral edema, hemorrhage, thrombophlebitis, venous ulceration, and chronic skin changes. In an effort to improve the consistency in diagnosing chronic venous

disorders, particularly for patient selection in clinical trials, an international consensus committee developed CEAP classification.[1] In this system, classification is based on clinical manifestations (C), etiology (E), anatomical distribution (A), and underlying pathophysiology (P). (See Appendix 1)

Note: The term "varicose veins" does not apply to the telangiectatic dermal veins, which may be described as "spider veins" or "broken blood vessels." While abnormal in appearance, these veins typically are not associated with any symptoms, such as pain or heaviness, and their treatment is considered cosmetic.

TREATMENT OF SUPERFICIAL VARICOSE VEINS

Conservative Therapy

Treatment of venous reflux/venous insufficiency is aimed at reducing abnormal pressure transmission from the deep to the superficial veins. Varicose veins can usually be treated with non-surgical measures. Symptoms often decrease when the legs are elevated periodically, when prolonged standing is avoided, and when elastic compression stockings are worn.

Operative Therapy

If conservative treatment measures fail, additional treatment options typically focus first on identifying and correcting the site of reflux, and second on redirecting venous flow through veins with intact valves. Thus, conventional surgical treatment of varicosities is based on the following three principles:

- Control of the most proximal point of reflux, typically at the saphenofemoral junction, as identified by preoperative Doppler ultrasonography. Surgical ligation and division of the saphenofemoral or saphenopopliteal junction is performed to treat the valvular incompetence.
- Removal or occlusion by ablation of the refluxing great and/or small saphenous vein from the circulation. The classic strategy for isolation is vein stripping in conjunction with vein ligation and division.
- Removal or occlusion of the refluxing varicose tributaries. Strategies for removal include phlebectomy (i.e., ligation/division/stripping, powered phlebectomy, or stab avulsion) or occlusion by injection sclerotherapy; either at the time of the initial treatment, or subsequently. Over the years various minimally invasive alternatives to ligation and stripping have been investigated, including sclerotherapy and thermal ablation using radiofrequency energy (high frequency radiowaves), laser energy, or cryoablation (also called cryotherapy).

Endovenous Ablation

The objective of endovenous ablation techniques is to cause injury to the vessel, causing retraction and subsequent fibrotic occlusion of the vein.

<u>Thermal Ablation</u>

Three endovenous thermal ablation techniques have been investigated as minimally invasive alternatives to vein ligation and stripping.

- Radiofrequency (RF) ablation is performed by means of a specially designed catheter inserted through a small incision in the distal medial thigh to within 1-2 cm of the saphenofemoral junction. High frequency radio waves (200-300 kHz) are delivered through the catheter electrode and cause direct heating of the vessel wall, causing the vein to collapse. The catheter is slowly withdrawn, closing the vein.

- Laser ablation is performed similarly; a laser fiber is introduced into the saphenous vein under ultrasound guidance; the laser is activated and slowly removed along the course of the saphenous vein. Laser ablation may be referred to as endovenous laser ablation (EVLA) or endovenous laser treatment (EVLT).

- Cryoablation uses extreme cold to cause injury to the vessel. Technical developments since thermal ablation procedures were initially introduced include the use of perivenous tumescent anesthesia which allows treatment of veins larger than 12 mm in diameter and helps to protect adjacent tissue from thermal damage during treatment of the lesser saphenous vein.

- There are two technologies that are not available in the United States:

    - Microwave ablation is performed via endovenous catheter using microwave energy to heat the vessel walls.

    - Steam ablation is catheter-based endovenous thermal ablation that uses high pressure pulses of steam to heat the vein to 120°C.

Mechanochemical Ablation

Endovenous mechanochemical ablation (MOCA) utilizes both sclerotherapy and mechanical damage to the lumen. Following ultrasound imaging, a disposable catheter with a motor drive is inserted into the distal end of the target vein and advanced to the saphenofemoral junction. As the catheter is pulled back, a wire rotates at 3500 rpm within the lumen of the vein, abrading the lumen. At the same time, a liquid sclerosant (sodium tetradecyl sulphate) is infused near the rotating wire. It is proposed that mechanical ablation allows for better efficacy of the sclerosant, without the need for the tumescent anesthesia used in thermal ablation.

Cyanoacrylate Adhesive

Cyanoacrylate adhesive is a clear, free-flowing liquate that polymerizes in the vessel via an anionic mechanism (i.e. polymerizes into a solid material upon contact with body fluids or tissues). The adhesive is gradually injected along the length of the vein in conjunction with ultrasound and manual compression. The acute coaptation halts blood flow through the vein until the implanted adhesive becomes fibrotically encapsulated and establishes chronic occlusion of the treated vein. Cyanoacrylate glue has been used as a surgical adhesive and sealant for a variety of indications, including gastrointestinal bleeding, embolization of brain arteriovenous malformations, and to seal surgical incisions or other skin wounds.

Sclerotherapy

The objective of sclerotherapy is to destroy the endothelium of the target vessel by injecting an irritant solution (either a detergent, osmotic solution, or a chemical irritant), ultimately resulting in the complete obliteration of the vessel. The success of the treatment depends on accurate injection of the vessel, an adequate injectant volume and concentration of sclerosant, and

post-procedure compression. Compression theoretically results in direct apposition of the treated vein walls to provide more effective fibrosis and may decrease the extent of the thrombosis formation.

Sclerotherapy is an accepted and effective treatment of telangiectatic vessels. Historically, larger veins and very tortuous veins were not considered to be good candidates for sclerotherapy. Technical improvements in sclerotherapy, including the routine use of Duplex ultrasound to target refluxing vessels, luminal compression of the vein with anesthetics, and foam sclerosant in place of liquid sclerosant, have improved its effectiveness in these veins. Other concerns have arisen with these expanded uses of sclerotherapy. For example, use of sclerotherapy in the treatment of varicose tributaries without prior ligation, with or without vein stripping creates issues regarding its effectiveness in the absence of the control of the point of reflux and isolation of the refluxing saphenous vein. Sclerotherapy of the great saphenous vein raises issues regarding appropriate volume and concentration of the sclerosant and the ability to provide adequate post-procedure compression. Moreover, the use of sclerotherapy, as opposed to the physical removal of the vein with stripping, raises the issue of recurrence due to recanalization.

TREATMENT OF PERFORATOR VEINS

Perforator veins cross through the fascia and connect the deep and superficial venous systems. Incompetent perforating veins were originally addressed with an open surgical procedure, called the Linton procedure, which involved a long medial calf incision to expose all posterior, medial, and paramedial perforators. While this procedure was associated with healing of ulcers, it was largely abandoned due to a high incidence of wound complications. The Linton procedure was subsequently modified by using a series of perpendicular skin flaps instead of a longitudinal skin flap to provide access to incompetent perforator veins in the lower part of the leg. The modified Linton procedure may be occasionally utilized for the closure of incompetent perforator veins that cannot be reached by less invasive procedures. Subfascial endoscopic perforator surgery (SEPS) is a less-invasive surgical procedure for treatment of incompetent perforators and has been reported since the mid-1980s. Guided by Duplex ultrasound scanning, small incisions are made in the skin and the perforating veins are clipped or divided by endoscopic scissors. The operation can be performed as an outpatient procedure. Endovenous ablation of incompetent perforator veins with sclerotherapy and radiofrequency has also been reported.

OTHER

Deep vein valve repair or reconstruction and replacement are being investigated.

Venous “glue” or “superglue” is not cleared for use in the United States for this indication. This is an adhesive delivered via endovenous catheter as a method for sealing the vein.

REGULATORY STATUS

Devices that have received specific U.S. Food and Drug Administration (FDA) marketing clearance for the endovenous treatment of superficial vein reflux include:

- The VenClose® radiofrequency system received FDA approval in 2016 and is approved for endovascular coagulation for superficial vein reflux.

- The Alma 810 nm diode tabletop laser received FDA approval in 2016 and is indicated for endoluminal or endovenous laser surgery for incompetent saphenous veins.

- The VenaSeal™ (Medtronic) Closure System was FDA approved in 2015. The system includes a liquid adhesive, catheter, guidewire, dispenser gun and tips, and syringes. The clear liquid adhesive, cyanoacrylate adhesive, is injected into the diseased vein and polymerizes into a solid material to permanently seal the vein.

- The CERMAVEIN Steam Vein Sclerosis (SVS™) system is being studied outside of the United States but does **not** have FDA approval or clearance for marketing.

- The ClariVein® Infusion Catheter (Vascular Insights) received marketing clearance through the 510(k) process in 2008 (K071468). It is used for mechanochemical ablation. Predicate devices were listed as the Trellis® Infusion System (K013635) and the Slip-Cath® Infusion Catheter (K882796). The system includes an infusion catheter, motor drive, stopcock and syringe and is intended for the infusion of physician-specified agents in the peripheral vasculature.

- Polidocanol is an injectable sclerosing agent that may be used for intravenous treatment of varicose veins.

    - Varithena® (Biocompatibles, Inc, a BTG group company), formerly Varisolve®, is a polidocanol sclerosant microfoam made with a proprietary gas mix that is dispersed from a canister with a controlled density and more consistent bubble size. FDA approval in 2013 was for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee.

    - In 2010, Asclera® (Merz North America, Inc) is an injectable solution with FDA approval for the treatment of uncomplicated spider veins (varicose veins $\leq$ 1mm in diameter) and reticular veins (varicose veins 1-3 mm in diameter) in the lower extremities.

- A modified Erbe Erbokryo® cryosurgical unit (Erbe USA) received FDA clearance for marketing in 2005. A variety of clinical indications are listed, including cryostripping of varicose veins of the lower limbs.

- The Trivex system is a device for transilluminated powered phlebectomy that received FDA clearance through the 510(k) process in October 2003. According to the label, the intended use is for “ambulatory phlebectomy procedures for the resection and ablation of varicose veins.”

- In 2002, the Diomed 810 nm surgical laser and EVLT ™ (endovenous laser therapy) procedure kit received FDA clearance through the 510(k) process, "… for use in the endovascular coagulation of the greater saphenous vein of the thigh in patients with superficial vein reflux."

- In 1999, the VNUS® Closure™ system (a radiofrequency device) received FDA clearance through the 510(k) process for "endovascular coagulation of blood vessels in patients with superficial vein reflux." The VNUS RFS and RFS*Flex* devices received FDA clearance in 2005 for “use in vessel and tissue coagulation including: treatment of

incompetent (i.e., refluxing) perforator and tributary veins. The modified VNUS® ClosureFAST™ Intravascular Catheter received FDA clearance through the 510(k) process in 2008.

EVIDENCE SUMMARY

Outcomes of interest for venous interventions include symptom control, healing and recurrence, recanalization of the vein, and neovascularization. Recanalization is the restoration of the lumen of a vein after it has been occluded; this occurs more frequently following treatment with endovenous techniques. Neovascularization is the proliferation of new blood vessels in tissue, and occurs more frequently following vein stripping. Direct comparisons of durability for endovenous and surgical procedures are complicated by these different mechanisms of recurrence. Relevant safety outcomes include the incidence of paresthesia, thermal skin injury, thrombus formation, thrombophlebitis, wound infection, and transient neurologic effects.

VARICOSE VEIN TREATMENT

Systematic Reviews

Kheirelseid (2017) published a systematic review (SR) of nine randomized control trials (RCTs) that evaluated long-term outcomes (five years or more) of endovenous laser therapy, radiofrequency ablation, or ultrasound guided foam sclerotherapy for great saphenous vein-related varicose veins.[2] No difference in recurrence rate was seen for endovenous laser therapy or radiofrequency ablation versus conventional surgery. The authors concluded this study was too small to make a definitive determination on long-term effectiveness for varied varicose vein procedures.

Hamann (2017) published a SR of RCTs evaluating the long-term (≥ five years) impact on health outcomes for different types of treatment for the great saphenous vein, including ligation and stripping, endovenous thermal ablation and ultrasound guided foam sclerotherapy, for great saphenous vein incompetence.[3] Three RCTs and 10 follow-up reports on RCTs were included, of which one could not be included in the meta-analysis. At five years, endovenous thermal ablation and ligation stripping were more successful than ultrasound guided foam sclerotherapy. The reoccurrence of reflux was lower for ligation and stripping, than for endovenous thermal ablation and ultrasound guided foam sclerotherapy. Venous clinical severity scores were similar for ligation and stripping and endovenous thermal ablation. The authors stated the included studies had methodological limitations including unknown or high risk of bias and that more long-term RCTs are needed to compare success rates and clinical outcomes.

Vemulapalli (2017) published a SR that evaluated treatments for lower extremity varicose veins and/or venous insufficiency, reflux, or incompetence.[4] Included in the review were 53 RCTs (10, 034 patients), which were poor to good quality and four additional studies. Various therapy comparisons could not be made because of heterogeneity in therapies, populations and outcomes. Long-term symptom scores were no different between high ligation/stripping and endovascular laser ablation. There were no short-term bleeding differences between high ligation/stripping and radiofrequency ablation. The authors stated there is lack of high quality evidence on the safety and effectiveness of treatments for chronic lower extremity venous disease. Additional studies must compare effectiveness and provide practice parameters.

Boersma (2016) published results from a SR and meta-analysis that compared the anatomical success rates and complication rates of six treatment modalities for small saphenous vein incompetence: surgery (n=9), endovenous laser ablation (EVLA) (n=28), radiofrequency ablation (RFA) (n=9), ultrasound-guided foam sclerotherapy (UGFS) (n=6), and mechanochemical endovenous ablation (MOCA) (n=1).[5] Although the review included 49 articles (five RCTs and 44 cohort studies), nine were specific to RFA and were cohort studies. The pooled anatomical success rate for RFA in 386 incompetent small saphenous veins was 97.1% (95% CI 94.3% to 99.9%). RFA had a relatively low neurological complication rate (mean 9.7%) when compared to the overall neurological complication rate (mean 19.6%). The pooled anatomical success rate for UGFS in 494 incompetent small saphenous veins was 63.6% (95% CI 47.1% to 80.1%); however, more research is needed to determine these effects. The 28 articles specific to EVLA included both RCT's and cohort studies. The pooled anatomical success rate for EVLA in 2,950 incompetent small saphenous veins was 98.5% (95% CI 97.7% to 99.2%). EVLA had a low neurological complication rate (mean 4.8%) when compared to the overall neurological complication rate (mean 19.6%). There was one study on mechanochemical ablation (MOCA) and although the authors reported an anatomical success rate of 94%, more research is needed to determine these effects. The authors concluded that EVLA/RFA should be a preferred treatment over surgery and foam sclerotherapy in small saphenous vein incompetence. An updated Cochrane review from 2014 compared RFA, EVLA, and foam sclerotherapy versus ligation/stripping for saphenous vein varices.[6] Included in the review were 13 randomized studies with a combined total of 3081 patients. The overall quality of the evidence was moderate. For EVLA versus surgery, there were no significant differences between the treatment groups for clinician noted or symptomatic recurrence, or for recanalization. Neovascularization and technical failure were reduced in the laser group (OR=0.05, p<0.001; and OR=0.29, p<0.001, respectively). For RFA versus surgery, there were no significant differences between the groups in clinician noted recurrence, recanalization, neovascularization, or technical failure. The authors concluded that sclerotherapy, EVLA, and RFA were at least as effective as surgery in the treatment of long saphenous vein varicose veins.

In 2012, a SR of RCTs and meta-analysis was published that compared the clinical outcomes of EVLA, RFA, UGFS, and surgery.[7] The review included 28 RCTs and reported no significant difference in primary failure and clinical recurrence with EVLA and RFA compared with surgery. The advantages of the endovenous ablation techniques over surgery were a lower rate of wound infections and hematoma, and a shorter recovery period.

RANDOMIZED CONTROL TRIALS

Lawaetz (2017) published a five-year follow-up on an RCT in which 500 patients (580 legs) received either endovenous radiofrequency ablation, endovenous laser ablation, ultrasound guided foam sclerotherapy or high ligation and stripping for great saphenous vein reflux.[8] Recanalization occurred more often after ultrasound guided foam sclerotherapy, but there was no difference in technical efficacy between the procedures. There was a higher unknown reason for reoccurrence after endovenous laser ablation and high ligation and stripping.

van der Velden (2015) published results from a five-year follow-up comparing conventional surgery, endovenous laser ablation, and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins.[9] A total of 224 legs were included (69 conventional surgery, 78 EVLA, and 77 UGFS), and 193 were evaluated at final follow up (86.2%). At the five-year follow-up, the Kaplan-Meier analysis showed obliteration or absence of the great saphenous

vein in 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA (not significantly different). Grade I neovascularization was higher in the conventional surgery group (27% vs 3%, p<0.001), while grade II neovascularization was similar in the two groups (17% vs 13%).

Brittenden (2014) reported a multicenter randomized trial that compared foam sclerotherapy, EVLA, and surgical treatment in 798 patients.[10] The study was funded by U.K.'s Health Technology Assessment Programme of the National Institute for Health Research.[11] Veins greater than 15 mm were excluded from the study. At the six-week follow-up visit, patients who were assigned to treatment with foam or laser had the option of treatment with foam for any residual varicosities; this was performed in 38% of patients in the foam group and 31% of patients in the EVLA group. Six months after treatment, mean disease-specific quality of life was slightly worse after sclerotherapy than after surgery (p=0.006), and there were more residual varicose veins, although the differences were small. Disease-specific quality of life was similar for the laser and surgery groups. The frequency of procedural complications was similar for the foam sclerotherapy (6%) and surgery (7%) groups, but was lower in the laser group (1%). The rate of complications at 6 months (primarily lumpiness and skin staining), was highest for the sclerotherapy group.

Five-year follow-up data from the Brittenden trial was published in 2019 on disease-specific and generic quality of life.[12] Disease-specific quality of life after five years was significantly better for those who received laser ablation or surgery compared to foam sclerotherapy.

Biemans (2013) published results from the MAGNA trial, which randomized 223 consecutive patients (240 legs) with long saphenous vein reflux to EVLA, ligation and stripping, or physician compounded foam sclerotherapy (1 ml aethoxysclerol 3#: 3ml air).[13] At one-year follow-up, the anatomic success rates were similar between EVLA and stripping (88.5% and 88.2%, respectively), which were superior to foam sclerotherapy (72.2%). Ten percent of the stripping group showed neovascularization. Health-related quality of life improved in all groups. The CEAP classification improved in all groups with no significant difference between the groups. Transient adverse events were reported in 11 patients after stripping, seven after EVLA, and five after sclerotherapy.

ENDOVENOUS ABLATION

Endovenous ablation of varicose veins has been proposed as an alternative to ligation and/or stripping. Outcomes of interest include short- and long-term functional improvement and recurrence rates related either to recanalization of the saphenous vein or neovascularization. In terms of safety, relevant outcomes include the incidence of paresthesias, thermal skin or nerve injuries, thrombus formation, thrombophlebitis, and wound infection.

Vein Diameter

There is currently no standardized range for saphenous vein diameter most likely to be associated with severe symptoms or for which endovenous ablation is recommended. In studies of the correlation between great saphenous vein diameter and the presence or absence of reflux, the best cutoff measurement to predict reflux varied between studies from 5.05 mm to 7.3 mm.[14-17] Sensitivity and specificity ranged from 76% to 87% and 60% to 87%, respectively. It is important to note that there is heterogeneity among the populations included in the studies. In addition, there was heterogeneity between studies in measurement techniques (e.g., location, position).

Endovenous Laser and Radiofrequency Ablation

Systematic Reviews

He (2017) conducted a SR which evaluated the effectiveness and safety of endovenous laser ablation compared to radiofrequency ablation for the treatment of varicose veins.[18] The SR included a total of 12 studies (N=1,577) (10 RCTs and 2 nonrandomized studies).The meta-analysis of the combined studies concluded that there were no significant differences in effectiveness and safety outcomes between the two groups.

Woźniak (2016) also evaluated laser ablation compared to radiofrequency ablation.[19] The study included 510 adults with five year follow-up and reported similar conclusions to He (2017) summarized above. A SR of EVLA versus surgery was published in 2009.[20] Fifty-nine studies were included, with seven studies that directly compared EVLA and surgery. Randomized and nonrandomized studies directly comparing outcomes for EVLA or surgery were included for the assessment of safety or effectiveness, while case series with a minimum patient population of 100 were included for the assessment of safety alone. For all studies, it was calculated that 5,759 patients (6,702 limbs) were treated with EVLA and 6,395 patients (7,727 limbs) underwent surgery. Few differences were apparent between treatments with respect to clinical effectiveness outcomes, although long-term follow-up was lacking. Nonclinical effectiveness outcomes generally favored EVLA over surgery in the first two months after treatment. The authors concluded that while EVLA offers short-term benefits and appears to be as clinically effective as surgery up to 12 months after treatment, clinical trials with a minimum of three years of follow-up are required to establish the enduring effectiveness of EVLA.

A number of SRs of RCTs comparing various types of ablation to surgical treatment have been published. These reviews consistently reported moderate quality of evidence. Most of the reviews compared EVLA, RFA, and surgical treatment of varicose veins. Overall, these techniques had similar, statistically significant improvement in function and in pain relief compared to preoperative scores. RFA and EVLA had low rates of technical procedure failure rates, and short-term recannulization rates. Adverse effects were generally minor for all techniques. Though intraoperative pain was not reported, EVLA consistently resulted in significantly greater pain and bruising when compared to RFA for one to two weeks following the procedure. RFA had significantly more occurrences of superficial phlebitis. Recanalization was similar for EVLA and RFA at one-year follow-up.

The primary limitation of the current evidence is the lack of long-term data on recanalization rates for ablation techniques and neovascularization rates for ligation and stripping. In addition, many of the available studies used first-generation technology and, therefore, do not provide data on newer devices. For example, newer laser technology may result in decreased pain during and after the procedure. Newer RFA technology (e.g., ClosureFast RF catheter) may result in higher rates of vein occlusion.

Randomized Controlled Trials

The ongoing, and largest randomized study on EVLA, comparing endovenous laser ablation with costectomy and stripping of the great saphenous vein (RELACS), schedule to follow patients for five years, randomized 400 patients to EVLA performed by a surgeon at one site or to ligation and stripping performed by a different surgeon at a second location.[21] Fifty-four patients withdrew from the study after receiving the randomization result (from an independent

site), due primarily to preference for the other treatment. At the two-year follow-up there was no significant difference between the groups for clinically recurrent varicose veins, medical condition on the Homburg Varicose Vein Severity Score, or disease-related quality of life. Saphenofemoral reflux was detected by ultrasonography more frequently after EVLA (17.8% vs 1.3%). At 5-year follow-up, Kaplan-Meier analysis showed obliteration or absence of the great saphenous vein in 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA (not significantly different).15 Grade I neovascularization was higher in the conventional surgery group (27% vs 3%, p<0.001), while grade II neovascularization was similar in the 2 groups (17% vs 13%).

Rasmussen (2012) reported the five-year follow-up data comparing EVLA (n=121) with ligation and stripping (n=68).[22] Data was available on 98% of the patients. There was no significant difference between the two groups for clinical recurrence (EVLA 36%, stripping 35%) or in the percentage of reoperations (EVLA 38.6%, stripping 37.7%).

Literature on isolated treatment of the anterior accessory saphenous vein is limited. In a 2009 study, outcomes from a cohort of 33 patients who underwent EVLA of the anterior accessory saphenous vein were compared with 33 matched controls undergoing EVLA of the greater saphenous vein.[23] In 21 of the patients (64%) in the accessory saphenous vein group there had been no previous treatment of the greater saphenous vein. At 12-month follow-up there was no evidence of reflux in these patients, and the treated accessory saphenous vein was not visible with ultrasound. The Aberdeen Varicose Vein Symptom Severity Score had improved in both groups, with no significant difference between the two groups. Patient satisfaction scores were also similar.

Nonrandomized Trials

Several case series have reported on endoluminal radiofrequency ablation.[24-27] The largest was reported by Merchant and colleagues, who analyzed the four-year data collected in the ongoing Closure Study Group registry focusing on the treatment of reflux of the long saphenous vein.[24] Data were available on 890 patients and 1,078 limbs treated at 32 centers. Clinical and duplex ultrasound follow-up was performed at one-week, six-months, and yearly for four-years. The vein occlusion rates were 91% at one week and 88.8% at four-years, although only 98 limbs had been followed up to the four-year mark. These results suggest that radiofrequency ablation results in durable occlusion. Radiofrequency ablation has typically been limited to vessels less than 12 mm in diameter. The rationale behind this patient selection criterion is that the electrodes must remain in direct contact with the vein wall during treatment and the largest diameter of the deployed radiofrequency electrodes is 12 mm. The authors noted that exsanguinations, perivenous tumescent infiltration, and external compression may promote electrode and vessel wall contact such that larger veins can be treated. However, in this large case series, there were only 58 limbs with vein sizes larger than 12 mm, and only 29 available for follow-up at six-months or one-year. While the occlusion rate was similar to that seen in smaller vessels, long-term data are inadequate to determine if this effect is durable.

Merchant and Pichot (2005) also reported the 5-year Closure Study Group registry data.[28] There were 1222 limbs in 1006 patients treated at 34 centers with radiofrequency ablation of various levels of the long saphenous vein, the short saphenous vein, and the accessory saphenous vein. At five-year follow-up using duplex ultrasound examination, 185 limbs were considered failures due to nonocclusion (12.4%), recanalization of a previously occluded vein (69.7%), or groin reflux of a vein with occluded trunk (17.8%). In the latter group, the groin

reflux often involved an accessory vein. Logistic regression analysis of risk factors of gender, age, body mass index [BMI], vein diameter, and catheter pullback speed showed that each unit increase in BMI over 25 was associated with increasing risk of long-term failure. In addition, a catheter pull-back speed over the standard speed of 3 cm/min was associated with failure to occlude or recanalization. The authors pointed out that this anatomical failure did not necessarily result in clinical failure; most patients experienced initial symptom relief that was maintained over 5 years.

Many other clinical trials on laser ablation of varicose veins are case series[29-33] and registry data[28]. Using historical controls for comparison is difficult since treatment outcomes are variably reported. There are no consistent definitions of success versus failure, either based on patient or clinical assessment. In general, recurrence rates after ligation and stripping are estimated at around 20%. Doppler or Duplex ultrasound are perhaps the most objective form of assessment of recurrence, but many of the reports of the long-term outcomes of ligation and stripping did not use ultrasound studies for postoperative assessment. Only two studies have reported objective results of ligation and stripping at 12 and 24 months. Jones and colleagues reported on the results of a study that randomized 100 patients with varicose veins to undergo either ligation alone or ligation in conjunction with stripping.[34] The results of the ligation and stripping group are relevant to this discussion. At one year, reflux was detected in 9% of patients, rising to 26% at two years. Rutgers and Kitslaar reported on the results of a trial that randomized 181 limbs to undergo either ligation and stripping or ligation combined with sclerotherapy.[35] At two years, Doppler ultrasound demonstrated reflux in approximately 10% of patients, increasing to 15% at three years. Therefore, based on this crude assessment, the reflux rate of 13% for radiofrequency ablation at one year[36] and 6% for laser ablation at two years[29] is roughly comparable to the reflux rate of 9-10% reported by Jones et al and Rutgers and Kitslaar.

Cryoablation

Disselhoff (2008, 2011) reported two and five-year outcomes from a randomized trial that compared cryostripping with EVLA.[37, 38] One hundred and twenty patients were included with symptomatic uncomplicated varicose veins (CEAP C2) with saphenofemoral incompetence and greater saphenous vein reflux. At 10 days after treatment, EVLA had better results than cryostripping with respect to pain score over the first 10 days (2.9 vs. 4.4), resumption of normal activity (75% vs. 45%) and induration (15% vs. 52%). At the two-year follow-up, freedom from recurrent incompetence was observed in 77% of patients after EVLA and 66% of patients after cryostripping (not significantly different). At five years, 36.7% of patients were lost to follow-up; freedom from incompetence and neovascularization was found in 62% of patients treated with EVLA and 51% of patients treated with cryostripping (not significantly different). Neovascularization was more common after cryostripping, but incompetent tributaries were more common after EVLA. There was no significant difference between groups in the Venous Clinical Severity Score or Aberdeen Varicose Vein Severity Score at either two or five years.

Klem (2009) published results from a randomized trial that found endovenous cryoablation (n=249) to be inferior to conventional stripping (n=245) for treating patients with symptomatic varicose veins.[39] The percentage of patients with greater saphenous vein remaining was 44% in the endovenous cryoablation group and 15% in the conventional stripping group. The Aberdeen Varicose Vein Questionnaire also showed better results for conventional stripping (score of 11.7) in comparison with cryoablation (score of 8.0). There were no differences

between the groups in SF-36 subscores, and neural damage was the same (12%) in both groups.

Cyanoacrylate Ablation

Amshar (2022) published a systematic review comparing cyanoacrylate embolization (CAE) and laser ablation (EVLA) in the treatment of saphenous vein insufficiency which included 1432 ablation procedures.[40] Venous closure rates and VCSS did not differ significantly between CAE group and EVLA group. Pooled data showed that CAE group was associated with less periprocedural pain score (P < 0.001), lower skin pigmentation rates (0.60% vs. 4.46%; P = 0.008), and lower nerve damage rates (0% vs. 3.94%; P = 0.007). Rates of phlebitis, deep vein thrombosis, and ecchymosis did not differ significantly between the groups. In addition, intervention time was significantly faster in CAE group compared to EVLA group. The authors concluded that CAE has similar efficacy compared to EVLA.

Garcia-Carpintero (2020) published a systematic review of endovenous cyanoacrylate adhesive treatment compared to radiofrequency ablation or endovenous laser ablation in 1057 participants.[41] The authors concluded that all three treatment types reduced disease severity and there was no significant difference across the three treatment options. There were fewer adverse events with participants who received cyanoacrylate adhesive treatment compared to the other ablation techniques.

Morrison (2017) published a report on the 12-month outcomes of the VeClose trial that compared endovenous cyanoacrylate closure to radiofrequency ablation for great saphenous vein incompetence.[42] Ninety-five patients who underwent endovenous cyanoacrylate closure and ninety-seven patients who underwent radiofrequency ablation presented at the one-year follow-up evaluation. The authors concluded that although endovenous cyanoacrylate closure showed faster closer rates and fewer reopening episodes, quality of life was the same for both procedures. The study was not blinded, but may not have been possible because of the differences in the way the procedures are performed.

Morrison (2018) published thirty-six month follow-up data to the VeClose trial with follow-up on 146 (66%) patients (72 from CAC and 74 from RFA)[43]. Loss to follow-up was similar in the two groups. The complete closure rates for CAC and RFA were 94.4% and 91.9% (p=0.005 for non-inferiority), respectively. Recanalization-free survival through 36 months was not statistically different for the two groups. No significant device- or procedure-related adverse events were reported for either group.

Morrison (2020) reported five year outcomes from the VeClose trial. 89 patients of the 220 patients enrolled in the original study completed the 60-month follow-up.[44] At five years, Kaplan-Meier estimates for freedom from recanalization in the randomized CAC and RFA groups were 91.4% and 85.2%. Noninferiority of CAC compared with RFA was demonstrated. Sustained improvements in EQ-5D and quality of life measures through 60 months were demonstrated in both groups. Whereas patients assigned to C0 or C1 clinical class were excluded from the original study, more than half of all returning patients (64% [57/89]) were now assigned to C0 or C1, suggesting an improved clinical class from baseline. 41.1% of returning CAC patients and 39.4% of returning RFA patients were shown to be at least two CEAP classes lower than their baseline class. No adverse events were reported in either group between 36- and 60-month follow-up.

Yasmin (2017) published a retrospective review on results of VariClose (n-butyl cyanoacrylate) treatment for varicose veins.[45] One hundred and eighty patients with great saphenous vein diameter > 5.5mm and small saphenous vein diameter > 4mm and reflux > 5 s were treated and followed up at between three and seven months. No recanalization was observed and the venous clinical severity scores dropped to an average of 3.9 three months after the procedure versus 10.2 before. No long-term results were reported.

Bozkurt (2016) conducted a one year prospective comparative study (n=310) evaluating cyanoacrylate glue compared to endovenous laser ablation for venous insufficiency.[46] The authors concluded that periprocedural pain, ecchymosis, permanent paresthesia were less in the cyanoacrylate ablation group. There were no significant differences in closure rates at 12 months follow-up. In addition, there were no significant differences in severity scores nor the Aberdeen Varicose Vein Questionnaire. Additional studies are needed to evaluate the effectiveness and safety of this technique.

Mechanochemical Ablation

Systematic Review

Witte (2017) published a SR of 13 studies evaluating the anatomic, technical, and clinical success of mechanochemical endovenous ablation (MOCA) using ClariVein® for the great and small saphenous veins.[47] Studies were of “moderate to good quality”. Two-three year pooled anatomic outcomes for the great saphenous vein and small saphenous vein reported were 91% and 87% respectively. The authors stated MOCA using the ClariVein® and liquid sclerosant is associated with an anatomic success rate of 87%-92% and the risk of complications is low, but no RCTs were available to compare MOCA to endothermal ablation.

Vos (2017) published a SR of 15 prospective studies evaluating the anatomic and technical success of MOCA and cyanoacrylate vein ablation (CAVA) for great saphenous vein incompetence.[48] MOCA and CAVA pooled anatomic success were 94.8% and 94.1% at six months and 94.1% and 89% at one year. The authors stated additional RCTs of high quality comparing MOCA and CAVA to conventional procedures are needed. These will assist in establishing clinical outcomes and practice parameters.

Randomized Controlled Trials

Belramman (2022) published a comparison of pain outcomes between mechanochemical ablation and cyanoacrylate adhesive in the treatment of varicose veins.[49] A total of 167 patients were randomized to treatment groups and the primary outcome measure was pain score immediately after ablation. There were no differences between groups in improvement in clinical severity, generic and disease-specific QoL scores, and complete occlusion rates as both groups demonstrated significant, but comparable improvement.

Mohamed (2020) published results of a trial comparing endovenous laser ablation and mechanochemical ablation using ClariVein in the management of superficial venous insufficiency.[50] Patients (n=150) were randomized to MOCA with 1.5% sodium tetradecyl sulfate or to EVLA. Occlusion rates were lower in the MOCA group 77% compared to the EVLA group (91%) with no significant difference between the two treatments in intraprocedural pain scores. Clinical severity and quality of life scores were not significantly different between the groups at one year follow-up. Additional follow-up is continuing to evaluate durability of the treatments.

Holewijn (2019) published a non-inferioty trial examining three percent policocanol in the Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation (MARADONA).[51] The trial included 213 patients who were randomized before reimbursement for the procedure was suspended. Pain scores in the 14 days after the procedure were slightly lower, but hyperpigmentation was higher. Anatomic failures were significantly greater in the MOCA group at 1 year and approached significance at 2-years. The study was underpowered for anatomic failures because of the early stoppage of the study. At 1 and 2-years follow-up, clinical and quality of life outcomes were similar in the two groups.

Lane (2017) published a multi-center RCT evaluating pain levels for 170 patients undergoing either mechanical occlusion chemically assisted ablation or radiofrequency ablation.[52] Pain, duplex ultrasound results, clinical outcomes and quality of life were evaluated at one and six months after treatment. Pain after mechanical occlusion chemically assisted ablation was lower than with radiofrequency ablation, but other outcomes including quality of life and safety did not differ.

Bootun (2014) published early one month results from an ongoing study comparing 119 patients randomized to mechanochemical ablation (MCA) (n=60) or RFA (n=59).[53] The maximum and average pain scores were significantly lower during MCA compared to RFA ($p<0.001$). At one-month follow-up, both groups showed complete or proximal occlusion rates of 92%, though data were available for only 67% of participants. These preliminary outcomes do not permit conclusions due to methodological limitations including the short-term follow-up and incomplete data. The authors noted that data from longer follow-up is being collected.

Nonrandomized Studies

Thierens (2019) published a prospective cohort study with five year follow up data. Anatomic and clinical follow-ups were performed at 4 weeks, 6 months, and 1, 3, and 5 years after the procedure. Less than half of the study population remained at 5 years, however 79% had freedom from anatomic failure and clinical measures had worsened. Nearly 15% of the recanalizations occurred in the first year, which the authors considered to be due to technical issues when the procedure was initially introduced. It should be noted, however, that the more recent MARADONA trial from the same group of investigators using 3% polidocanol (described above) also saw a rate of recanalization of 16.5% in the first year and 20% in the second year. Without a control condition, it cannot be determined whether the loss of clinical improvement in this cohort study is due to recanalization or the usual progression of venous disease over time.

Tang (2017) published single-center study outcomes for 300 patients who received ClariVein® treatment for varicose veins.[54] Veins treated included great saphenous vein (n=184), bilateral great saphenous veins (n=62), short saphenous vein (n=23), and bilateral short saphenous veins (n=6). Evaluations occurred two months after the procedures. At two months, 13 out of 393 veins or 3.3% had to be retreated with ultrasound-guided foam sclerotherapy. The authors stated there were no adverse findings and results are promising, but these results are from a one surgeon’s experience and RCTs with long-term follow-up are needed.

The remainder of the evidence on MCA of varicose veins is limited to nonrandomized series and cohort studies.[55-60] In the only comparative study, van Eekeren and colleagues compared postoperative pain and early quality of life in 68 patients treated with either RFA or MCA of great saphenous veins.[58] Patients who did not want to be treated with MCA were offered treatment with RFA; this study design could potentially lead to selection bias. There was no significant between-group difference in procedure-related pain. Compared with RFA, patients

treated with MCA had a 14.3 mm reduction in pain measured on a 100 mm visual analog scale (VAS) measured over the first 3 postoperative days (6.2 vs. 20.5) and a 13.8 mm reduction in pain (4.8 vs. 18.6 mm; p<.001) over the first two weeks. MCA patients treated also had a significantly earlier return to normal activities (1.2 vs. 2.4 days) and return to work (3.3 vs. 5.6 days; p=.02). There was a similar improvement in quality of life for the two groups when measured at six weeks. Longer studies are required to determine the durability of these effects.

Microwave Ablation

This technique has not been approved or cleared for marketing by the FDA. Two clinical trial reports were found. The first, a preliminary randomized trial, compared endovenous microwave ablation (EMA) with high ligation and stripping (HLS).[61] At 24-months follow-up, there was no significant difference in outcomes between the two groups. The second, a retrospective comparison between laser (n=163 limbs in 138 patients) and microwave (n=143 limbs in 121 patients) ablation of the greater saphenous vein, found significantly lower ecchymosis, skin burn, and paresthesia in the laser ablation.[62] However, the recanalization rate was significantly higher in the laser ablation group at one week and six months postoperatively (p<0.01). Loss to follow-up at 24-months was about 19% in each group.

Steam Ablation

This technique has not been approved or cleared for marketing by the FDA. There is currently no published clinical trial evidence on this technique.

SCLEROTHERAPY

In general, reported outcomes of uncontrolled studies have varied for sclerotherapy, as have the periods of follow-up. In many studies the outcomes are reported in terms of cure rates, but the criteria for cure or failure are poorly defined. Studies have also reported subjective patient-assessed outcomes or physician assessment, both of which may be poorly defined. More recent studies included results of Doppler or duplex ultrasonography; however, the relationship between finding ultrasonographic evidence of recurrent reflux and clinical symptoms is uncertain. Finally, it should be noted that sclerotherapy of the long saphenous vein is a fundamentally different approach than stripping. With stripping, recurrences are likely related to an incomplete surgical procedure or to revascularization. With sclerotherapy, recurrences may be additionally related to recanalization of an incompletely fibrosed saphenous vein.

Systematic Reviews A SR from 2008 found that foam sclerotherapy of varicose veins is associated with a higher recurrence rate in patients with saphenofemoral incompetence compared to the rates of endovenous laser therapy or radiofrequency obliteration, while a 2009 SR suggested that outcomes from sclerotherapy are worse than those of surgery (ligation and stripping) for saphenous vein reflux.[63, 64]

Randomized Controlled Trials

Yin (2017) reported on a randomized control study for patients who received ultrasound guided foam sclerotherapy combined with great saphenous vein high ligation (n= 73) or stripping and multistab avulsion or transilluminated powered phlebectomy of the great saphenous vein (n=90).[65] Only 73 patients who received ultrasound guided foam sclerotherapy and 74 patients in the control group completed follow-up at one, six, and 12 months following treatment. At 12 months reflux recurrence rate was 13.8% after ultrasound guided foam

sclerotherapy and 13.5% for the control treatment. Minor and major complications, venous filling index, VCSS, and AVVQ scores were similar. Patient satisfaction, operating times, and hospital costs were more favorable for ultrasound guided foam sclerotherapy.

Gibson (2017) reported on a multi-center randomized placebo-controlled trial evaluating the safety and efficacy of Varithena®.[66] Patients with symptomatic varicose veins received Varithena® (n=39) or a placebo (n=38). Assessments took place at baseline and at weeks one, four, eight and 12 after treatment. The authors stated Varithena® improves vein appearance and symptoms in patients with varicose veins. The study had methodological limitations including small sample size and potential author conflicts of interest. In addition, outcomes for appearance and symptoms may be viewed as subjective; thus, additional larger RCTs, with long-term follow-up are needed to validate health outcomes for Varithena®.

Several controlled trials comparing sclerotherapy of varicose tributaries or the saphenous vein, with and without associated ligation and stripping, have reported that the absence of ligation and stripping was associated with an increased frequency of recurrence. These trials are difficult to interpret due to the lack of clarity about which vein– either the varicose tributaries or the saphenous vein itself – have undergone sclerotherapy. Nonetheless, these trials established the importance of control of the site of reflux (ligation) and isolation of the refluxing portion of the saphenous vein (stripping). The following are examples of these studies:

Results from the five year follow up published by van der Velden (2015) examined ultrasound-guided foam sclerotherapy in 77 legs.[9] The authors found obliteration or absence of the greater saphenous vein was observed in only 23% of patients treated with sclerotherapy compared to 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA. Thirty-two percent of legs treated initially with sclerotherapy required one or more reinterventions during follow-up compared with 10% in the conventional surgery and EVLA groups. However, clinically relevant grade II neovascularization was higher in the conventional surgery and EVLA groups (17% and 13%, respectively), compared with the sclerotherapy group (4%). EuroQol-5D scores improved equally in all groups.

King (2015) published results from the VANISH-1 study, a manufacturer-funded multicenter placebo RCT undertaken to evaluate the efficacy of relief of symptoms and safety of Varithena (0.5%, 1%, and 2%) compared with 0.125% (control) and placebo.[67] Seven-hundred and eighty patients were screened; 279 patients met the study criteria and were treated with either placebo (n=56), or Varithena 0.125% (n=57), 0.5% (n=51), 1% (n=52), or 2% (n=63). Patients rated the duration and intensity of nine symptoms and activity levels during the previous 24 hours using the VVSymQscore instrument. At week eight VVSymQscores for pool Varithena (0.5% +1%+2%) patients were significantly superior to placebo (p=<.001), and VVSymQscores decreased significantly (p<.001) from baseline at eight weeks for all Varithena individual doses. There were no serious AE's and no PE's; however, patients receiving higher Varithena dose concentrations (1% and 2%) had higher rates of treatment-emergent AE's, which occurred in ≥ 3% of patients. The most common kinds of treatment-emergent AE's included pain, superficial thrombophlebitis, and hematoma at the injection site.

Vasquez and Gasparis (2015) published results from a manufacturer sponsored multicenter randomized placebo-controlled study. The purpose of the study was to determine the efficacy and safety of Varithena (0.5%, 1.0%) and placebo, each administered with endovenous thermal ablation.[68] A total of 234 patients were screened; 117 patients met the study criteria and received treatment (38 placebo, 39 Varithena 0.5%, and 40 Varithena 1%). Patients were

assessed using the Quality of Life/Symptoms (mVEINES-QOL/Sym) questionnaire, Patients Self-Assessment of Visible Varicose Veins (PA-V) and the Independent Photography Review-Visible Varicose Veins (IPR-V) instruments. Efficacy showed baseline scores were greater at week eight for pooled Variethena than for placebo for both IPR-V (−1.2 vs. −0.8 points, $p = 0.001$) and PA-V (−1.8 vs. −1.6 points, $p = 0.16$), however, only IPR-V change score reached statistical significance. The comparison of the individual dose concentrations of Variethena (0.5%, 1.0%) with placebo showed a similar pattern for both IPR-V and PA-V scores. Although no patients presented spontaneously with symptoms of thrombus, six patients were found to have venous thrombi, and all occurred during the first eight weeks post treatment. Through six months of follow-up, there were no reports of visual disturbance or migraine among Varithena recipients, no pulmonary emboli, and no AE-related study withdrawals. There was one serious AE, breast cancer, considered unrelated to the study drug.

Microfoam sclerotherapy was studied in the 2014 VANISH-2 study, an ongoing five year manufacturer-funded pivotal double-blind RCT undertaken to obtain FDA marketing approval for Varithena microfoam (BTG).[69] The study compared 0.5% or 1.0% polidocanol microfoam with subtherapeutic foam dose (0.125%) and endovenous placebo in 232 patients. The authors reported early eight week follow-up data[70] finding elimination of reflux and/or occlusion of the previously incompetent vein in 85.6% of the combined 0.5% and 1.0% groups, 59.6% in the 0.125% “subtherapeutic” group, and 1.8% of the placebo group. The improvement in the venous clinical severity score was significantly greater in the 0.5% and 1.0% groups (-5.10) compared with placebo (-1.52), but was not reported for the 0.125% group. The 1.0% dose of Varithena was selected for the 2013 FDA approval. Adverse events occurred in 60% of patients receiving foam sclerotherapy compared to 39% of placebo; 95% were mild or moderate and transient. The most common adverse events were retained coagulum, leg pain, and superficial thrombophlebitis. Deep vein thrombosis was detected by ultrasound in 2.8% of Varithena-treated patients with 1% having proximal symptomatic thrombi treated with anticoagulants. No pulmonary emboli were detected and no clinically significant cardiac or cardiopulmonary, neurologic, or visual adverse events were reported. In the short-term the rates of occlusion with this microfoam sclerotherapy were similar to those reported for EVLA or stripping. RCTs comparing EVLA or stripping with microfoam sclerotherapy with long-term outcomes are needed to evaluate comparative effectiveness. In 2015, Todd and Wright published an update to the VANISH-2 study and reported on findings at one year.[71] Results at year one showed symptoms improved when compared to week 8 (64% with total VVSymQ scores of 3 or less at week eight vs 85% at year one). Reductions from baseline in the individual symptom scores that compose the VVSymQ score were also demonstrated, with all five HASTI symptoms showing a continued decrease from over time. In addition, improvements from baseline in appearance as assessed by both the patients themselves (PA-V score) and blinded experts reading standardized photographs (IPR-V score) were maintained, with a small trend toward further improvement between week eight and one year. Ten patients of the 232 in the total population had 12 AEs reported during the long-term follow-up period through year one, including one death; however, all were unrelated to treatment. Of the patients who had venous thrombus AEs during the main eight week trial, none had recurrent venous thrombus AEs, and all clots stabilized or resolved completely. No post-thrombotic syndrome or other clinically important sequelae were reported. No patient developed a new venous thrombus AE in the one year follow-up, and no pulmonary emboli were diagnosed at any time through the one year in this study.

A 2012 study was a noninferiority trial of foam sclerotherapy versus ligation and stripping in 430 patients.[72] Analysis was per protocol. Forty patients (17%) had repeat sclerotherapy. At two years, the probability of clinical recurrence was similar in the two groups (11.3% sclerotherapy vs 9.0% ligation and stripping), although reflux was significantly more frequent in the sclerotherapy group (35% vs 21%). Thrombophlebitis occurred in 7.4% of patients after sclerotherapy. There were two serious adverse events in the sclerotherapy group (deep venous thrombosis and pulmonary emboli) that occurred within one week of treatment.

Blaise (2010) reported three-year follow-up from a multicenter double-blind randomized trial (143 patients) that compared treatment of the greater saphenous vein with either 1% or 3% polidocanol foam.[73] Additional treatment with foam sclerotherapy was carried out at six weeks, three and six months if required to abolish persistent venous reflux. There were 49 additional injections in the 1% polidocanol group and 29 additional injections in the 3% group. At the three-year follow-up, venous reflux was observed in 21% of patients in the 1% group and 22% of patients in the 3% polidocanol group.

Neglen (1993) reported on a “partially randomized” trial that compared the outcomes of three different treatment strategies: 1) sclerotherapy alone; 2) ligation and stripping, or 3) ligation combined with sclerotherapy.[74] It was difficult to determine the target of the sclerotherapy. As described in the article, sclerosant was injected into all points of control (presumably at the junction of the perforator veins) and, "if possible, into the main stem of the long saphenous vein." Thus, it seems that the intent of the sclerotherapy was not the obliteration of the long saphenous vein as an alternative to stripping, but as a treatment of the varicose tributaries. Therefore, among those patients who underwent ligation plus sclerotherapy, this trial tested whether or not stripping could be eliminated from the overall approach. In the group who received sclerotherapy alone, almost 70% of patients self-reported a cure immediately postoperatively, which declined to about 30% after five years. This gradual recurrence rate for sclerotherapy alone is similar to that reported in the above studies. For the ligation and sclerotherapy group, 70% reported a cure immediately postoperatively, dropping to 50% after five years. The best long-term results were reported for the ligation and stripping group, which reported an 80% immediate cure rate, dropping to 70% after five years. The physician assessment of treatment outcome showed greater differences among the three groups. For example, based on physician assessment (observation and foot volumetric measurements), only 5% of the sclerotherapy group were considered cured after 5 years, compared to 10% in the ligation and sclerotherapy group and 60% in the ligation and stripping group.

Rutgers (1994) reported on a trial that randomized 156 patients with varicose veins and saphenofemoral incompetence to undergo either ligation and stripping or ligation and sclerotherapy.[35] The site of sclerotherapy was not described. At the three years follow-up, the cosmetic results were better in those limbs that had undergone stripping. Additionally, the clinical and Doppler ultrasound evidence of reflux was significantly less in those undergoing stripping.

Nonrandomized Studies

There has also been interest in injecting sclerosant into the saphenous vein either in conjunction with ligation as an alternative to stripping, as a stand-alone procedure, or as an alternative to both ligation and stripping.

Myers (2007) published results from a three-year follow-up prospective observational study of sclerotherapy in 489 patients with refluxing saphenous veins and related tributaries.[75] Out of

807 veins treated, 56% were associated with the great saphenous vein and 22% with the small saphenous vein; 22% were tributaries alone. Ultrasound at three to five days after each treatment showed successful occlusion in an average of 1.5 sessions for the group as a whole (65% in one session and 26% in two sessions). The Kaplan-Meier analysis showed three-year survival rates of 83% for tributaries, 53% for great saphenous veins, and 36% for small saphenous veins. These results do not support the use of sclerotherapy for refluxing saphenous veins.

Kanter and Thibault (1996) published result from a case series, which included 172 patients with 202 limbs who had varicose veins with associated saphenofemoral incompetence.[76] Using ultrasound guidance, sclerosant was injected into the long saphenous vein 3-4 cm distal to the saphenofemoral junction. Injections were given at 30- to 90-second intervals, proceeding distally as previously injected segments were observed to spasm. Immediately after therapy, a thigh compression stocking was applied. Two weeks after the initial procedure, patients were reevaluated with Duplex ultrasound and were re-treated if found to have persistent reflux. There was a clinical recurrence rate of 22.8% at one year.

Ninja published two case series (1996; 1997) evaluating sclerotherapy for patients with symptomatic vulvar varicosities.[77, 78] The first study included seven women and the second study included five women. Both studies concluded that all patients noticed marked improvements in symptoms after treatment. However, the sample sizes in these two studies were very small and they lacked a comparator group.

Adverse Effects

Although long-term sequelae have not been reported with sclerotherapy, transient adverse effects have been found in up to 8% of patients, including cerebrovascular accidents, transient ischemic attacks, speech and/or visual disturbance, migraine, shortness of breath, dizziness, and numbness.[79, 80] Bubbles appear in the right side of the heart between 9 and 59 seconds after injection and emboli have been detected in the middle cerebral artery following sclerotherapy of saphenous trunks and varices. Deep venous occlusion after ultrasound-guided sclerotherapy has also been reported; risk was found to be greater when treating veins $\geq$5 mm in diameter (odds ratio of 3.7) and injecting 10 mL or more of foamed sclerosant (odds ratio of 3.6).[81] A SR of visual disturbance following sclerotherapy found this adverse effect to be rare and transient; further research was recommended to clarify the mechanism of action of sclerosants.[82]

Other Treatments

FDA approval of the VenaSeal™ Closure System, which uses adhesive, was based on three manufacturer-sponsored clinical studies, one of which was a randomized controlled noninferiority trial. In the VeClose Study, 222 subjects with symptomatic long saphenous vein incompetence were randomized to undergo either the VenaSeal closure (n=108) or RFA (n=114).[83] A three-month follow-up was conducted during which no adjunctive procedures were allowed. There were a number of methodological limitations in this study, which include but are not limited to, a 14% loss of data, which was accounted for using various methods such as imputing missing data. While these analyses supported noninferiority, their reliability is unclear. These results require validation in large RCTs with lower rates of data loss and longer-term follow-up.

PRACTICE GUIDELINE SUMMARY

AMERICAN VEIN AND LYMPHATIC SOCIETY (AVLS)

The AVSL guidelines committee (2016) published a consensus statement on treatment options for incompetent accessory saphenous veins.[84] They performed a SR to evaluate clinical outcomes and treatment options. They stated treatment recommendations for symptomatic great saphenous veins should include endovenous thermal ablation (laser or radiofrequency) and ultrasound-guided foam sclerotherapy (Grade 1C-strong recommendation, low quality evidence).

The AVLS (2014) published a practice guideline for treatment of superficial veins of the lower leg.[85] Recommendations for the treatment of saphenous veins included laser and radiofrequency ablation, for the small and great saphenous veins and the anterior and posterior accessory of the great saphenous vein (Grade 1B-strong recommendation, moderate quality evidence). Mechanical or Chemical ablation could be used for truncal veins (Grade 2B-weak recommendation, moderate quality evidence). Open surgery is not recommended, unless the conditions do not respond to other recommended treatments (Grade 1B evidence). Nonvisible symptomatic tributary veins could be treated with ultrasound-guided foam sclerotherapy or chemical ablation (Grade 1B evidence).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

NICE (2013) published a clinical guideline for the diagnosis and management of varicose veins.[86] No new evidence was found in 2016 that would change the guideline recommendations.

“1.3.2 For people with confirmed varicose veins and truncal reflux:

- Offer endothermal ablation (see radiofrequency ablation of varicose veins [NICE interventional procedures guidance 8] and endovenous laser treatment of the long saphenous vein [NICE interventional procedures guidance 52]).
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (see ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedures guidance 440]).
- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

  If incompetent varicose tributaries are to be treated, consider treating them at the same time.

1.3.3 If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days.”

INTERSOCIETAL ACCREDITATION COMMISSION

In 2016, the Intersocietal Accreditation Commission (IAC) published standards and guidelines on vascular testing for accreditation.[87] The IAC has recommendations for peripheral venous testing in section 4B. The guideline for documentation of lower extremity venous duplex for reflux states the following (section 4.7.2B):

4.7.2.1B Transverse grayscale images without and with transducer compressions (when anatomically possible or not contraindicated) must be documented as required by the protocol and must include at a minimum: i. common femoral vein;

ii. saphenofemoral junction;
iii. mid femoral vein;
iv. great saphenous vein;
v. popliteal vein;
vi. small saphenous vein.

4.7.2.2B Spectral Doppler waveforms with the extremity(s) in a dependent position, demonstrating baseline flow and response to distal augmentation and if reflux is present, duration of retrograde flow measured with calipers and documented as required by the protocol and must include at a minimum: i. common femoral vein;

ii. saphenofemoral junction;
iii. great saphenous vein;
iv. mid femoral vein;
v. popliteal vein;
vi. small saphenous vein.

4.7.2.3B Transverse grayscale images of *diameter measurement* must be documented as required by the protocol and must include at a minimum:

i. saphenofemoral junction;
ii. great saphenous vein at proximal thigh;
iii. great saphenous vein at knee;
iv. small saphenous vein (at saphenopopliteal junction).

CYANOACRYLATE GLUE

National Institute for Health and Care Excellence (NICE)

NICE (2015) published a guidance on cyanoacrylate glue occlusion for varicose veins.[88] NICE recommendations included using cyanoacrylate glue occlusion for special circumstances. Evidence was limited in quantity and quality.

ENDOVENOUS ABLATION

Society for Vascular Surgery and the American Venous Forum

The 2011 Society for Vascular surgery (SVS) and the American Venous Form (AVF) clinical practice guidelines on varicose veins and chronic venous disease included recommendations for endovenous radiofrequency or laser ablation for the treatment of incompetent long saphenous veins.[89]

- A Grade 1B recommendation was made in favor of endovenous thermal ablation over foam sclerotherapy and high ligation and stripping due to the reduced convalescence, pain, and morbidity. A Grade 1B recommendation was defined as a strong recommendation based on moderate quality evidence.
- A Grade 1B recommendation was made against treatment of incompetent perforator veins with CEAP class C2, but recommend treating these veins if they are located

underneath a healed or active ulcer (Grade 2B recommendation defined as a weak recommendation based on moderate quality evidence.)
- The guideline does not make recommendations for saphenous vein diameter.

The 2014 SVS/AVF guidelines for management of venous ulcers included the following recommendations in favor of standard compressive therapy and ablation of incompetent superficial veins that have axial reflux directed to the bed of the ulcer[90]:

- In a patient with a venous leg ulcer and incompetent superficial veins to 1) improve ulcer healing (Grade 2B recommendation defined as a weak recommendation based on moderate quality evidence), and 2) prevent recurrence (Grade 1C recommendation defined as a strong recommendation based on low- to very low-quality evidence)
- To prevent ulceration in a patient with skin changes at risk for venous leg ulcer, and incompetent superficial veins (Grade 2C recommendation defined as a weak recommendation based on low- to very low- quality evidence)
- To aid in ulcer healing and to prevent recurrence in a patient who also has pathological perforating veins located beneath or associated with the ulcer bed (Grade 2C recommendation defined as a weak recommendation based on low- to very low- quality evidence)
- To prevent ulceration or ulcer recurrence in a patient with skin changes at risk for venous leg ulcer or healed venous ulcer and incompetent superficial veins (Grade 2C recommendation defined as a weak recommendation based on low- to very low-quality evidence).
- If a patient is expected to benefit from pathologic perforator vein ablation, percutaneous ablation with ultrasound-guided sclerotherapy or endovenous RFA or EVLA is recommended over open venous perforator surgery (Grade 1C recommendation defined as a strong recommendation based on low- to very low-quality evidence)

National Institute for Health and Care Excellence (NICE)

NICE (2016) published guidance on endovenous mechanochemical ablation for varicose veins.[91]

“Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins appears adequate to support the use of this procedure provided that standard arrangements are in place for consent, audit and clinical governance. Clinicians are encouraged to collect longer-term follow-up data.”

NICE published a guidance in 2004 for endovenous laser treatment of the long saphenous vein.[92]

“Current evidence on the safety and efficacy of endovenous laser treatment of the long saphenous vein appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. Current evidence on the efficacy of this procedure is limited to case series with up to 3 years follow-up. Clinicians are encouraged to collect longer-term follow-up data.”

NICE published a guidance in 2003 for radiofrequency ablation of varicose veins.[93]

"Current evidence on the safety and efficacy of radiofrequency ablation of varicose veins appears adequate to support the use of this procedure as an alternative to saphenofemoral ligation and stripping, provided that the normal arrangements are in place for consent, audit and clinical governance."

American College of Radiology[94]

The 2012 the American College of Radiology (ACR) published appropriateness criteria for the treatment of lower-extremity venous insufficiency considered endovenous radiofrequency or laser ablation at least as effective as surgery. Cryoablation and mechanochemical ablation are not addressed. The criteria do not include patient selection criteria related to vein size. They also stated injection sclerotherapy may be appropriate in specific situations, but has not shown to have long-term effectiveness for the great saphenous veins.

Society of Interventional Radiography, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology, Canadian Interventional Radiology Association[95]

The 2010 the Society of Interventional Radiography (SIR), Cardiovascular Interventional Radiological Society of Europe (CIRSE), American College of Phlebology (ACP), Canadian Interventional Radiology Association (CIRA) published a joint consensus statement on endovenous thermal ablation using either laser or radiofrequency devices under imaging guidance and monitoring an effective treatment of extremity venous reflux and varicose veins under the following conditions:

I. The endovenous treatment of varicose veins may be medically necessary when one of the following indications (A–E) is present:

   A. Persistent symptoms interfering with activities of daily living in spite of conservative/nonsurgical management. Symptoms include aching, cramping, burning, itching, and/or swelling during activity or after prolonged standing.
   B. Significant recurrent attacks of superficial phlebitis
   C. Hemorrhage from a ruptured varix
   D. Ulceration from venous stasis where incompetent varices are a contributing factor
   E. Symptomatic incompetence of the great or small saphenous veins (symptoms as in A above)

II. A trial of conservative, nonoperative treatment has failed. This would include mild exercise, avoidance of prolonged immobility, periodic elevation of legs, and compressive stockings.

III. The patient's anatomy is amenable to endovenous ablation.

SCLEROTHERAPY

National Institute for Health and Care Excellence (NICE)

NICE published a guidance in 2013 for sclerotherapy.[96]

"1.1 Current evidence on the efficacy of ultrasound-guided foam sclerotherapy for varicose veins is adequate. The evidence on safety is adequate, and provided that patients are warned

of the small but significant risks of foam embolisation (see section 1.2), this procedure may be used with normal arrangements for clinical governance, consent and audit."

"1.2 During the consent process, clinicians should inform patients that there are reports of temporary chest tightness, dry cough, headaches and visual disturbance, and rare but significant complications including myocardial infarction, seizures, transient ischaemic attacks and stroke."

Society for Vascular Surgery and the American Venous Forum

The 2011 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) published practice guidelines[89] and included the following recommendations concerning sclerotherapy in varicose vein treatment:

- Grade 1B (strong recommendation based on moderate quality evidence) recommendation for the use of sclerotherapy to treat varicose tributaries
- Grade 1B recommendation against selective treatment of perforating vein incompetence in patients with simple varicose veins
- Grade 2B (weak recommendation based on moderate quality evidence) for sclerotherapy to treat pathologic perforating veins (i.e., outward flow of $\geq$ 500 ms duration and a diameter of $\geq$ 3.5 mm) located under healed or active ulcers (CEAP class C5-C6)

The 2014 SVS/AVF guidelines[90] for management of venous ulcers included the following recommendations:

- Grade 1C (Strong recommendation, low quality or very-low quality evidence) For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromise skin.

SUMMARY

There is enough research to determine that treatment of certain symptomatic varicose veins using ligation, phlebectomy, endovenous treatment with radiofrequency or laser ablation, endovenous glue/adhesive, and sclerotherapy may improve short-term clinical outcomes (e.g., pain and return to work). Therefore, these procedures may be considered medically necessary in select patients when the policy criteria are met. Procedures not meeting the policy Criteria are considered not medically necessary. In addition, follow-up venous studies performed within six months following the most recent treatment in the absence of complications is considered not medically necessary.

There is not enough research to show improvement in health outcomes for endovenous ablation or sclerotherapy of the investigational indications listed in the medical policy Criteria. Further, the current evidence has limitations including no comparator groups, small study population, and short-term follow-up.

There is not enough research to show that mechanochemical ablation of varicose veins improves patient outcomes and is safe. Therefore, the use of mechanochemical ablation of any vein is considered investigational.

Appendix 1: CEAP Classification	
Clinical classification (C)	C0: no visible or palpable signs of venous disease C1: telangiectasias or reticular veins C2: varicose veins (≥3 mm diameter) C3: edema C4: skin and subcutaneous tissue changes C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche C5: healed venous ulcer C6: active venous ulcer
Each clinical class is further characterized by a subscript for symptomatic (S) or asymptomatic (A), for example, C2A or C5S.	
Etiologic classification (E)	Ec: congenital Ep: primary Es: secondary (postthrombotic) En: no venous cause identified
Anatomic classification (A)	As: superficial veins Ap: perforator veins Ad: deep veins An: no venous location identified
Pathophysiologic classification	
Basic CEAP	Pr: reflux Po: obstruction Pr,o: reflux and obstruction Pn: no venous pathophysiology identifiable
Advanced CEAP includes the addition of any of following 18 venous segments as locators:	
Superficial veins	Telangiectasias or reticular veins Great saphenous vein above knee Great saphenous vein below knee Small saphenous vein Nonsaphenous veins
Deep veins	Inferior vena cava Common iliac vein Internal iliac vein External iliac vein Pelvic: gonadal, broad ligament veins, other Common femoral vein Deep femoral vein Femoral vein Popliteal vein Crural: anterior tibial, posterior tibial, peroneal veins (all paired) Muscular: gastrocnemial, soleal veins, other
Perforating veins	Thigh Calf

REFERENCES

1. Eklof B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2004;40(6):1248-52. PMID: 15622385
2. Kheirelseid EAH, Crowe G, Sehgal R, et al. Systematic review and meta-analysis of randomized controlled trials evaluating long-term outcomes of endovenous management of lower extremity varicose veins. *Journal of vascular surgery Venous and lymphatic disorders.* 2017. PMID: 29292115
3. Hamann SAS, Giang J, De Maeseneer MGR, et al. Editor's Choice - Five Year Results of Great Saphenous Vein Treatment: A Meta-analysis. *Eur J Vasc Endovasc Surg.* 2017;54(6):760-70. PMID: 29033337
4. Vemulapalli S, Parikh K, Coeytaux R, et al. Systematic review and meta-analysis of endovascular and surgical revascularization for patients with chronic lower extremity venous insufficiency and varicose veins. *American heart journal.* 2018;196:131-43. PMID: 29421005
5. Boersma D, Kornmann VN, van Eekeren RR, et al. Treatment Modalities for Small Saphenous Vein Insufficiency: Systematic Review and Meta-analysis. *J Endovasc Ther.* 2016;23:199-211. PMID: 26564912
6. Nesbitt C, Bedenis R, Bhattacharya V, et al. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus open surgery for great saphenous vein varices. *Cochrane Database Syst Rev.* 2014;7:CD005624. PMID: 25075589
7. Siribumrungwong B, Noorit P, Wilasrusmee C, et al. A systematic review and meta-analysis of randomised controlled trials comparing endovenous ablation and surgical intervention in patients with varicose vein. *Eur J Vasc Endovasc Surg.* 2012;44(2):214-23. PMID: 22705163
8. Lawaetz M, Serup J, Lawaetz B, et al. Comparison of endovenous ablation techniques, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Extended 5-year follow-up of a RCT. *International angiology : a journal of the International Union of Angiology.* 2017;36(3):281-88. PMID: 28217989
9. van der Velden SK, Biemans AA, De Maeseneer MG, et al. Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. *The British journal of surgery.* 2015;102(10):1184-94. PMID: 26132315
10. Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. *The New England journal of medicine.* 2014;371(13):1218-27. PMID: 25251616
11. Brittenden J, Cotton SC, Elders A, et al. Clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins: results from the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) randomised controlled trial. *Health Technol Assess.* 2015;19(27):1-342. PMID: 25858333
12. Brittenden J, Cooper D, Dimitrova M, et al. Five-Year Outcomes of a Randomized Trial of Treatments for Varicose Veins. *The New England journal of medicine.* 2019;381(10):912-22. PMID: 31483962
13. Biemans JM, van Balken MR. Efficacy and effectiveness of percutaneous tibial nerve stimulation in the treatment of pelvic organ disorders: a systematic review. *Neuromodulation : journal of the International Neuromodulation Society.* 2013;16(1):25-33; discussion 33. PMID: 22985128
14. Joh JH, Park HC. The cutoff value of saphenous vein diameter to predict reflux. *Journal of the Korean Surgical Society.* 2013;85(4):169-74. PMID: 24106683

15. Mendoza E, Blattler W, Amsler F. Great saphenous vein diameter at the saphenofemoral junction and proximal thigh as parameters of venous disease class. *Eur J Vasc Endovasc Surg.* 2013;45(1):76-83. PMID: 23219416
16. Navarro TP, Delis KT, Ribeiro AP. Clinical and hemodynamic significance of the greater saphenous vein diameter in chronic venous insufficiency. *Arch Surg.* 2002;137:1233-7. PMID: 12413308
17. Engelhorn C, Engelhorn A, Salles-Cunha S, et al. Relationship between reflux and greater saphenous vein diameter. *J Vasc Technol.* 1997;21(3):167-72. PMID: No PMID Entry
18. He G, Zheng C, Yu MA, et al. Comparison of ultrasound-guided endovenous laser ablation and radiofrequency for the varicose veins treatment: An updated meta-analysis. *International journal of surgery (London, England).* 2017;39:267-75. PMID: 28119106
19. Wozniak W, Mlosek RK, Ciostek P. Complications and Failure of Endovenous Laser Ablation and Radiofrequency Ablation Procedures in Patients With Lower Extremity Varicose Veins in a 5-Year Follow-Up. *Vasc Endovascular Surg.* 2016;50(7):475-83. PMID:
20. Hoggan BL, Cameron AL, Maddern GJ. Systematic review of endovenous laser therapy versus surgery for the treatment of saphenous varicose veins. *Ann Vasc Surg.* 2009;23(2):277-87. PMID: 19128927
21. Rass K, Frings N, Glowacki P, et al. Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein: two-year results of a randomized clinical trial (RELACS study). *Archives of dermatology.* 2012;148(1):49-58. PMID: 21931012
22. Rasmussen L, Lawaetz M, Bjoern L, et al. Randomized clinical trial comparing endovenous laser ablation and stripping of the great saphenous vein with clinical and duplex outcome after 5 years. *J Vasc Surg.* 2013;58(2):421-6. PMID: 23768792
23. Theivacumar NS, Darwood RJ, Gough MJ. Endovenous laser ablation (EVLA) of the anterior accessory great saphenous vein (AAGSV): abolition of sapheno-femoral reflux with preservation of the great saphenous vein. *Eur J Vasc Endovasc Surg.* 2009;37(4):477-81. PMID: 19201621
24. Merchant RF, Pichot O, Myers KA. Four-year follow-up on endovascular radiofrequency obliteration of great saphenous reflux. *Dermatol Surg.* 2005;31(2):129-34. PMID: 15762202
25. Chandler JG, Pichot O, Sessa C, et al. Treatment of Primary Venous Insufficiency by Endovenous Saphenous vein Obliteration. *Vasc Endovascular Surg.* 2000;34(3):201-14. PMID: No PMID Entry
26. Goldman MP. Closure of the greater saphenous vein with endoluminal radiofrequency thermal heating of the vein wall in combination with ambulatory phlebectomy: preliminary 6-month follow-up. *Dermatol Surg.* 2000;26(5):452-6. PMID: 10816234
27. Manfrini S, Gasbarro V, Danielsson G, et al. Endovenous management of saphenous vein reflux. Endovenous Reflux Management Study Group. *J Vasc Surg.* 2000;32(2):330-42. PMID: 10917994
28. Merchant RF, Pichot O. Long-term outcomes of endovenous radiofrequency obliteration of saphenous reflux as a treatment for superficial venous insufficiency. *J Vasc Surg.* 2005;42(3):502-9; discussion 09. PMID: 16171596
29. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long-term results. *J Vasc Interv Radiol.* 2003;14(8):991-6. PMID: 12902556

30. Theivacumar NS, Dellagrammaticas D, Mavor AI, et al. Endovenous laser ablation (EVLA) of great saphenous vein to abolish "paradoxical reflux" in the Giacomini vein: a short report. *Eur J Vasc Endovasc Surg.* 2007;34(2):229-31. PMID: 17331749
31. Gibson KD, Ferris BL, Polissar N, et al. Endovenous laser treatment of the small [corrected] saphenous vein: efficacy and complications. *J Vasc Surg.* 2007;45(4):795-801; discussion 01-3. PMID: 17306952
32. Ravi R, Rodriguez-Lopez JA, Trayler EA, et al. Endovenous ablation of incompetent saphenous veins: a large single-center experience. *J Endovasc Ther.* 2006;13(2):244-8. PMID: 16643080
33. Myers K, Fris R, Jolley D. Treatment of varicose veins by endovenous laser therapy: assessment of results by ultrasound surveillance. *Med J Aust.* 2006;185(4):199-202. PMID: 16922664
34. Jones L, Braithwaite BD, Selwyn D, et al. Neovascularisation is the principal cause of varicose vein recurrence: results of a randomised trial of stripping the long saphenous vein. *Eur J Vasc Endovasc Surg.* 1996;12(4):442-5. PMID: 8980434
35. Rutgers PH, Kitslaar PJ. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. *Am J Surg.* 1994;168(4):311-5. PMID: 7943585
36. Rautio T, Ohinmaa A, Perala J, et al. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. *J Vasc Surg.* 2002;35(5):958-65. PMID: 12021712
37. Disselhoff BC, der Kinderen DJ, Kelder JC, et al. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. *The British journal of surgery.* 2008;95(10):1232-8. PMID: 18763255
38. Disselhoff BC, der Kinderen DJ, Kelder JC, et al. Five-year results of a randomized clinical trial comparing endovenous laser ablation with cryostripping for great saphenous varicose veins. *The British journal of surgery.* 2011;98(8):1107-11. PMID: 21633948
39. Klem TM, Schnater JM, Schutte PR, et al. A randomized trial of cryo stripping versus conventional stripping of the great saphenous vein. *J Vasc Surg.* 2009;49(2):403-9. PMID: 19028042
40. Amshar M, Nugraha RA, Batubara EAD, et al. Cyanoacrylate Embolization versus Endovenous Laser Ablation in Treating Saphenous Vein Insufficiency: A Systematic Review and Meta-Analysis. *Ann Vasc Surg.* 2022;80:313-24. PMID: 34780939
41. García-Carpintero E, Carmona M, Chalco-Orrego JP, et al. Systematic review and meta-analysis of endovenous cyanoacrylate adhesive ablation for incompetent saphenous veins. *Journal of vascular surgery Venous and lymphatic disorders.* 2020;8(2):287-96. PMID: 31917181
42. Morrison N, Gibson K, Vasquez M, et al. VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. *Journal of vascular surgery Venous and lymphatic disorders.* 2017;5(3):321-30. PMID: 28411697
43. Morrison N, Kolluri R, Vasquez M, et al. Comparison of cyanoacrylate closure and radiofrequency ablation for the treatment of incompetent great saphenous veins: 36-Month outcomes of the VeClose randomized controlled trial. *Phlebology.* 2018:268355518810259. PMID: 30403154
44. Morrison N, Gibson K, Vasquez M, et al. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins.

Journal of vascular surgery Venous and lymphatic disorders. 2020;8(6):978-89. PMID: 32205125
45. Yasim A, Eroglu E, Bozoglan O, et al. A new non-tumescent endovenous ablation method for varicose vein treatment: Early results of N-butyl cyanoacrylate (VariClose(R)). *Phlebology.* 2017;32(3):194-99. PMID: 27022011
46. Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. *Phlebology.* 2016;31(1 Suppl):106-13. PMID:
47. Witte ME, Zeebregts CJ, de Borst GJ, et al. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review. *Phlebology.* 2017;32(10):649-57. PMID: 28403687
48. Vos CG, Unlu C, Bosma J, et al. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. *Journal of vascular surgery Venous and lymphatic disorders.* 2017;5(6):880-96. PMID: 29037363
49. Belramman A, Bootun R, Tang TY, et al. Pain Outcomes Following Mechanochemical Ablation vs Cyanoacrylate Adhesive for the Treatment of Primary Truncal Saphenous Vein Incompetence: The MOCCA Randomized Clinical Trial. *JAMA Surg.* 2022;157(5):395-404. PMID: 35385061
50. Mohamed AH, Leung C, Wallace T, et al. A Randomized Controlled Trial of Endovenous Laser Ablation Versus Mechanochemical Ablation With ClariVein in the Management of Superficial Venous Incompetence (LAMA Trial). *Annals of surgery.* 2020. PMID: 31977509
51. Holewijn S, van Eekeren R, Vahl A, et al. Two-year results of a multicenter randomized controlled trial comparing Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial). *Journal of vascular surgery Venous and lymphatic disorders.* 2019;7(3):364-74. PMID: 31000063
52. Lane T, Bootun R, Dharmarajah B, et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. *Phlebology.* 2017;32(2):89-98. PMID: 27221810
53. Bootun R, Lane T, Dharmarajah B, et al. Intra-procedural pain score in a randomised controlled trial comparing mechanochemical ablation to radiofrequency ablation: The Multicentre Venefit versus ClariVein(R) for varicose veins trial. *Phlebology.* 2014. PMID: 25193822
54. Tang TY, Kam JW, Gaunt ME. ClariVein(R) - Early results from a large single-centre series of mechanochemical endovenous ablation for varicose veins. *Phlebology.* 2017;32(1):6-12. PMID: 26908638
55. Elias S, Raines JK. Mechanochemical tumescentless endovenous ablation: final results of the initial clinical trial. *Phlebology.* 2012;27(2):67-72. PMID: 21803800
56. Bishawi M, Bernstein R, Boter M, et al. Mechanochemical ablation in patients with chronic venous disease: A prospective multicenter report. *Phlebology.* 2013. PMID: 23820117
57. Boersma D, van Eekeren RR, Werson DA, et al. Mechanochemical endovenous ablation of small saphenous vein insufficiency using the ClariVein((R)) device: one-year results of a prospective series. *Eur J Vasc Endovasc Surg.* 2013;45(3):299-303. PMID: 23312507

58. van Eekeren RR, Boersma D, Konijn V, et al. Postoperative pain and early quality of life after radiofrequency ablation and mechanochemical endovenous ablation of incompetent great saphenous veins. *J Vasc Surg.* 2013;57(2):445-50. PMID: 23141679
59. Kim PS, Bishawi M, Draughn D, et al. Mechanochemical ablation for symptomatic great saphenous vein reflux: A two-year follow-up. *Phlebology.* 2016. PMID: 26811425
60. Vun SV, Rashid ST, Blest NC, et al. Lower pain and faster treatment with mechanico-chemical endovenous ablation using ClariVein(R). *Phlebology.* 2015;30:688-92. PMID: 25300311
61. Yang L, Wang XP, Su WJ, et al. Randomized clinical trial of endovenous microwave ablation combined with high ligation versus conventional surgery for varicose veins. *Eur J Vasc Endovasc Surg.* 2013;46(4):473-9. PMID: 23911734
62. Mao J, Zhang C, Wang Z, et al. A retrospective study comparing endovenous laser ablation and microwave ablation for great saphenous varicose veins. *European review for medical and pharmacological sciences.* 2012;16(7):873-7. PMID: 22953634
63. Luebke T, Brunkwall J. Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. *J Cardiovasc Surg (Torino).* 2008;49(2):213-33. PMID: 18431342
64. Leopardi D, Hoggan BL, Fitridge RA, et al. Systematic review of treatments for varicose veins. *Ann Vasc Surg.* 2009;23(2):264-76. PMID: 19059756
65. Yin H, He H, Wang M, et al. Prospective Randomized Study of Ultrasound-Guided Foam Sclerotherapy Combined with Great Saphenous Vein High Ligation in the Treatment of Severe Lower Extremity Varicosis. *Ann Vasc Surg.* 2017;39:256-63. PMID: 27671459
66. Gibson K, Kabnick L. A multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena(R) (polidocanol endovenous microfoam 1%) for symptomatic, visible varicose veins with saphenofemoral junction incompetence. *Phlebology.* 2017;32(3):185-93. PMID: 27013511
67. King JT, O'Byrne M, Vasquez M, et al. Treatment of Truncal Incompetence and Varicose Veins with a Single Administration of a New Polidocanol Endovenous Microfoam Preparation Improves Symptoms and Appearance. *Eur J Vasc Endovasc Surg.* 2015;50(6):784-93. PMID: 26384639
68. Vasquez M, Gasparis AP. A multicenter, randomized, placebo-controlled trial of endovenous thermal ablation with or without polidocanol endovenous microfoam treatment in patients with great saphenous vein incompetence and visible varicosities. *Phlebology.* 2016. PMID: 26957489
69. Todd KL, 3rd, Wright D. The VANISH-2 study: a randomized, blinded, multicenter study to evaluate the efficacy and safety of polidocanol endovenous microfoam 0.5% and 1.0% compared with placebo for the treatment of saphenofemoral junction incompetence. *Phlebology.* 2014. PMID: 23864535
70. U.S. Food and Drug Administration Center for Drug Evaluation and Research. 205098 Varithena Summary Review. 2013. [cited 5/13/2023]. 'Available from:' http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205098Orig1s000SumR.pdf.
71. Todd KL, 3rd, Wright D. Durability of treatment effect with polidocanol endovenous microfoam on varicose vein symptoms and appearance (VANISH-2). *Journal of Vascular Surgery; Venous and Lymphatic Disorders.* 2015;3(3):258-64. PMID:
72. Shadid N, Ceulen R, Nelemans P, et al. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. *The British journal of surgery.* 2012;99(8):1062-70. PMID: 22627969

73. Blaise S, Bosson JL, Diamand JM. Ultrasound-guided sclerotherapy of the great saphenous vein with 1% vs. 3% polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. *Eur J Vasc Endovasc Surg.* 2010;39(6):779-86. PMID: 20206556
74. Neglen P, Einarsson E, Eklof B. The functional long-term value of different types of treatment for saphenous vein incompetence. *J Cardiovasc Surg (Torino).* 1993;34(4):295-301. PMID: 8227108
75. Myers KA, Jolley D, Clough A, et al. Outcome of ultrasound-guided sclerotherapy for varicose veins: medium-term results assessed by ultrasound surveillance. *Eur J Vasc Endovasc Surg.* 2007;33(1):116-21. PMID: 17067832
76. Kanter A, Thibault P. Saphenofemoral incompetence treated by ultrasound-guided sclerotherapy. *Dermatol Surg.* 1996;22(7):648-52. PMID: 8680788
77. Ninia JG. Treatment of vulvar varicosities by injection-compression sclerotherapy. *Dermatol Surg.* 1997;23(7):573-4; discussion 74-5. PMID: 9236876
78. Ninia JG, Goldberg TL. Treatment of vulvar varicosities by injection-compression sclerotherapy and a pelvic supporter. *Obstetrics and gynecology.* 1996;87(5 Pt 1):786-8. PMID: 8677087
79. Coleridge Smith P. Sclerotherapy and foam sclerotherapy for varicose veins. *Phlebology.* 2009;24(6):260-9. PMID: 19952382
80. Sarvananthan T, Shepherd AC, Willenberg T, et al. Neurological complications of sclerotherapy for varicose veins. *J Vasc Surg.* 2012;55(1):243-51. PMID: 21840152
81. Myers KA, Jolley D. Factors affecting the risk of deep venous occlusion after ultrasound-guided sclerotherapy for varicose veins. *Eur J Vasc Endovasc Surg.* 2008;36(5):602-5. PMID: 18718772
82. Willenberg T, Smith PC, Shepherd A, et al. Visual disturbance following sclerotherapy for varicose veins, reticular veins and telangiectasias: a systematic literature review. *Phlebology.* 2012. PMID: 23202140
83. Morrison N, Gibson K, McEnroe S, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). *J Vasc Surg.* 2015;61(4):985-94. PMID: 25650040
84. Kathleen G, Neil K, Marlin S, et al. American College of Phlebology Guidelines – Treatment of refluxing accessory saphenous veins. *Phlebology.* 2016;32(7):448-52. PMID:
85. Phlebology ACo. Practice Guidelines Superficial Venous Disease. [cited 4/25/2022]. 'Available from:' http://www.phlebology.org/wp-content/uploads/2015/03/VaricoseVeinGuidelines3.9.15.pdf.
86. (NICE) NIfHaCE. Varicose veins: diagnosis and management. Clinical guideline [CG168]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/cg168/chapter/1-Recommendations#assessment-and-treatment-in-a-vascular-service-2.
87. Intersocietal Accreditation Commission. IAC Standards and Guidelines for Vascular Testing Accreditation. . [cited 5/13/2023]. 'Available from:' http://www.intersocietal.org/vascular/main/vascular_standards.htm.
88. (NICE) NIfHaCE. Cyanoacrylate glue occlusion for varicose veins. Interventional procedures guidance [IPG670]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg670.
89. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for

Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(5 Suppl):2S-48S. PMID: 21536172
90. O'Donnell TF, Jr., Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. *J Vasc Surg.* 2014;60(2 Suppl):3S-59S. PMID: 24974070
91. (NICE) NIfHaCE. Endovenous mechanochemical ablation for varicose veins. Interventional procedures guidance [IPG557]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg557.
92. (NICE) NIfHaCE. Endovenous laser treatment of the long saphenous vein. Interventional procedures guidance [IPG52]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg52/chapter/1-Guidance.
93. (NICE) NIfHaCE. Radiofrequency ablation of varicose veins. Interventional procedures guidance [IPG8]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg8.
94. Rochon PJ, Vu CT, Ray Jr CE, et al. ACR appropriateness criteria; radiologic management of lower-extremity venous insufficiency. 2012. [cited 5/13/2023]. 'Available from:' http://www.acr.org/Quality-Safety/Appropriateness-Criteria/~/media/2DF084BCCF3D4B10A2D6E443489728C4.pdf.
95. Khilnani NM, Grassi CJ, Kundu S, et al. Multi-society consensus quality improvement guidelines for the treatment of lower-extremity superficial venous insufficiency with endovenous thermal ablation from the Society of Interventional Radiology, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology and Canadian Interventional Radiology Association. *J Vasc Interv Radiol.* 2010;21:14-31. PMID: 20123189
96. (NICE) NIfHaCE. Ultrasound-guided foam sclerotherapy for varicose veins. Interventional procedures guidance [IPG440]. [cited 5/13/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg440.

CODES

NOTES:

- This policy uses the nomenclature great saphenous vein and small saphenous vein, also known as greater or long and lesser or short saphenous veins, respectively. Current CPT nomenclature uses long and short saphenous veins.
- There is no specific CPT code for mechanochemical treatment devices (e.g., the ClariVein® device) which should be reported with an unlisted procedure code such as 37799. Per CPT definitions, it is inappropriate to use codes 37241-37244 or 37475-37479 to report this procedure.
- Varithena is not separately reimbursable using any CPT or HCPCS Code.
- There is no specific CPT code for transilluminated powered phlebectomy. Providers might elect to use CPT codes describing stab phlebectomy (37765 or 37766), excision of varicose vein cluster(s) (37785), or unlisted vascular surgery procedure (37799).
- There is no specific CPT for microfoam sclerotherapy. Providers might elect to use CPT codes describing sclerotherapy (36468-36471) or the unlisted vascular surgery procedure code 37799. Use of codes 36475-36476 would be inappropriate as the procedure is not ablation therapy.

Codes	Number	Description
CPT	0524T	Endovenous catheter directed chemical ablation with balloon isolation of incompetent extremity vein, open or percutaneous, including all vascular access, catheter manipulation, diagnostic imaging, imaging guidance and monitoring
	36465	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein)
	36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; multiple incompetent truncal veins (eg, great saphenous vein, accessory saphenous vein), same leg
	36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
	36470	Injection of sclerosing solution; single incompetent vein
	36471	Injection of sclerosing solution; multiple incompetent veins, same leg
	36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated
	36474	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
	36476	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
	36479	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36482	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated
	36483	;subsequent vein(s) treated in a single extremity, each through separate access sites (list separately in addition to code for primary procedure)
	37700	Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions
	37718	Ligation, division, and stripping, short saphenous vein (for bilateral procedure, use modifier 50)
	37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
	37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia
	37760	Ligation of perforators veins, subfascial, radical (Linton type) including skin graft, when performed, open, 1 leg
	37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg
	37765	Stab phlebectomy of varicose veins, one extremity; 10-20 stab incisions
	37766	Stab phlebectomy of varicose veins, one extremity; more than 20 incisions

Codes	Number	Description
	37780	Ligation and division of short saphenous vein at saphenopopliteal junction
	37785	Ligation, division, and/or excision of varicose vein cluster(s), one leg
		Unlisted procedure, vascular surgery
	93970	Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
	93971	Duplex scan of extremity veins including responses to compression and other maneuvers; unilateral or limited studies
HCPCS	J3490	Unclassified drugs
	S2202	Echosclerotherapy

Date of Origin: *October 1999*

Regence

Medical Policy Manual Surgery, Policy No. 109

Percutaneous Angioplasty and Stenting of Veins

Effective: February 1, 2024

Next Review: September 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Dilation and/or stent placement in veins is intended to restore blood flow in a narrowed or collapsed vein.

MEDICAL POLICY CRITERIA

Note: This policy addresses percutaneous angioplasty and stenting of **veins** only. This policy does *not* address percutaneous angioplasty and stenting of peripheral arteries, including repair of aneurysms, which may be considered medically necessary. Extracranial carotid angioplasty is addressed in a separate policy (see Cross References section).

I. Percutaneous transluminal angioplasty, with or without stenting, may be considered **medically necessary** for the treatment of venous stenoses in the following instances:

   A. Stenotic lesions of arteriovenous dialysis fistulas and grafts, and ipsilateral venous stenosis in the outflow of a functioning dialysis fistula and graft

   B. Superior or inferior vena cava syndrome with significant symptoms, from either extrinsic compression or intrinsic stenosis/occlusion [when standard treatments (i.e., radiation and/or chemotherapy) have failed]

C. Left iliac vein compression syndrome (May-Thurner Syndrome)

D. As an adjunct to prior or concurrent ipsilateral first rib resection for venous thoracic outlet syndrome due to persistent extrinsic compression (Paget-Schroetter syndrome) documented by pre-procedure imaging (i.e., ultrasound, venography, CT, or MRI)

E. Pulmonary vein stenosis

F. Thrombotic obstruction of major hepatic veins (Budd-Chiari syndrome)

G. Post-operative venous narrowing due to repair of sinus venosus atrial septal defect

H. Pulmonary artery stenosis and/or hypoplasia

I. Venous obstruction of an atrial baffle following Mustard or Senning repair of transposition of the great arteries

J. Symptomatic venous occlusion due to electrical device lead or central line placement

K. Portal vein stenosis in a liver transplant recipient

II. The use of angioplasty and/or endoprostheses for creation of intrahepatic shunt connections between the portal venous system and hepatic vein may be considered **medically necessary**.

III. Percutaneous transluminal angioplasty, with or without stenting, is considered **investigational** when policy criteria are not met and for all other venous indications, including but not limited to:

A. Deep vein thrombosis, venous stenosis, or venous insufficiency that is not related to the medically necessary indications above (I.A.- K.)

B. Chronic cerebrospinal venous insufficiency in multiple sclerosis or other conditions

C. Venous sinus obstruction or occlusion in idiopathic intracranial hypertension

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments

CROSS REFERENCES

1. Extracranial Carotid Angioplasty/Stenting, Surgery, Policy No. 93

BACKGROUND

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF THE VEINS

Percutaneous transluminal angioplasty (PTA) of the veins is a procedure that has been used as an alternative to open vascular surgery in order to restore blood flow through narrowed veins. Techniques may include balloon angioplasty, laser angioplasty, and stent placement.

INTRAVASCULAR STENTS

Intravascular stents are used as an adjunct to angioplasty to prevent vessel wall collapse. They can be placed via transluminal catheters or placed with catheters during open vascular procedures. Drug-eluting stents are intended to prevent restenosis by reducing the growth of neointimal tissue. A number of different drugs are being evaluated for this use, including paclitaxel and sirolimus. These stents are coated with a mixture of synthetic polymers blended with the drug. A second coat of drug-free polymers is then added to serve as a diffusion barrier, thus allowing the gradual release of drug to the precise site of interest while avoiding systemic side effects.

ILIAC VEIN COMPRESSION SYNDROME

Iliac vein compression syndrome (IVCS) is deep vein thrombosis (DVT) that occurs as a result of compression of the left common iliac vein between the overlying right common iliac artery and the body of the fifth lumbar vertebra. This syndrome is relatively uncommon. If DVT occurs, it is treated with anticoagulation therapy. However, the underlying mechanical compression must be treated with surgery or stent placement. Left untreated it may result in recurrent DVT or postthrombotic syndrome (PTS) characterized by chronic swelling and pain in the affected extremity. Some patients also develop varicosities and stasis ulcers. This condition may also be referred to by other terms including but not limited to May-Thurner syndrome, non-thrombotic iliac vein lesions (NIVL), and Cockett syndrome.

PROXIMAL UPPER EXTREMITY VENOUS THROMBOSIS

Proximal upper extremity venous thrombosis occurs as a result of mechanical compression of the subclavian vein at the thoracic outlet. The natural history of the disorder is typically one of chronic venous obstruction with development of a painful, swollen extremity.[1, 2] Thrombosis may affect the brachiocephalic, subclavian, and/or axillary veins. Typical management of this condition involves thrombolysis and surgical decompression after a variable interval of oral anticoagulation. Venous stent placement may be helpful in maintaining patency of the vein following thoracic outlet decompression surgery that includes first rib resection. This condition may also be referred to by other terms including but not limited to axillary-subclavian venous thrombosis, effort thrombosis, Paget-Schroetter syndrome, or venous thoracic outlet syndrome.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension (IIH) is characterized by elevated intracranial pressure (ICP). The most common symptoms are headache and papilledema. Other symptoms include transient visual obscurations, pulsatile tinnitus, diplopia, and sustained visual loss. Initial evaluation of patients presenting with headache and papilledema consists of CT or MRI scan for possible hydrocephalus or tumor. Occlusion of the venous sinus, particularly the transverse sinus, is considered an uncommon cause of increased ICP. There has been some debate as to whether this occlusion is the cause or the effect of ICP. The hypothesis is that obstruction of venous return decreases venous outflow from the brain which also decreases

cerebrospinal fluid (CSF) outflow with subsequent increase in intracranial CSF pressure. Medical treatment includes medications that lower CSF production and/or therapeutic lumbar puncture. Since most patients with IIH are obese, weight loss is commonly recommended. If medical treatment fails to control IIH, surgical treatments include ventriculoperitoneal shunting, optic nerve sheath fenestration (optic nerve decompression), and subtemporal decompression. Angioplasty with stenting has been proposed for maintaining venous sinus patency. IIH may also be referred to as pseudotumor cerebri or benign intracranial hypertension, though these terms are considered inadequate and IIH is the preferred term.

CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is generally considered a chronic inflammatory demyelinating disease of the central nervous system (brain, spinal cord, and optic nerve) believed to be triggered by an autoimmune response to myelin. However, in part due to the periventricular predilection of the lesions of MS, vascular etiologies have also been considered. The core foundation of this vascular theory is that venous drainage from the brain is abnormal due to outflow obstruction in the draining jugular vein and/or azygos veins. This abnormal venous drainage, which is characterized by special ultrasound criteria, is said to cause intracerebral flow disturbance or outflow problems that lead to periventricular deposits. In the chronic cerebrospinal venous insufficiency (CCSVI) theory, these deposits have a similarity to the iron deposits seen around the veins in the legs of patients with chronic deep vein thrombosis. Balloon dilatation, with or without stenting, has been proposed as a means to treat the outflow problems, thereby alleviating CCSVI and MS complaints.

REGULATORY STATUS

While there are several types of stents that are approved by the U.S. Food and Drug Administration (FDA) for improvement of outflow for arteriovenous (A-V) access grafts in hemodialysis patients, and for the creation of intrahepatic shunt connections between the portal venous system and hepatic vein [i.e., transjugular intrahepatic portosystemic shunt (TIPS)], there are currently no stents with FDA approval for use in veins for any other indications.

In March 2017, the FDA issued a safety communication regarding the use of balloon angioplasty devices to treat autonomic dysfunction. This supplemented an earlier warning from the FDA concerning the potential for adverse events following endovascular interventions to treat CCSVI. Reports of adverse events obtained by the FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This communication included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption due to potential for harms.

EVIDENCE SUMMARY

The following discussion focuses on the investigational indications noted in Criterion III above.

DEEP VEIN THROMBOSIS (DVT)

There are several objectives for treatment of venous thromboembolism including:[3, 4]

- Prevention of pulmonary embolism;
- Restoration of unobstructed blood flow through the thrombosed vein;

- Preservation of venous valve function; and
- Prevention of recurrent thrombosis.

The current standard of treatment for achieving these goals is anticoagulant therapy (i.e., intravenous unfractionated heparin) to achieve a therapeutic partial thromboplastin time (PTT). After completion of an initial course of anticoagulation therapy, patients with venous thromboembolism (VTE) require continuing therapy to prevent recurrence. Thus, anticoagulation therapy is the standard against which PTA with or without stenting must be compared in order to evaluate the safety, efficacy, and final health outcomes. In addition, long-term follow-up is needed to determine the rates of restenosis, device failure, reoperation, and VTE recurrence.

The following literature appraisal is focused on the published evidence for DVT that is not related to left iliac vein compression syndrome or proximal upper extremity venous thrombosis.

Systematic Reviews

No systematic reviews were identified.

Randomized Controlled Trials

There are no randomized controlled clinical trials (RCTs) in which PTA with or without stenting was compared to standard medical management of DVT.

Nonrandomized Studies

- The bulk of the current literature investigating thrombolysis followed by angioplasty and stenting is limited to small (n<50), non-randomized, non-comparative retrospective reviews and case series of short- to medium-term duration.[4-9]
- The majority of studies are for DVT related to extrinsic compression (e.g., May-Thurner syndrome), or have heterogeneous patient populations that include both compression-related and non-compression-related DVT.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Studies for the diagnosis and treatment of idiopathic intracranial hypertension (IIH) must answer the following questions:

1. Is venous sinus occlusion the cause or the effect of increased intracranial pressure (ICP)?
2. Is venous PTA with or without stenting safe and effective in reducing ICP compared with conventional treatment?

To assess the effectiveness and safety of intracranial venous stenting as a treatment of IIH, health outcomes must be compared with current standard treatments. The ideal clinical trial design is random allocation of similar patients to active or sham venous angioplasty, and/or conventional medical or surgical treatments.

Systematic Reviews

Kalyvas (2021) published a systematic review of controlled and observational studies on surgical treatments of IIH, including CSF diversion techniques, optic nerve sheath fenestration, bariatric surgery, and venous sinus stenting.[10] One hundred and nine publications were

included in the review, consisting of three prospective observational studies, 74 retrospective case series, and 31 case reports. No randomized controlled trials were identified for inclusion in the review. Of the 2,302 predominately female (84.3%) patients included across studies, 825 underwent venous sinus stenting. Data specific to venous sinus stenting were from 47 studies, of which three were prospective, 29 were retrospective case series, and 14 were single case reports. Improved papilledema, visual fields and headaches following venous sinus stenting was reported as 87.1%, 72.7% and 72.1% of the patients respectively. Restenting or supplementary intervention was needed due to venography-documented restenosis in 3.4% of patents. Adequate data to generate estimates of 12-month failure rate for venous sinus stenting of 13.1% was available from 20 studies. Major complications were reported in 19 patients (2.3%) including subdural hematoma, intracerebral hematoma, subarachnoid hemorrhage, cerebellar hematoma, obstructive hydrocephalus, and death.

A 2015 updated Cochrane review evaluated the evidence for IIH interventions, and included RCTs in which any intervention used to treat IIH had been compared to placebo or another form of treatment.[11] Stenting of the transverse intracerebral venous sinus was assessed as a treatment, however the reviewers found no studies that met their inclusion criteria due to the lack of a control group for comparison. The review excluded five small case series, one retrospective review and two small clinical trials.

A 2014 systematic review of various treatments for IIH found only case series, of which 30 had extractable data.[12] Of the 332 total patients, 88 had venous sinus stenting. However, the studies only reported secondary outcomes related to symptoms of headache, papilledema, and visual acuity. The primary outcome of increased intracranial pressure was not reported. The authors concluded that the evidence was insufficient to recommend for or against any treatment modalities for IIH.

Randomized Controlled Trials

There are no randomized controlled clinical trials in which PTA with or without stenting was compared to standard medical or surgical management of IIH.

Nonrandomized Studies

Current evidence is limited to mainly small retrospective reviews and case series.[13-16] One of the largest studies was a retrospective review of 52 patients at a single center who underwent stenting due to IIH unresponsive to maximum acceptable medical treatment.[17] The follow-up period ranged from two months to nine years. All 52 patients were reported to have immediate elimination of the transverse sinus stenosis gradient and rapid improvement in IIH symptoms including resolution of papilledema. Six patients had relapse of symptoms (headache) and increased venous pressure with recurrent stenosis adjacent to the previous stent. In these patients, an additional stent was placed, with response similar to that following the first stent placement. Another retrospective study, published by Boddu (2019), included 70 consecutive patients who underwent venous sinus stenting for IIH and reported that 13% of the patients had impaired drainage of the vein of Labbé following treatment.[18]

ILIOFEMORAL VENOUS OBSTRUCTIVE DISEASE

Systematic Reviews

Ferreira (2021) published a systematic review of available data on mid-term (30 days to three years) stent patency rates and clinical outcomes of iliac stenting in post-thrombotic

syndrome.[19] Data from 1008 patients reported in 18 publications were included. The pooled technical success rate was 96%. The pooled primary and secondary patency rates were 98.2% and 100% at 30 days, 78.1% and 94.5% at 12 months and 66.3% and 89.4% at 36 months, respectively. Pooled rates of ulcer healing, pain and edema relief were 78.1%, 53.4% and 48.8%, respectively. Intraoperative venous injury was reported in four studies, with a pooled proportion rate of 28.0% (95% CI 14.1 to 44.5, I^2=91.4%). The most common minor complication, postoperative back pain, was reported in three studies at a rate of 57.1% (95% CI 46.3 to 67.6, I^2=73.9%). Two studies reported stent fracture at a rate of 5.9% (95% CI 3.1 to 9.4, I^2=18.6%). Stent migration was reported in one study. Bias at the outcome level was evaluated with the GRADE system in 14 of the studies; serious or very serious risk of bias was found in nine of the 14 studies assessed and the quality of all studies assessed was low or very low.

Nonrandomized Studies

A retrospective analysis of forty-two patients (27 women and 15 men with a mean age of 47.3 years) who underwent venous recanalization, pre-dilatation and stenting of the narrowed or occluded iliac and/or femoral veins to treat chronic femoro-iliac venous obstructive disease was published by Guillen (2020).[20] Severity of post-thrombotic syndrome (PTS) and quality of life were assessed at baseline and three months after the intervention respectively, using Villalta score and Chronic Venous Insufficiency Questionnaire (CIVIQ-20) scale. Results: Immediate technical success was achieved in 41/42 (97.6%) patients, without any major complications. Primary patency, primary assisted patency and secondary patency at the end of the median imaging follow-up of 18.1 months (IQR, 9.7 to 34.4) were achieved in 29/42 (66.7%) patients, 33/42 (78.6%) patients and 37/42 (88.1%) patients, respectively. Median Villalta and CIVIQ-20 scores decreased from 14 (IQR, 10 to 19) and 57 (IQR, 39 to 72) at baseline, respectively, to 5 (IQR, 2 to 9) and 30 (IQR, 24 to 50) three months after the procedure, respectively ($p<0.0001$), indicating significant decrease in the severity of PTS and improvement in quality of life. Of note, early in-stent thrombosis within one month occurred in 9/42 (21.4%) patients. This study is limited by its retrospective design, heterogeneity in the stent used, and lack of long-term outcome data.

Results of the VIRTUS trial (VIRTUS Safety and Efficacy of the Veniti Vici Venous Stent System When Used to Treat Clinically Significant Chronic Non-Malignant Obstruction of the Iliofemoral Venous Segment) were published by Razavi (2019).[21] This prospective, international, single-arm, FDA-IDE pivotal study evaluated the safety and effectiveness of a dedicated endovenous stent for symptomatic iliofemoral venous obstruction. One hundred and seventy patients (127 chronic post-thrombotic, mean age 54 years, 56.4% female) at 22 sites were treated with a self-expanding nitinol stent developed for dedicated use in the venous system (Vici Venous Stent System). Patients included those with ≥50% obstruction on venography and Clinical, Etiology, Anatomic, Pathophysiology clinical classification ≥3, or at least moderate leg pain with a Venous Clinical Severity Score of two or greater. Results: Freedom from a major adverse event through 30 days was 98.8%. Through one year, 54 device or procedure-related serious adverse events were reported in 28 (16.5%) of the patients. The one-year primary patency rate for the entire group was 84.0%. Venographic patency rates for the nonthrombotic and chronic post-thrombotic groups were 96.2% and 79.8%, respectively. At 12 months, 64% (85/132) of patients demonstrated at least a three-point reduction in Venous Clinical Severity Score. Long-term (five-year) outcomes are anticipated. This study was funded by both Veniti, Inc. and Boston Scientific, and at least one study author holds financial interest in the sponsoring company.

CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY (CCSVI) IN MULTIPLE SCLEROSIS (MS)

Systematic Reviews

A Cochrane review[22] and five systematic reviews[23-27] with critical analyses of the current literature concluded that there is insufficient evidence to verify a relationship between CCSVI and MS. The authors noted the high degree of heterogeneity between study outcomes, sensitivity, and specificity, and marked variability of odds ratios.

Two meta-analyses[28, 29] reported outcomes after exclusion of outlier studies (e.g., studies with a disproportionately high odds ratio (OR) and/or potential bias). Tsivgoulis (2014) reported on the association between CCSVI and MS and included 19 studies with a total of 1,250 MS patients and 899 healthy controls.[28] When data from all 19 studies were pooled, CCSVI was associated with MS with an OR of 8.35 (95% confidence interval [CI] 3.44 to 20.31, p<0.001). However, in additional sensitivity analyses, the OR associating CCSVI and MS decreased. In the most conservative sensitivity analysis, which excluded eight outlier studies, MS was not associated with CCSVI with an OR of 1.35 (95% CI 0.62 to 2.93, p=0.453). The Zwischenberger (2013) meta-analysis of 13 studies with a total of 1141 MS patients and 738 healthy controls reported CCSVI and MS was associated with MS (OR 2.57, p<0.001).[29] In a subsequent analysis of nine studies with four outliers (studies with disproportionately high ORs) removed, the OR decreased, but still associated CCSVI with MS.

A systematic review of the association between CCSVI and MS was published by Laupacis (2011).[26] This review included eight studies that used ultrasound to diagnose CCSVI by the Zamboni criteria and compared the rate of CCSVI in patients with MS to those without MS. These studies were mostly small, with the median number of patients with MS of 50. A large degree of heterogeneity existed across studies in the rate of CCSVI among MS patients. Two smaller studies reported a rate of 0% for CCSVI in a total of 20 and 56 patients with MS. In contrast, the original study by Zamboni (2009a) reported a 100% rate of CCSVI in 109 patients with MS.[30] A small study of 25 patients also reported a very high rate of CCSVI at 84% (21/25). There was no obvious reason identified for this large discrepancy in CCSVI rates; the authors hypothesized that the most likely reason was variability in ultrasound technique and interpretation. The analysis suggested a significant association of CCSVI with MS in combined analysis, with an OR of 13.5 (95% CI, 2.6 to 71.4). A substantial degree of heterogeneity existed in this measure as well, with a reported I2 of 89%. Several sensitivity analyses showed marked variability of the OR from a low of 3.7 to more than 58,000. However, in all cases the association of CCSVI with MS remained significant.

Another systematic review published in 2011 included a smaller number of studies (n=4) but reached conclusions similar to the other analyses.[27] The rate of CCSVI in MS patients ranged from 7% to 100%, and the rate in non-MS patients ranged from 2% to 36%. A significant association was detected between MS and CCSVI but with a high degree of heterogeneity (I^2=96%) and an OR for association that varied widely, from approximately 2 to more than 26,000.

A recently updated Cochrane review evaluated the evidence for PTA to treat CCSVI in patients with MS and included three RCTs, described in greater detail below (total n=238).[31] Two of the studies were judged to be at unclear risk of bias for one item (random sequence generation in one study and blinding in the other), but otherwise at low risk of bias. The authors concluded

that there was moderate-quality evidence that venous PTA did not improve health outcomes for patients with MS and that further study was not necessary.

Randomized Controlled Trials

A randomized wait list study by Napoli (2019) included 66 MS patients with a diagnosis of CCSVI who were randomized to receive venous PTA immediately or after six months.[32] A number of outcomes were assessed, including clinical-functional measures, evoked potentials and upper limb kinematic measures. While there were some statistically significant differences between groups for a composite functional outcome, there were no differences in evoked potential or upper limb kinematic measures.

The following three studies were included in the Cochrane review described above:

Traboulsee (2018) published a double-blind, sham-controlled RCT of balloon venoplasty for MS patients with narrowing of the extracranial jugular and azygos veins.[33] The trial included 104 patients, 49 randomized to venoplasty and 55 to sham treatment, and 103 patients completed the trial with 48 weeks of follow-up. Narrowing of the veins >50% was confirmed by venography prior to randomization. The primary outcome of the trial was change in the MS Quality of Life-54 (MSQOL-54) questionnaire from baseline at 48 weeks. Additional clinical and MRI outcomes were also evaluated. There was no difference found between groups for any of the study's outcomes, and the authors concluded that "for patients with MS, balloon venoplasty of extracranial jugular and azygous veins is not beneficial in improving patient-reported, standardized clinical, or MRI outcomes."

Results from the Brave Dreams trial were published by Zamboni (2018).[34] This was a double-blind, sham-controlled RCT conducted at six MS centers in Italy and included a total of 115 CCSVI patients. These patients were randomized to either venous PTA (n=76) or catheter venography without angioplasty (sham, n=39). There were two primary endpoints assessed at 12 months: the number of new or expanded cerebral lesions by MRI, and a functional measure that included walking control, manual dexterity, balance, postvoid residual urine volume, and visual acuity. There were no significant differences in these endpoints between groups, and no adverse events were reported. The authors concluded that venous PTA was "a safe but largely ineffective technique; the treatment cannot be recommended in patients with MS."

Siddiqui (2014) published results from a prospective, double-blind, sham-controlled RCT of venous angioplasty in MS patients with CCSVI.[35] This trial enrolled nine patients in intervention group and 10 in the sham-controlled group. All patients met the criteria for diagnosis of CCSVI.[36] The primary end points of the trial included safety at 24 hours and 30 days postangioplasty; greater than 75% restoration of venous outflow at 30 days; the presence of new MS lesions; and relapse rate over six months. Secondary end points included changes in disability scores, brain volume, cognitive test scores, and quality-of-life measures. All patients tolerated the procedures well; no operative or postoperative complications were identified. One patient in the angioplasty group experienced an episode of symptomatic bradycardia. No significant differences were observed in venous outflow characteristics between the treated and control groups, nor were any significant improvements observed in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients. However, the failure to show a beneficial effect of venous angioplasty on MS activity supports a lack of efficacy for this treatment.

Nonrandomized Studies

The studies that focused on the potential relationship between CCSVI and MS reported varying and contradictory outcomes. For example, while Zamboni (2009a) and other authors[30, 37-39] reported a strong association between CCSVI and MS, numerous studies have reported insignificant or no difference in the prevalence of CCSVI in MS patients compared to healthy controls, or no association between CCSVI and MS occurrence or symptoms[36, 38, 40-46].

The studies that focused on outcomes of PTA with or without stent placement reported few adverse events, but mixed efficacy outcomes.[47-53] For example, while Zamboni (2009b).[48] reported significant improvement in all measures for patients with relapsing-remitting MS, Kostecki (2011) reported a significant improvement only in heat intolerance and fatigue severity six months post endovascular treatment.[47] No trials were found that compared PTA with concurrent control groups. All authors noted the need for well-designed randomized clinical trials. Many authors asserted that PTA with or without stenting in these patients should not be performed outside the clinical trial setting.

Adverse Events

Burton (2011) described five patients who had undergone venoplasty and presented with complications of the procedure.[54] The complications were internal jugular vein stent thrombosis, cerebral sinovenous thrombosis, stent migration, cranial nerve injury, and injury associated with venous catheterization. There was not a denominator in these studies to determine the rate of these events.

Petrov (2011) reported on the safety profile of 495 venoplasty procedures performed in 461 patients with MS, including 98 stent implantations.[49] There were no deaths, major bleeding events, or acute exacerbations of MS. The most common procedure-related complication was vein dissection, which occurred in 3.0% of cases. Other complications included cardiac arrhythmias (1.2%), groin hematoma (1.0%), vein rupture (0.4%), and acute stent thrombosis (1.6%).

Mandato (2012) reported adverse events within 30 days of endovascular intervention for 240 patients with MS over an 8-month period.[55] Neck pain occurred in 15.6% of patients, most commonly following stent implantation. Headache occurred in 8.2% of patients and was persistent past 30 days in 1 patient (0.4%). Intraprocedural arrhythmias occurred in 1.3%, and one patient was diagnosed with a stress-induced cardiomyopathy following the procedure.

An FDA alert issued in May 2012 reported the potential for adverse events following endovascular interventions for MS.[56] Reports of adverse events obtained by FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This alert included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption because of the potential for harms.

PERCUTANEOUS TRANS-HEPATIC BALLOON AND/OR STENT ANGIOPLASTY

Systematic Reviews

Kyaw (2022) performed a systematic review to determine the efficacy and safety of percutaneous trans-hepatic balloon and/or stent angioplasty in the management of portal vein (PV) stenosis following pediatric liver transplantation.[57] There were 213 pediatric liver recipients who underwent PTA for PV stenosis in 19 included studies published between 1991 and 2019. Balloon angioplasty was the initial treatment in the majority (n=153). Primary stent

placement (n=34) was performed for elastic recoil, intimal tears and PV kinks and rescue stent placement (n=14) for recurrent PV stenosis following primary balloon angioplasty. The technical success was 97.6% to 100% overall, 97.6% to 100% for balloon angioplasty only, and 100% for primary stenting. The clinical success was 50% to 100% overall, 50% to 100% for balloon angioplasty only, and 100% for primary stenting. Long-term PV patency was 50% to 100% overall, 37.5% to 100% for balloon angioplasty only, and 100% for primary stenting. The authors comment that "Stent placement may be a primary option in selected cases and a reliable rescue option for recurrent portal vein stenosis following balloon-angioplasty-only".

PRACTICE GUIDELINE SUMMARY

DEEP VEIN THROMBOSIS

Two consensus-based clinical practice guidelines from the Society of Interventional Radiology and the American Heart Association, respectively, provided evidence appraisals and noted a benefit in venous stenting for DVT.[58, 59] However, the majority of the references listed were related to May-Thurner syndrome which is caused by extrinsic compression for which stenting is considered medically necessary. Both guidelines graded the available evidence as very limited.

The American Society of Hematology

The American Society of Hematology published a 2020 guideline for the treatment of deep vein thrombosis and pulmonary embolism which does not discuss venous angioplasty or venous stenting.[60]

Society of Vascular Surgery / American Venous Forum

In the 2014 joint guidelines published by Society of Vascular Surgery and American Venous Forum on the management of proximal chronic total venous occlusion/severe stenosis.[61] The guideline states the following:

> *In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, that is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.*

This was a grade 1 recommendation (strong) but the evidence was considered low/very low quality which was primarily focused on May-Thurner syndrome.

American College of Radiology (ACR)

ACR Appropriateness Criteria® for radiologic management of lower extremity venous insufficiency recommendation guidelines was updated in 2023 with no change to criterion related to this policy.[62]

The 2012 ACR Appropriateness Criteria® for radiologic management of lower extremity venous insufficiency recommendation did not address angioplasty or stenting for these indications.[62, 63] However, they suggest that patients with venous insufficiency and associated venous occlusion or stenosis of the common iliac vein may require venous recanalization with

angioplasty and stenting as an adjunctive treatment, based on three case reports and one small retrospective analysis.

CHRONIC ILIOFEMORAL VENOUS OBSTRUCTION

Society of Interventional Radiology

A 2023 position statement on the endovascular placement of metallic stents for the management of chronic iliofemoral venous obstruction by the Society of Interventional Radiology (SIR) concluded that "the use of endovascular stent placement for chronic iliofemoral venous obstruction to be likely to help selected patients, but the risks and benefits have not been fully quantified in well-designed randomized studies."[64] They recommended the urgent completion of such studies.

CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY IN MULTIPLE SCLEROSIS (MS)

Society of Interventional Radiology

In 2010 the SIR published a position statement on the association of CCSVI with MS and the efficacy of endovascular treatments.[65] Their recommendations included the following statements:

- At present, SIR considers the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS.
- SIR strongly supports the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies, and is actively working to promote and expedite the completion.

SUMMARY

There is enough research to show that percutaneous venous angioplasty, with or without stenting, can improve health outcomes for patients with certain types of venous stenosis. Therefore, this angioplasty may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that percutaneous venous angioplasty, with or without stenting, can improve health outcomes for patients that do not meet the policy criteria, including patients with deep vein thrombosis that is not related to upper extremity venous compression requiring rib resection or iliac vein compression syndrome, or in patients with chronic cerebrospinal venous insufficiency venous sinus obstruction or occlusion in idiopathic intracranial hypertension. Therefore, this procedure is considered investigational when policy criteria are not met.

REFERENCES

1. Braunwald. *Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Copyright ©*: W. B. Saunders Company, p. 1498, pp.

2. Urschel HC, Jr., Patel AN. Paget-Schroetter syndrome therapy: failure of intravenous stents. *Ann Thorac Surg.* 2003;75(6):1693-6; discussion 96. PMID: 12822601
3. AbuRahma AF, Perkins SE, Wulu JT, et al. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. *Ann Surg.* 2001;233(6):752-60. PMID: 11371733
4. Cho YP, Ahn JH, Choi SJ, et al. Endovascular management of iliofemoral deep venous thrombosis due to iliac vein compression syndrome in patients with protein C and/or S deficiency. *J Korean Med Sci.* 2004;19(5):729-34. PMID: 15483352
5. Jeon YS, Yoon YH, Cho JY, et al. Catheter-directed thrombolysis with conventional aspiration thrombectomy for lower extremity deep vein thrombosis. *Yonsei Med J.* 2010;51(2):197-201. PMID: 20191009
6. Kim BJ, Chung HH, Lee SH, et al. Single-session endovascular treatment for symptomatic lower extremity deep vein thrombosis: a feasibility study. *Acta Radiol.* 2010;51(3):248-55. PMID: 20201636
7. Kurklinsky AK, Bjarnason H, Friese JL, et al. Outcomes of venoplasty with stent placement for chronic thrombosis of the iliac and femoral veins: single-center experience. *Journal of vascular and interventional radiology : JVIR.* 2012;23(8):1009-15. PMID: 22698971
8. Engelberger RP, Fahrni J, Willenberg T, et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis. *Thromb Haemost.* 2014;111:1153-60. PMID: 24477468
9. Karageorgiou J, Fowler K, Vedantham S, et al. Endovascular intervention for deep venous thrombosis in patients with inferior vena cava filters. *Vascular medicine (London, England).* 2016;21(5):459-66. PMID: 27178760
10. Kalyvas A, Neromyliotis E, Koutsarnakis C, et al. A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH). *Neurosurg Rev.* 2021;44(2):773-92. PMID: 32335853
11. Piper RJ, Kalyvas AV, Young AM, et al. Interventions for idiopathic intracranial hypertension. *The Cochrane database of systematic reviews.* 2015(8):CD003434. PMID: 26250102
12. Lai LT, Danesh-Meyer HV, Kaye AH. Visual outcomes and headache following interventions for idiopathic intracranial hypertension. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia.* 2014;21(10):1670-78. PMID: 24974193
13. Kumpe DA, Bennett JL, Seinfeld J, et al. Dural sinus stent placement for idiopathic intracranial hypertension. *Journal of neurosurgery.* 2012;116(3):538-48. PMID: 22149379
14. Fields JD, Javedani PP, Falardeau J, et al. Dural venous sinus angioplasty and stenting for the treatment of idiopathic intracranial hypertension. *Journal of neurointerventional surgery.* 2013;5(1):62-8. PMID: 22146571
15. Bussiere M, Falero R, Nicolle D, et al. Unilateral transverse sinus stenting of patients with idiopathic intracranial hypertension. *AJNR American journal of neuroradiology.* 2010;31(4):645-50. PMID: 19942702
16. Radvany MG, Solomon D, Nijjar S, et al. Visual and neurological outcomes following endovascular stenting for pseudotumor cerebri associated with transverse sinus stenosis. *Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society.* 2013;33(2):117-22. PMID: 23502837

17. Ahmed RM, Wilkinson M, Parker GD, et al. Transverse sinus stenting for idiopathic intracranial hypertension: a review of 52 patients and of model predictions. *AJNR American journal of neuroradiology.* 2011;32(8):1408-14. PMID: 21799038
18. Boddu SR, Gobin YP, Dinkin M, et al. Impaired drainage of vein of Labbe following venous sinus stenting for idiopathic intracranial hypertension. *Journal of neurointerventional surgery.* 2019;11(3):300-06. PMID: 30219791
19. Ferreira AM, Oliveira-Pinto J, Duarte-Gamas L, et al. Mid-term patency of iliac venous stenting for post-thrombotic syndrome. *Int Angiol.* 2021;40(3):196-205. PMID: 33739078
20. Guillen K, Falvo N, Nakai M, et al. Endovascular stenting for chronic femoro-iliac venous obstructive disease: Clinical efficacy and short-term outcomes. *Diagnostic and interventional imaging.* 2020;101(1):15-23. PMID: 31036535
21. Razavi MK, Black S, Gagne P, et al. Pivotal Study of Endovenous Stent Placement for Symptomatic Iliofemoral Venous Obstruction. *Circulation Cardiovascular interventions.* 2019;12(12):e008268. PMID: 31833414
22. van Zuuren EJ, Fedorowicz Z, Pucci E, et al. Percutaneous transluminal angioplasty for treatment of chronic cerebrospinal venous insufficiency in people with multiple sclerosis: a summary of a Cochrane systematic review. *Journal of neurology, neurosurgery, and psychiatry.* 2014;85(4):405-10. PMID: 23781006
23. Awad AM, Marder E, Milo R, et al. Multiple sclerosis and chronic cerebrospinal venous insufficiency: a critical review. *Ther Adv Neurol Disord.* 2011;4(4):231-5. PMID: 21765873
24. Zecca C, Gobbi C. Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis (MS): A Critical Review. *CNS Neurol Disord Drug Targets.* 2011. PMID: 21838669
25. Bagert BA, Marder E, Stuve O. Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis. *Arch Neurol.* 2011. PMID: 21747006
26. Laupacis A, Lillie E, Dueck A, et al. Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2011;183(16):E1203-12. PMID: 21969411
27. Thapar A, Lane T, Nicholas R, et al. Systematic review of sonographic chronic cerebrospinal venous insufficiency findings in multiple sclerosis. *Phlebology / Venous Forum of the Royal Society of Medicine.* 2011;26(8):319-25. PMID: 22021635
28. Tsivgoulis G, Sergentanis TN, Chan A, et al. Chronic cerebrospinal venous insufficiency and multiple sclerosis: a comprehensive meta-analysis of case-control studies. *Ther Adv Neurol Disord.* 2014;7:114-36. PMID: 24587827
29. Zwischenberger BA, Beasley MM, Davenport DL, et al. Meta-analysis of the correlation between chronic cerebrospinal venous insufficiency and multiple sclerosis. *Vasc Endovascular Surg.* 2013;47:620-4. PMID: 24005191
30. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry.* 2009;80(4):392-9. PMID: 19060024
31. Jagannath VA, Pucci E, Asokan GV, et al. Percutaneous transluminal angioplasty for treatment of chronic cerebrospinal venous insufficiency (CCSVI) in people with multiple sclerosis. *The Cochrane database of systematic reviews.* 2019;5:CD009903. PMID: 31150100
32. Napoli V, Berchiolli R, Carboncini MC, et al. Percutaneous Venous Angioplasty in Patients with Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency: A

Randomized Wait List Control Study. *Annals of vascular surgery.* 2019. PMID: 31445091
33. Traboulsee AL, Machan L, Girard JM, et al. Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial. *Neurology.* 2018;91(18):e1660-e68. PMID: 30266886
34. Zamboni P, Tesio L, Galimberti S, et al. Efficacy and Safety of Extracranial Vein Angioplasty in Multiple Sclerosis: A Randomized Clinical Trial. *JAMA neurology.* 2018;75(1):35-43. PMID: 29150995
35. Siddiqui AH, Zivadinov R, Benedict RH, et al. Prospective randomized trial of venous angioplasty in MS (PREMiSe). *Neurology.* 2014;83(5):441-9. PMID: 24975855
36. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology.* 2011;77(2):138-44. PMID: 21490322
37. Floris R, Centonze D, Fabiano S, et al. Prevalence study of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: preliminary data. *La Radiologia medica.* 2012;117(5):855-64. PMID: 22228125
38. Centonze D, Floris R, Stefanini M, et al. Proposed chronic cerebrospinal venous insufficiency criteria do not predict multiple sclerosis risk or severity. *Ann Neurol.* 2011;70(1):51-8. PMID: 21786298
39. Weinstock-Guttman B, Ramanathan M, Marr K, et al. Clinical correlates of chronic cerebrospinal venous insufficiency in multiple sclerosis. *BMC neurology.* 2012;12:26. PMID: 22587224
40. Auriel E, Karni A, Bornstein NM, et al. Extra-cranial venous flow in patients with multiple sclerosis. *J Neurol Sci.* 2011;309(1-2):102-4. PMID: 21820131
41. Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol.* 2011;69(1):90-9. PMID: 21280079
42. Baracchini C, Perini P, Causin F, et al. Progressive multiple sclerosis is not associated with chronic cerebrospinal venous insufficiency. *Neurology.* 2011;77(9):844-50. PMID: 21849656
43. Doepp F, Paul F, Valdueza JM, et al. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol.* 2010;68(2):173-83. PMID: 20695010
44. Mayer CA, Pfeilschifter W, Lorenz MW, et al. The perfect crime? CCSVI not leaving a trace in MS. *Journal of neurology, neurosurgery, and psychiatry.* 2011;82(4):436-40. PMID: 21296899
45. Barreto AD, Brod SA, Bui TT, et al. Chronic cerebrospinal venous insufficiency: Case-control neurosonography results. *Ann Neurol.* 2013;73(6):721-8. PMID: 23418024
46. Zivadinov R, Cutter G, Marr K, et al. No association between conventional brain MR imaging and chronic cerebrospinal venous insufficiency in multiple sclerosis. *AJNR American journal of neuroradiology.* 2012;33(10):1913-7. PMID: 22576891
47. Kostecki J, Zaniewski M, Ziaja K, et al. An endovascular treatment of Chronic Cerebro-Spinal Venous Insufficiency in Multiple Sclerosis patients - 6 month follow-up results. *Neuro Endocrinol Lett.* 2011;32(4). PMID: 21876515
48. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg.* 2009;50(6):1348-58 e1-3. PMID: 19958985
49. Petrov I, Grozdinski L, Kaninski G, et al. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Endovasc Ther.* 2011;18(3):314-23. PMID: 21679067

50. Ludyga T, Kazibudzki M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? *Phlebology / Venous Forum of the Royal Society of Medicine.* 2010;25(6):286-95. PMID: 21107001
51. Zamboni P, Galeotti R, Weinstock-Guttman B, et al. Venous angioplasty in patients with multiple sclerosis: results of a pilot study. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2012;43(1):116-22. PMID: 21839654
52. Hubbard D, Ponec D, Gooding J, et al. Clinical improvement after extracranial venoplasty in multiple sclerosis. *Journal of vascular and interventional radiology : JVIR.* 2012;23(10):1302-8. PMID: 22951366
53. Ulivelli M, Monti L, Ballerini M, et al. Prospective study of clinical, neurophysiological and urodynamic findings in multiple sclerosis patients undergoing percutaneous transluminal venous angioplasty. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2019;130(1):138-44. PMID: 30537671
54. Burton JM, Alikhani K, Goyal M, et al. Complications in MS Patients after CCSVI Procedures Abroad (Calgary, AB). *Can J Neurol Sci.* 2011;38(5):741-6. PMID: 21856578
55. Mandato KD, Hegener PF, Siskin GP, et al. Safety of endovascular treatment of chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. *Journal of vascular and interventional radiology : JVIR.* 2012;23(1):55-9. PMID: 22088659
56. FDA News Release: FDA issues alert on potential dangers of unproven treatment for multiple sclerosis. [cited 10/14/2016]. 'Available from:' http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm303538.htm?source=govdelivery.
57. Kyaw L, Lai NM, Iyer SG, et al. Percutaneous transhepatic interventional therapy of portal vein stenosis in paediatric liver transplantation: A systematic review of efficacy and safety. *Pediatr Transplant.* 2022;26(2):e14187. PMID: 34724594
58. Vedantham S, Millward SF, Cardella JF, et al. Society of Interventional Radiology position statement: treatment of acute iliofemoral deep vein thrombosis with use of adjunctive catheter-directed intrathrombus thrombolysis. *Journal of vascular and interventional radiology : JVIR.* 2009;20(7 Suppl):S332-5. PMID: 19560020
59. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011;123(16):1788-830. PMID: 21422387
60. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4:4693-738. PMID: 33007077
61. O'Donnell TF, Jr., Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. *J Vasc Surg.* 2014;60(2 Suppl):3S-59S. PMID: 24974070
62. American College of Radiology Appropriateness Criteria® for radiologic management of lower extremity venous insufficiency- Update. [cited 11/28/2023]. 'Available from:' https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria.
63. American College of Radiology Appropriateness Criteria® for radiologic management of lower extremity venous insufficiency. [cited 11/28/2023]. 'Available from:' https://acsearch.acr.org/docs/69507/Narrative/.

64. Vedantham S, Weinberg I, Desai KR, et al. Society of Interventional Radiology Position Statement on the Management of Chronic Iliofemoral Venous Obstruction with Endovascular Placement of Metallic Stents. *Journal of vascular and interventional radiology : JVIR.* 2023;34(10):1643-57.e6. PMID: 37330211
65. Vedantham S, Benenati JF, Kundu S, et al. Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association. *Journal of vascular and interventional radiology : JVIR.* 2010;21(9):1335-7. PMID: 20800776

CODES

Codes	Number	Description
CPT	36481	Percutaneous portal vein catheterization by any method
	36901	Introduction of needle(s) and/or catheter(s), dialysis circuit, with diagnostic angiography of the dialysis circuit, including all direct puncture(s) and catheter placement(s), injection(s) of contrast, all necessary imaging from the arterial anastomosis and adjacent artery through entire venous outflow including the inferior or superior vena cava, fluoroscopic guidance, radiological supervision and interpretation and image documentation and report
	36902	;with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty
	36903	;with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis segment
	36904	Percutaneous transluminal mechanical thrombectomy and/or infusion for thrombolysis, dialysis circuit, any method, including all imaging and radiological supervision and interpretation, diagnostic angiography, fluoroscopic guidance, catheter placement(s), and intraprocedural pharmacological thrombolytic injection(s)
	36905	;with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty
	36906	;with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis circuit
	36907	Transluminal balloon angioplasty, central dialysis segment, performed through dialysis circuit, including all imaging and radiological supervision and interpretation required to perform the angioplasty (List separately in addition to code for primary procedure)
	36908	Transcatheter placement of intravascular stent(s), central dialysis segment, performed through dialysis circuit, including all imaging radiological supervision and interpretation required to perform the stenting, and all angioplasty in the central dialysis segment (List separately in addition to code for primary procedure)
	36909	Dialysis circuit permanent vascular embolization or occlusion (including main circuit or any accessory veins), endovascular, including all imaging and radiological supervision and interpretation necessary to complete the intervention (List separately in addition to code for primary procedure)

	37238	Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; initial vein
	37239	; each additional vein (List separately in addition to code for primary procedure)
	37248	Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; initial vein
	37249	;each additional vein (List separately in addition to code for primary procedure)
HCPCS	C2623	Catheter, transluminal angioplasty, drug-coated, non-laser

Date of Origin: *January 1996*

Regence

Medical Policy Manual Surgery, Policy No. 110

Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)

Effective: January 1, 2024

Next Review: November 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transesophageal endoscopic therapies are a group of minimally invasive antireflux procedures being investigated as alternatives to medical management or fundoplication surgery in the treatment of GERD.

MEDICAL POLICY CRITERIA

Transesophageal endoscopic therapies are considered **investigational** for the treatment of gastroesophageal reflux disease (GERD). These procedures include but are not limited to the following:

I. Transesophageal endoscopic gastroplasty procedure (i.e., MUSE)
II. Transoral incisionless fundoplication (TIF) procedure, (i.e., EsophyX)
III. Transesophageal radiofrequency energy procedure (i.e., Stretta)
IV. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (i.e., Durasphere, polymethylmethacrylate [PMMA] beads, the Gatekeeper Reflux Repair system)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Bariatric Surgery, Surgery, Policy No. 58
2. Gastric Reflux Surgery, Surgery, Policy No. 186
3. Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD), Surgery, Policy No. 190

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common disorder characterized by heartburn and other symptoms related to reflux of stomach acid into the esophagus. Nearly all individuals experience such symptoms at some point in their lives; a smaller number have chronic symptoms and are at risk for complications of GERD. The prevalence of GERD has been estimated to be 10% to 20% in the Western world, with a lower prevalence in Asia.[1]

The pathophysiology of GERD involves excessive exposure to stomach acid, which occurs for several reasons. There can be an incompetent barrier between the esophagus and stomach, either due to dysfunction of the lower esophageal sphincter (LES) or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid by the esophagus. In this situation, delayed clearance leads to an increased reservoir of stomach acid and a greater tendency to reflux.

In addition to troubling symptoms, some patients will have more serious disease, which results in complications such as erosive esophagitis, dysphagia, Barrett esophagus, and esophageal carcinoma. Pulmonary complications may result from aspiration of stomach acid into the lungs and can include asthma, pulmonary fibrosis and bronchitis, or symptoms of chronic hoarseness, cough, and sore throat.

Guidelines on the management of GERD emphasize initial medical management. Weight loss, smoking cessation, head of bed elevation, and elimination of food triggers are all recommended in recent practice guidelines.[1] Proton pump inhibitors (PPIs) have been shown to be the most effective medical treatment. In a Cochrane systematic review, PPIs demonstrated superiority to H_2-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.[2]

The most common surgical procedure used for GERD remains laparoscopic Nissen fundoplication, however, the utilization of this procedure steadily declined between 2009 and 2013 with the advancement of novel nonmedical (endoscopic and surgical) techniques.[3] Fundoplication involves wrapping a portion of the gastric fundus around the distal esophagus to increase LES pressure. If a hiatal hernia is present, the procedure also restores the position of the LES to the correct location. Laparoscopic fundoplication was introduced in 1991 and has been rapidly adopted because it avoids complications associated with an open procedure.

Although fundoplication results in a high proportion of patients reporting symptom relief, complications can occur, and sometimes require conversion to an open procedure. Patients who have relief of symptoms of GERD after fundoplication may have dysphagia or gas-bloat syndrome (excessive gastrointestinal gas).

Due in part to the high prevalence of gastroesophageal reflux disease, there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. This type of procedure may be

considered natural orifice transluminal surgery. Three types of procedures have been investigated.

1. Transesophageal endoscopic gastroplasty (gastroplication, transoral incisionless fundoplication) can be performed as an outpatient procedure. During this procedure, the fundus of the stomach is folded, and then held in place with staples or fasteners that are deployed by the device. The endoscopic procedure is designed to recreate a valve and barrier to reflux.

2. Radiofrequency (RF) energy has been used to produce submucosal thermal lesions at the gastroesophageal junction. (This technique has also been referred to as the Stretta procedure). Specifically, RF energy is applied through four electrodes inserted into the esophageal wall at multiple sites both above and below the squamocolumnar junction. The mechanism of action of the thermal lesions is not precisely known but may be related to ablation of the nerve pathways responsible for sphincter relaxation or may induce a tissue-tightening effect related to heat-induced collagen contraction and fibrosis.

3. Submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter has also been investigated.

One bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®), has been evaluated. The Gatekeeper™ Reflux Repair System (Medtronic) utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa, and with time, the prosthesis absorbs water and expands, creating bulk in the region of implantation. However, the only identified RCT on this system was terminated early due to lack of efficacy (NCT00200044). Endoscopic submucosal implantation of polymethylmethacrylate (PMMA) beads into the lower esophageal folds has also been investigated.

REGULATORY STATUS

In 2007, EsophyX® (EndoGastric Solutions, Redmond, WA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing (K160960) by FDA through the 510(k) process for use in transoral tissue approximation, full thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernia of 2 cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD).[4] In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and in patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces the hernia to 2 cm or less.[5] FDA product code: ODE.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus) was cleared for marketing by FDA through the 510(k) process in 2012 (K120299) and 2014 (K132151). MUSE is intended for endoscopic placement of surgical staples in the soft tissue of the esophagus and stomach to create anterior partial fundoplication for treatment of symptomatic chronic GERD in patients who require and respond to pharmacologic therapy. FDA product code: ODE.

In 2000, the CSM Stretta® System was cleared for marketing by FDA through the 510(k) process for general use in the electrosurgical coagulation of tissue and is specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics (Greenwich, CT). FDA product code: GEI.

Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence. Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the United States "intended to treat problems associated with GERD."

EVIDENCE SUMMARY

MULTIPLE ENDOSCOPIC PROCEDURES

Systematic Reviews

A 2005 report of the Agency for Healthcare Research and Quality (AHRQ), on "Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease," indicated additional efficacy and safety data on new endoscopic approaches were needed.[6] A 2011 update of the AHRQ report excluded Enteryx and the NDO Plicator, since they were no longer available in the U.S., and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review.[7] The 2011 update reported the following:

> The AHRQ report concluded that for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remains substantially uncertain for the long-term management of GERD. While some clinical benefits were observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating; complications which are also side effects associated with laparoscopic fundoplication[8] Higher quality studies are needed to determine the role and value of endoscopic procedures in the treatment of patients with GERD. A 2015 review of endoscopic treatment of GERD noted that EndoCinch is no longer manufactured.[9]

A systematic review was conducted in 2009 to examine 7 endoscopic treatments for GERD that included 33 studies, only 2 of which were RCTs.[10] The remainder were case series. The authors concluded, "…despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long term."

TRANSESOPHAGEAL ENDOSCOPIC GASTROPLASTY AND TRANSORAL INCISIONLESS FUNDOPLICATION (TIF)

Systematic Reviews

Haseeb (2023) conducted a systematic review and meta-analysis that assessed the efficacy of TIF, using the EsophyX device, which uses a minimally invasive endoscopic fundoplication method, for atypical GERD symptoms in patients with chronic or refractory GERD.[11] All study types were included that assessed atypical GERD using the reflux symptom index questionnaire. Data on TIF with concomitant hiatal hernia repair were also included. 10 studies (n=564 patients) were analyzed. At 6- and 12- month follow-up, there was a mean reduction of 15.72 (95% confidence interval, 12.15 to 19.29) and 14.73 (95% confidence interval, 11.74 to 17.72) points, respectively, in the reflux symptom index score post-TIF. At both follow-ups,

more than two-thirds of patients were satisfied with their health condition and approximately three-fourths of patients were no longer taking daily proton pump inhibitors. Limitations of this meta-analysis include heterogeneity across studies for self-reported patient satisfaction and methodological quality of included studies.

Testoni (2021) published a systematic review with meta-analysis focusing on long-term (≥3 years) outcomes of patients with GERD undergoing TIF (using either EsophyX or MUSE).[12] Outcomes of interest included patient satisfaction, QOL, and PPI use. The mean follow-up time across studies was 5.3 years (range: 3 to 10 years). Daily PPI use was 100% in five studies, 97% in one study, and was not provided in the other two studies. Overall, the pooled proportion of patient-reported satisfaction before and after TIF was 12.3% and 70.6%, respectively. Additionally, the pooled rates of patients completely off, or on occasional, PPIs post-TIF was 53.8% and 75.8%. The analysis was limited by various factors including the nature of included studies, which involved only one open-label RCT among the eight studies included, and the high heterogeneity across studies for patient reported overall satisfaction after the TIF procedure.

McCarty (2018) published a systematic review of RCTs and nonrandomized studies that showed significant improvement in a number of clinical outcomes for patients treated with TIF.[13] For example, 89% of TIF patients discontinued PPI therapy after the procedure, and the Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire, Gastroesophageal Reflux Symptom Score, and Reflux Symptom Index (RSI) measures showed significant improvement. The review had several limitations, including the risk of heterogeneity bias, due to the inclusion of studies of first- and second-generation TIF devices and protocols.

Richter (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication (LNF) with sham or PPIs.[14] The meta-analysis was limited by low-quality studies (one did not report randomization method, others lacked data on allocation concealment, blinding of outcome assessors, or other aspects of study protocol). It should be noted that a reason behind for scarcity of direct comparisons between TIF and LNF is the discrepancy in populations requiring the respective treatments: consequently, TIF studies included patients with mild esophagitis and small hiatal hernias (<2 cm), while LNF studies included patients with Los Angeles grade A, B, C, or D esophagitis and all sizes of hiatal hernias.

Randomized Controlled Trials

In 2018, Trad reported five-year outcomes on the manufacturer-sponsored TEMPO randomized controlled trial (RCT).[15] Three-year results were reported in 2016[16], other interim results were previously reported as well.[17, 18] Below are highlights from each publication:

- Participants with small or absent hiatal hernias (<2cm) and GERD symptoms while on PPI therapy for at least six months who also had abnormal esophageal acid exposure (EAE) were randomized to either EsophyX® (n=40) treatment or PPI therapy (n=23). After six months of evaluation, 21 remaining PPI therapy participants elected to crossover to EsophyX.
- At three years follow-up, 52 participants were assessed for (1) GERD symptom resolution, (2) healing of esophagitis using endoscopy, (3) EAE, and (4) discontinuation of PPI use. Two participants required revision surgery. As assessed by questionnaire

(the Reflux Disease Questionnaire [RDQ], and the Reflux Symptom Index [RSI]), primary outcomes of GERD resolution and elimination of all troublesome atypical symptoms was observed in 37/40 participants, and 42/48 participants, respectively.

- At five years follow-up, data were available for 44 patients, of whom 37 (86%) showed elimination of troublesome regurgitation at 5 years. Twenty (43%) patients were completely off PPIs at the 5-year follow-up, and 31 (70%) patients expressed satisfaction with the procedure, as assessed by the GERD-HRQL scores. While data on pH normalization were available for 24 patients at the 3-year follow-up, at 5 years, 22% (n=5) of these patients could not be assessed for pH normalization.
- Although mean symptom scores were reportedly improved, standard deviations for primary (and secondary) outcomes suggest a wide range of responses and further well-designed studies may be warranted.

In 2015, four RCTs that compared the EsophyX® device to proton pump inhibitor (PPI) treatment or to a sham control were identified, two of which were industry sponsored. The studies differed in whether patients' symptoms were or were not controlled on PPI therapy, in the control used (i.e., sham, sham plus PPI, PPI alone), whether patients were blinded to treatment, and in outcome measures. Included in the studies were patients on daily PPI therapy for moderate-to-severe GERD symptoms. Exclusion criteria common to the RCTs are body mass index (BMI) over 35 kg/m^2, hiatal hernia greater than 2 cm; esophagitis grade C or D; Barrett esophagus greater than 2 cm, and esophageal ulcer. Most studies allowed crossover to the other intervention with continued follow-up after the randomized portion of the study.

The largest RCT with the lowest risk of bias was an industry-sponsored, double-blind, sham-controlled multicenter study (RESPECT) that evaluated TIF in patients whose symptoms were not well controlled on PPIs.[19] Of 696 patients screened, 129 met inclusion and exclusion criteria and were randomized in a 2:1 ratio; 87 patients received TIF with EsophyX®-2 combined with 6 months of placebo (TIF/placebo) and 42 patients received sham surgery with 6 months of daily PPI therapy (sham/PPI). The primary outcome measure was elimination of troublesome regurgitation, defined as mild symptoms for 2 or more days per week or moderate-to-severe symptoms for more than 1 day per week. Crossover was allowed at 3 months in the case of treatment failure or at 6 months when the blind was broken. Lack of response at 3 months was observed in 36% of patients in the sham/PPI group compared with 11% in the TIF/placebo group (p=0.002). Self-reported regurgitation was eliminated in 22% more patients following TIF compared to continued PPI therapy patients (67% vs 45%, p=0.023), while reductions in GERD symptoms scores were similar in the 2 groups. The objective measure of control of esophageal pH was significantly reduced after TIF (mean percent time esophageal pH <4 decreased from 9.3% to 6.3%, p<0.001), but not after sham surgery (from 8.6% to 8.9%). By the 18-month follow-up, 71% of patients in the sham/PPI group had crossed over to TIF, compared with 28% of patients in the TIF/placebo group who resumed PPI therapy (p<0.001). There were 5 moderate-to-severe complications in the TIF group compared to one in the sham group. Strengths of this study include the use of both sham surgery and placebo control to maintain double-blinding, adequate power, objective as well as subjective outcome measures, and use of intention-to-treat analysis. A limitation is the relatively short duration of follow-up for most outcome measures.

Several other RCTs from 2015 have evaluated TIF in patients whose symptoms are at least partially controlled by PPI therapy.

Hakonsson reported a double-blind, sham-controlled randomized trial with 44 patients who had moderate-to-severe GERD symptoms without PPI therapy.[20] Controls received a sham procedure, and the primary outcome was the time in remission, which was longer following TIF than sham (197 days vs 107 days, p<0.0001). Secondary outcomes measuring GERD symptoms showed results consistent with more favorable outcomes in the TIF group, however, no statistical between-group analysis was reported for these outcomes. Dysphagia, bloating, and flatulence were reported in twice as many patients undergoing TIF (4, 4, and 2 respectively) compared with sham (2, 2, and 1, respectively). These were reported as not statistically different, however, it is unlikely that the study was powered to detect differences in these outcomes.

Witteman reported an unplanned interim analysis of an RCT of 60 patients randomized to TIF using EsophyX®-2 or continued PPI therapy.[21] Sixty of the planned 120 patients had been recruited at the time of analysis. The patients' symptoms were adequately controlled by PPIs but they wanted to avoid lifelong PPI therapy. At 6 months, subjective GERD symptoms improved to a greater extent in the TIF group (p<0.001), and satisfaction scores were higher (50% satisfied vs 0%), but there was no significant difference in esophageal acid exposure (p=0.228) or pH normalization (50% vs 63%) between the TIF and PPI groups, respectively. At 12 months after TIF, normalization of pH was achieved in only 29% of patients and there was deteriorated valve appearance at endoscopy; 61% of TIF patients had resumed use of PPIs.

Trad reported 6- and 12-month results of an industry-funded, multicenter RCT (TEMPO) that compared TIF using EsophyX®-2 (n=40) versus maximal dose PPI therapy (n=23) in partial responders to PPI therapy.[17, 18] At the 6-month follow-up, the subjective measure of troublesome regurgitation was eliminated in 97% of TIF patients versus 50% of PPI patients (relative risk, 1.9; p=0.006). At 6 months, 90% of patients in the TIF group had completely stopped PPI therapy. However, the objective measure of normalized esophageal acid exposure did not differ significantly between groups (TIF=54% vs PPI=52%, p=0.914). At 12 months after TIF, 77% of patients had symptom control, 82% had stopped PPI therapy, 100% had healed esophagitis, and 45% had normalized esophageal acid exposure.

Additional controlled trials (RCTs) comparing transesophageal endoscopic gastroplasty or plication procedures to sham or other endoscopic procedures have been identified.[18, 22-27] Though these studies showed a promising decrease in PPI use and symptom control at 3 to 12 months, they do not allow conclusions regarding long-term health outcomes, safety or durability of the procedure in patients with GERD for one or more of the following reasons:

Insufficient study durations – Only short-term follow-up of 3 to 12 months is available, which does not address the long-term safety and durability of the procedures.[18, 23-28] For example, there may be suture loss over time. One study reported up to 29 % of study subjects required a second procedure at 12-month follow-up.[23] Of these patients, 72% of sutures were still present but only 19% were judged functional. A second study noted marked loss of sutures with 67% remaining at 12 months.[25]

Small sample size – Given the prevalence of GERD in the general population, available randomized trials include very small sample sizes. The largest study of 159 patients had an almost 10% loss in reported data with an intention to treat analysis that did not include these patients. All other studies include sample sizes of 60 or fewer patients. It is unclear if these studies are adequately powered.[18, 23, 25-29]

Unreliable endpoints – The use of subjective, point in time GERD questionnaires as a primary endpoint may give variable results depending upon symptoms present at the time the subject completes the questionnaire.[18, 23, 24]

Improvement over the gold standard procedures was not demonstrated. In order to establish the efficacy of transoral procedures, an improvement in symptoms of gastric reflux over the current open or laparoscopic anti-reflux procedures, must be shown.[18, 27, 29]

There is a single randomized trial of the TIF procedure, which compares TIF to Nissen laparoscopic fundoplication.[28] Although the authors reported comparable results at 12 months, conclusions based upon this trial are limited by the small sample size (n=52) and the different methods used for TIF (both the Plicator® and the EsophyX).

Nonrandomized Studies

Observational studies[30-63], registry data[64, 65] nonrandomized comparative studies[66] of gastroplication and fundoplication (specifically, transoral incisionless fundoplication) procedures do not allow conclusions about their long-term effectiveness and durability.

Case Series

Bell (2021) evaluated the durability of TIF with the EsophyX2 in 151 patients via a single institution prospective registry between November 2008 and July 2015.[62] Of these patients, the average duration of GERD symptoms was 11.3 years and 78% reported moderate to severe ongoing symptoms preoperatively despite PPI therapy. Eighty-six percent (n=131) were available for follow-up at a median of 4.92 years (0.7 to 9.7 years). Results revealed a reduction in the median GERD-HRQL scores from 21 (off PPI) and 14 (on PPI) at baseline to 4 (at 4.92 years) and 5 (at 5 to 9 years post-TIF). A successful (>50%) reduction in GERD-HRQL score at 4.92 years was seen in 64% of evaluable patients and 68% of patients followed for ≥5 years. Thirty-three (22%) of TIP patients underwent laparoscopic revisional surgery at a median of 14.7 months after surgery. Approximately 70% of patients remained free of daily PPI use throughout follow-up. The authors concluded that TIF provides durable relief of GERD symptoms for up to 9 years with a significant portion of patients having a successful outcome by symptom response and PPI use.

Harms

Although harms are not systematically reported across observational studies, there have been several publications on potential harms of TIF procedures.

Ramai (2021) published a report of complications associated with TIF from post-marketing surveillance data from the FDA Manufacturer and User Facility Device Experience (MAUDE) database from Jan 2011 through Jan 2021.[67] During the period studied, approximately 95 event cases were reported to the FDA and approximately 131 patient complications were identified. The most common adverse events were perforation (19.8%), laceration 17.6%, bleeding (9.2%), and pleural effusion (9.2%). Patient complications were treated using endoscopic clips (12.3%), chest tube or drain insertion (12.3%), use of endoscopic retriever device (11.1%), esophageal stent (8.6%), and emergent or open surgery (11.1%).

Furnee reported an increased risk of gastric injury with laparoscopic Nissen fundoplication after failed EsophyX fundoplication.[68] Of 88 patients in their database who underwent EsophyX fundoplication, 11 (12.5%) subsequently underwent Nissen fundoplication for

persistent or recurrent symptoms at a mean 8.1 months after the primary procedure. Endoscopy showed partial or total disruption of fasteners in 8 of the 11 patients (72.7%). Nissen fundoplication after EsophyX resulted in gastric perforation (n=2), conversion to laparotomy (n=1), subphrenic abscess requiring surgical exploration (n=1) and symptom-worsening in four patients.

In 2017, Huang conducted a systematic review with meta-analysis of TIF for the treatment of GERD.[69] Authors included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF 2 procedure. Efficacy results from the RCTs were combined for patients whose symptoms were controlled by PPIs and for those whose symptoms were not controlled by PPIs and are not further discussed here. Follow-up out to six years in prospective observational studies indicated a decrease in efficacy over time. The reported incidence of severe adverse events, consisting of gastrointestinal perforation and bleeding, was 19 (2.4%) out of 781 patients. This included seven perforations, five cases of post-TIF bleeding, four cases of pneumothorax, one case requiring intravenous antibiotics, and one case of severe epigastric pain.

TRANSESOPHAGEAL RADIOFREQUENCY ENERGY (I.E., THE STRETTA PROCEDURE)

Systematic Reviews

Xie (2021) published a systematic review and network meta-analysis of 10 RCTs that evaluated the comparative effects of Stretta, TIF, and PPIs in patients with GERD.[70] Of the included RCTs, five compared Stretta to control (PPI or sham + PPI) and five compared TIF to control (PPI or sham + PPI). Results of the network meta-analysis revealed that improvements in the HRQoL score in patients treated by Stretta were not significantly different than the improvements seen with TIF (mean difference [MD], 2.45; 95% CI, -2.37 to 7.26); however, both Stretta and TIF were significantly superior to PPIs in this outcome. Additionally, both Stretta and TIF were significantly better than PPIs at improving heartburn scores. Regarding reduction in PPI use and esophagitis incidence, no significant difference between TIF and Stretta was observed. This network meta-analysis had several limitations including a lack of assessment of long-term efficacy, the inclusion of only 10 studies with even fewer studies evaluated for each individual outcome, and lack of RCTs directly comparing Stretta and TIF. Additionally, some of the comparisons were significantly affected by heterogeneity and the evidence quality of each outcome (as assessed by GRADE) ranged from moderate to very low.

Fass (2017) published a meta-analysis of cohort studies and RCTs evaluating the Stretta procedure for patients with GERD (N=2468 total, 9-558 per study).[71] The meta-analysis included 4 RCTs, 23 cohort studies, and one registry. Follow-up time varied from 3 to 120 months. When RCT and cohort results were pooled, there were clinically significant treatment effects for several of end points; however, the analysis was limited by the lack of control groups in many studies. Also, only 1 end point was shared between the four included RCTs.

A meta-analysis of four RCTs (total N=165 patients) was published by Lipka in 2015.[72] Three trials compared Stretta with sham, and one trial compared Stretta with PPI therapy. Results of the individual sham-controlled trials were inconsistent, generally supporting some improvement in symptoms, but not in objective measures of esophageal acid exposure. For example, Corley (2008) reported improvement in heartburn symptoms, quality of life, and general physical quality of life in the active treatment group compared with the sham group, but there were no significant differences in medication use and esophageal acid exposure.[73] Aziz (2010) found

statistically significant improvements in GERD-HRQL in all treatment groups.[74] Arts (2012) reported that the symptom score and quality-of-life score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter pressure after RF.[75] Pooled results of the meta-analysis showed no significant difference between Stretta and either sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy. The overall quality of evidence was considered to be very low with a high risk of bias, and the meta-analysis was limited by heterogeneity in the included studies, which may be due to small sample sizes, differences in measures, and differences in follow-up time.

A 2014 systematic review and meta-analysis of four randomized trials; three reviewed previously[73-75] and one trial which compared Stretta with PPI therapy,[76] included a total of 165 patients. The overall quality of the evidence was considered to be very low with a high risk of bias. The pooled results showed no significant difference between Stretta and sham or PPI management for the measured outcomes. The meta-analysis was limited by heterogeneity in the included studies, which may be due to small sample sizes, differences in measures, and differences in follow-up time. The author also identified significant risks associated with Stretta, including pneumonia, gastroparesis, esophageal perforation, cardiac arrest, and at least 4 deaths from review of the Manufacturer and User Facility Device Experience database.

A meta-analysis completed by Perry, included 20 studies, only 2 of which were RCTs. This meta-analysis was limited by the inclusion of lower quality studies and by the analysis, which only examined within-subject differences and did not include between-subject differences, as reported in the RCTs.[77]

Randomized Controlled Trials

Zerbib (2020) published a double-blind RCT that compared Stretta plus PPI therapy (n=29) to sham plus PPI therapy (n=33) in individuals with PPI-refractory heartburn.[78] The primary endpoint was clinical success at week 24, defined as an intake of fewer than seven PPI doses over the previous two weeks and adequate subjective patient-reported symptom control. Fewer patients achieved the primary endpoint in the Stretta group, but the difference was not statistically significant (3.4% vs 15.1%; odds ratio [OR]=0.20; 95% CI, 0.02 to 1.88). Severe adverse events were more frequent in the Stretta group (7 vs 2) and included epigastric pain (n = 3), delayed gastric emptying, vomiting, headache, and 1 leiomyoma. Limitations of this RCT include that pH-impedance monitoring was not performed either at enrollment or during follow-up. Thus, baseline status of GERD diagnosis is unclear and the physiologic effects of Stretta are unknown.

There are several randomized trials comparing transesophageal radiofrequency (RF) energy with a sham procedure that involved balloon inflation but no needle deployment or RF energy delivery.[73-75]

Results of the first study failed to include 20% of the randomized patients in analysis of primary endpoints, and no intention to treat analysis was provided. Therefore, reported results of improved heartburn symptoms and GERD quality of life scores are not reliable.

Results of the second, third and fourth studies were flawed due to a small patient population and inadequate timeframe for follow up.

Other small RCT's have been published. Two compared RF to PPI therapy. One trial showed promising short-term (6 months) results but does not permit conclusions about mid- to long-term effectiveness and durability.[76] Another compared RF with PPI therapy to PPI therapy alone.[79] Results at 3 months appeared favorable to the Stretta group, however, the study sample was small (N=20) and power calculations were not conducted.

Nonrandomized Studies

Other clinical studies concerning transesophageal radiofrequency are limited to observational case series that do not allow conclusions about long-term effectiveness and durability.[22, 80-92] Though several case series report up to 4-10 year outcomes, there was a significant loss to follow-up in these studies such that conclusions on durability and health outcomes cannot be made.[93]

INJECTION OR IMPLANTATION OF BIOCOMPATIBLE POLYMERS

Randomized Controlled Trials

The available evidence for the Gatekeeper Reflux Repair System consists of one RCT.[94] This industry-funded sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper (n=75) or sham (n=43) treatment. An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with 4 Gatekeeper prostheses. At three months, 44% of implanted patients received retreatment with up to four additional prostheses due to unsatisfactory symptom control. The primary safety end point was reduction in serious device- and procedure-related adverse device effects, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end point was reduction in heartburn symptoms using the GERD-HRQL questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at six months, but there was no significant difference between the two groups. The study was terminated early due to a lack of efficacy.

There is one randomized sham-controlled trial which reports results of patients randomized to receive either injection of Enteryx biopolymer or a sham procedure.[95] At 3- and 6-months follow-up, patients in the Enteryx group had greater reductions in PPI use and more improvement in GERD health-related quality of life heartburn scores. However, the small size and short duration of the study limit interpretation of findings.

Nonrandomized Studies

Other data on injectable or implantable polymers consists of very small case series.[22, 96] The small number of patients and lack of long-term follow-up precludes scientific analysis.

PRACTICE GUIDELINE SUMMARY

Several clinical practice guidelines consider the use of transoral fundoplication or other endoscopic procedures, although none were able to recommend this treatment based upon high level evidence.

AMERICAN SOCIETY OF GENERAL SURGEONS

The American Society of General Surgeons (ASGS) consensus-based position statement on transoral fundoplication states, “the ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”[97]

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

The 2008 Medical Position Statement of the American Gastroenterological Association (AGA), makes no recommendation for or against “the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome” based on insufficient evidence (Grade Insufficient).[98]

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2022, the American College of Gastroenterology (ACG) released updated guidelines for the diagnosis and management of gastroesophageal reflux disease.[99] The guidelines state the following:

- Because data on the efficacy of radiofrequency energy (Stretta) as an antireflux procedure is inconsistent and highly variable, we cannot recommend its use as an alternative to medical or surgical antireflux therapies (conditional recommendation, low level of evidence).
- We suggest consideration of TIF for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm (conditional recommendation, low level of evidence).
- For patients who have regurgitation as their primary PPI-refractory symptom and who have had abnormal gastroesophageal reflux documented by objective testing, we suggest consideration of antireflux surgery or TIF (conditional recommendation, low level of evidence).

SOCIETY OF AMERICAN GASTROINTESTINAL ENDOSCOPIC SURGEONS

In 2021, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published guidelines for the surgical treatment of gastroesophageal reflux (GERD).[100] Although several recommendations regarding fundoplication were provided, the guideline does not mention transesophageal endoscopic approaches.

In 2017, SAGES updated its evidence-based guidelines on endoluminal treatments for GERD.[101] SAGES gave a strong recommendation based on moderate quality evidence that TIF with EsophyX can be performed with an acceptable safety risk in selected patients. SAGES concluded that EsophyX results in better control of GERD symptoms compared with proton pump inhibitor (PPI) treatment in the short term (six months) but leads to similar improvement in objective GERD measures compared with PPIs. TIF appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that the surgical fundoplication can be used safely after TIF failure. SAGES gave a strong recommendation based on moderate quality evidence that Stretta is safe for adults and significantly improves health-related quality of life

score, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD. Stretta is more effective than PPI, but less so than fundoplication.

SUMMARY

There is not enough research to show that transesophageal endoscopic therapies for the treatment of gastroesophageal reflux disease (GERD) improves health outcomes. Although clinical guidelines based on research may recommend treating GERD with one or more of the therapies mentioned, there is not enough research to know if or how well these procedures work to treat people with GERD. This does not mean that it does not work, but more research is needed to know. Therefore, the use of any of these procedures is considered investigational for the treatment of GERD.

REFERENCES

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108(3):308-28; quiz 29. PMID: 23419381
2. van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *The Cochrane database of systematic reviews.* 2010(11):CD002095. PMID: 21069670
3. Khan F, Maradey-Romero C, Ganocy S, et al. Utilisation of surgical fundoplication for patients with gastro-oesophageal reflux disease in the USA has declined rapidly between 2009 and 2013. *Aliment Pharmacol Ther.* 2016;43(11):1124-31. PMID: 27060607
4. U.S. Food and Drug Administration (FDA), 510(k) Summary: EsophyX K160960. May 1, 2016. [cited 11/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf16/K160960.pdf.
5. U.S. Food and Drug Administration (FDA), 510(k) Summary: EsophyX K171307. June 22, 2016. [cited 11/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171307.pdf.
6. Ip S, Bonis P, Tatsioni A, et al. Comparative Effectiveness of Management Strategies For Gastroesophageal Reflux Disease. *AHRQ Comparative Effectiveness Reviews.* 2005. PMID: 21348043
7. Ip S, Chung M, Moorthy D, et al. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update. *AHRQ Comparative Effectiveness Reviews.* 2011;Report No.: 11-EHC049-EF. PMID: 22091471
8. Humphries LA, Hernandez JM, Clark W, et al. Causes of dissatisfaction after laparoscopic fundoplication: the impact of new symptoms, recurrent symptoms, and the patient experience. *Surg Endosc.* 2013;27(5):1537-45. PMID: 23508812
9. Hummel K, Richards W. Endoscopic treatment of gastroesophageal reflux disease. *The Surgical clinics of North America.* 2015;95(3):653-67. PMID: 25965137
10. Chen D, Barber C, McLoughlin P, et al. Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. *Br J Surg.* 2009;96(2):128-36. PMID: 19160349
11. Haseeb M, Brown JRG, Hayat U, et al. Impact of second-generation transoral incisionless fundoplication on atypical GERD symptoms: a systematic review and meta-analysis. *Gastrointest Endosc.* 2023;97(3):394-406.e2. PMID: 36402203

12. Testoni S, Hassan C, Mazzoleni G, et al. Long-term outcomes of transoral incisionless fundoplication for gastro-esophageal reflux disease: systematic-review and meta-analysis. *Endosc Int Open.* 2021;9(2):E239-E46. PMID: 33553587
13. McCarty TR, Itidiare M, Njei B, et al. Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. *Endoscopy.* 2018;50(7):708-25. PMID: 29625507
14. Richter JE, Kumar A, Lipka S, et al. Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. *Gastroenterology.* 2018;154(5):1298-308 e7. PMID: 29305934
15. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. *Surg Innov.* 2018;25(2):149-57. PMID: 29405886
16. Trad KS, Fox MA, Simoni G, et al. Transoral fundoplication offers durable symptom control for chronic GERD: 3-year report from the TEMPO randomized trial with a crossover arm. *Surg Endosc.* 2016. PMID: 27655380
17. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. *Surg Innov.* 2015;22(1):26-40. PMID: 24756976
18. Trad KS, Simoni G, Barnes WE, et al. Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: a randomized, multicenter, open label, crossover study. *BMC gastroenterology.* 2014;14:174. PMID: 25284142
19. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. *Gastroenterology.* 2015;148(2):324-33 e5. PMID: 25448925
20. Hakansson B, Montgomery M, Cadiere GB, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. *Aliment Pharmacol Ther.* 2015;42(11-12):1261-70. PMID: 26463242
21. Witteman BP, Conchillo JM, Rinsma NF, et al. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. *Am J Gastroenterol.* 2015;110(4):531-42. PMID: 25823768
22. TEC Assessment 2003. "Transesophageal Endoscopic Treatment for Gastroesophageal Reflux Disease." BlueCross BlueShield Association Technology Evaluation Center, Vol. 18, Tab 20.
23. Schwartz MP, Wellink H, Gooszen HG, et al. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial. *Gut.* 2007;56(1):20-8. PMID: 16763053
24. Rothstein R, Filipi C, Caca K, et al. Endoscopic full-thickness plication for the treatment of gastroesophageal reflux disease: A randomized, sham-controlled trial. *Gastroenterology.* 2006;131(3):704-12. PMID: 16952539
25. Montgomery M, Hakanson B, Ljungqvist O, et al. Twelve months' follow-up after treatment with the EndoCinch endoscopic technique for gastro-oesophageal reflux disease: a randomized, placebo-controlled study. *Scand J Gastroenterol.* 2006;41(12):1382-9. PMID: 17101568
26. Domagk D, Menzel J, Seidel M, et al. Endoluminal gastroplasty (EndoCinch) versus endoscopic polymer implantation (Enteryx) for treatment of gastroesophageal reflux

disease: 6-month results of a prospective, randomized trial. *Am J Gastroenterol.* 2006;101(3):422-30. PMID: 16542275
27. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of Transoral Fundoplication vs Omeprazole for Treatment of Regurgitation in a Randomized Controlled Trial. *Gastroenterology.* 2014. PMID: 25448925
28. Svoboda P, Kantorova I, Kozumplik L, et al. Our experience with transoral incisionless plication of gastroesophageal reflux disease: NOTES procedure. *Hepato-gastroenterology.* 2011;58(109):1208-13. PMID: 21937380
29. Kaindlstorfer A, Koch OO, Antoniou SA, et al. A randomized trial on endoscopic full-thickness gastroplication versus laparoscopic antireflux surgery in GERD patients without hiatal hernias. *Surg Laparosc Endosc Percutan Tech.* 2013;23:212-22. PMID: 23579521
30. Repici A, Fumagalli U, Malesci A, et al. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-month follow-up in a single-center experience. *J Gastrointest Surg.* 2010;14(1):1-6. PMID: 19902310
31. Testoni PA, Corsetti M, Di Pietro S, et al. Effect of transoral incisionless fundoplication on symptoms, PPI use, and ph-impedance refluxes of GERD patients. *World J Surg.* 2010;34(4):750-7. PMID: 20091308
32. Cadiere GB, Rajan A, Germay O, et al. Endoluminal fundoplication by a transoral device for the treatment of GERD: A feasibility study. *Surg Endosc.* 2008;22(2):333-42. PMID: 18071818
33. Filipi CJ, Lehman GA, Rothstein RI, et al. Transoral, flexible endoscopic suturing for treatment of GERD: a multicenter trial. *Gastrointest Endosc.* 2001;53(4):416-22. PMID: 11275879
34. Swain CP. Endoscopic suturing. *Baillieres Best Pract Res Clin Gastroenterol.* 1999;13(1):97-108. PMID: 11030637
35. Mahmood Z, McMahon BP, Arfin Q, et al. Endocinch therapy for gastro-oesophageal reflux disease: a one year prospective follow up. *Gut.* 2003;52(1):34-9. PMID: 12477756
36. Thomson M, Fritscher-Ravens A, Hall S, et al. Endoluminal gastroplication in children with significant gastro-oesophageal reflux disease. *Gut.* 2004;53(12):1745-50. PMID: 15542508
37. Chadalavada R, Lin E, Swafford V, et al. Comparative results of endoluminal gastroplasty and laparoscopic antireflux surgery for the treatment of GERD. *Surg Endosc.* 2004;18(2):261-5. PMID: 14691698
38. Abou-Rebyeh H, Hoepffner N, Rosch T, et al. Long-term failure of endoscopic suturing in the treatment of gastroesophageal reflux: a prospective follow-up study. *Endoscopy.* 2005;37(3):213-6. PMID: 15731936
39. Schiefke I, Zabel-Langhennig A, Neumann S, et al. Long term failure of endoscopic gastroplication (EndoCinch). *Gut.* 2005;54(6):752-8. PMID: 15888777
40. Pleskow D, Rothstein R, Kozarek R, et al. Endoscopic full-thickness plication for the treatment of GERD: long-term multicenter results. *Surg Endosc.* 2007;21(3):439-44. PMID: 17180259
41. Mahmood Z, Byrne PJ, McMahon BP, et al. Comparison of transesophageal endoscopic plication (TEP) with laparoscopic Nissen fundoplication (LNF) in the treatment of uncomplicated reflux disease. *Am J Gastroenterol.* 2006;101(3):431-6. PMID: 16542276
42. Rothstein RI. Endoscopic therapy of gastroesophageal reflux disease: outcomes of the randomized-controlled trials done to date. *J Clin Gastroenterol.* 2008;42(5):594-602. PMID: 18364577

43. Cadiere GB, Buset M, Muls V, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. *World J Surg.* 2008;32(8):1676-88. PMID: 18443855
44. Pleskow D, Rothstein R, Kozarek R, et al. Endoscopic full-thickness plication for the treatment of GERD: Five-year long-term multicenter results. *Surg Endosc.* 2008;22(2):326-32. PMID: 18027032
45. Cadiere GB, Van Sante N, Graves JE, et al. Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. *Surg Endosc.* 2009;23(5):957-64. PMID: 19288158
46. von Renteln D, Schiefke I, Fuchs KH, et al. Endoscopic full-thickness plication for the treatment of gastroesophageal reflux disease using multiple Plicator implants: 12-month multicenter study results. *Surg Endosc.* 2009;23(8):1866-75. PMID: 19440792
47. Velanovich V. Endoscopic, endoluminal fundoplication for gastroesophageal reflux disease: initial experience and lessons learned. *Surgery.* 2010;148(4):646-51; discussion 51-3. PMID: 20708763
48. Bell RC, Freeman KD. Clinical and pH-metric outcomes of transoral esophagogastric fundoplication for the treatment of gastroesophageal reflux disease. *Surg Endosc.* 2011;25(6):1975-84. PMID: 21140170
49. Barnes WE, Hoddinott KM, Mundy S, et al. Transoral incisionless fundoplication offers high patient satisfaction and relief of therapy-resistant typical and atypical symptoms of GERD in community practice. *Surg Innov.* 2011;18(2):119-29. PMID: 21307014
50. Trad KS, Turgeon DG, Deljkich E. Long-term outcomes after transoral incisionless fundoplication in patients with GERD and LPR symptoms. *Surg Endosc.* 2012;26(3):650-60. PMID: 21959689
51. Ihde GM, Besancon K, Deljkich E. Short-term safety and symptomatic outcomes of transoral incisionless fundoplication with or without hiatal hernia repair in patients with chronic gastroesophageal reflux disease. *Am J Surg.* 2011;202(6):740-6; discussion 46-7. PMID: 22014853
52. Petersen RP, Filippa L, Wassenaar EB, et al. Comprehensive evaluation of endoscopic fundoplication using the EsophyX(TM) device. *Surg Endosc.* 2011. PMID: 22042587
53. Chen S, Jarboe MD, Teitelbaum DH. Effectiveness of a transluminal endoscopic fundoplication for the treatment of pediatric gastroesophageal reflux disease. *Pediatr Surg Int.* 2012;28(3):229-34. PMID: 22124618
54. Testoni PA, Vailati C, Testoni S, et al. Transoral incisionless fundoplication (TIF 2.0) with EsophyX for gastroesophageal reflux disease: long-term results and findings affecting outcome. *Surg Endosc.* 2011. PMID: 22170317
55. Narsule CK, Burch MA, Ebright MI, et al. Endoscopic fundoplication for the treatment of gastroesophageal reflux disease: initial experience. *J Thorac Cardiovasc Surg.* 2012;143(1):228-34. PMID: 22070927
56. Nguyen A, Vo T, Nguyen XM, et al. Transoral incisionless fundoplication: initial experience in patients referred to an integrated academic institution. *Am Surg.* 2011;77(10):1386-9. PMID: 22127095
57. Muls V, Eckardt AJ, Marchese M, et al. Three-year results of a multicenter prospective study of transoral incisionless fundoplication. *Surg Innov.* 2013;20:321-30. PMID: 22968006
58. Wendling MR, Melvin WS, Perry KA. Impact of transoral incisionless fundoplication (TIF) on subjective and objective GERD indices: a systematic review of the published literature. *Surg Endosc.* 2013;27(10):3754-61. PMID: 23644835

59. Testoni PA, Testoni S, Mazzoleni G, et al. Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study. *Surg Endosc.* 2014. PMID: 25480624
60. Bell RC, Barnes WE, Carter BJ, et al. Transoral incisionless fundoplication: 2-year results from the prospective multicenter U.S. study. *Am Surg.* 2014;80(11):1093-105. PMID: 25347499
61. Stefanidis G, Viazis N, Kotsikoros N, et al. Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus.* 2017;30(3):1-8. PMID: 27868281
62. Bell RCW, Freeman K, Heidrick R, et al. Transoral incisionless fundoplication demonstrates durability at up to 9 years. *Therap Adv Gastroenterol.* 2021;14:17562848211004827. PMID: 33948113
63. Testoni SGG, Cilona MB, Mazzoleni G, et al. Transoral incisionless fundoplication with Medigus ultrasonic surgical endostapler (MUSE) for the treatment of gastro-esophageal reflux disease: outcomes up to 3 years. *Surg Endosc.* 2021. PMID: 34799745
64. Bell RC, Mavrelis PG, Barnes WE, et al. A Prospective Multicenter Registry of Patients with Chronic Gastroesophageal Reflux Disease Receiving Transoral Incisionless Fundoplication. *Journal of the American College of Surgeons.* 2012. PMID: 22939637
65. Wilson EB, Barnes WE, Mavrelis PG, et al. The effects of transoral incisionless fundoplication on chronic GERD patients: 12-month prospective multicenter experience. *Surg Laparosc Endosc Percutan Tech.* 2014;24(1):36-46. PMID: 24487156
66. Frazzoni M, Conigliaro R, Manta R, et al. Reflux parameters as modified by EsophyX or laparoscopic fundoplication in refractory GERD. *Aliment Pharmacol Ther.* 2011;34(1):67-75. PMID: 21539587
67. Ramai D, Shapiro A, Barakat M, et al. Adverse events associated with transoral incisionless fundoplication (TIF) for chronic gastroesophageal reflux disease: a MAUDE database analysis. *Surg Endosc.* 2021. PMID: 34750704
68. Furnee EJ, Broeders JA, Draaisma WA, et al. Laparoscopic Nissen fundoplication after failed EsophyX fundoplication. *Br J Surg.* 2010;97(7):1051-5. PMID: 20632271
69. Huang X, Chen S, Zhao H, et al. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. *Surg Endosc.* 2017;31(3):1032-44. PMID: 27495332
70. Xie P, Yan J, Ye L, et al. Efficacy of different endoscopic treatments in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. *Surg Endosc.* 2021;35(4):1500-10. PMID: 33650003
71. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. *Surg Endosc.* 2017;31(12):4865-82. PMID: 28233093
72. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2015;13(6):1058-67 e1. PMID: 25459556
73. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. *Gastroenterology.* 2003;125(3):668-76. PMID: 12949712

74. Aziz AM, El-Khayat HR, Sadek A, et al. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. *Surg Endosc.* 2010;24(4):818-25. PMID: 19730952
75. Arts J, Bisschops R, Blondeau K, et al. A Double-Blind Sham-Controlled Study of the Effect of Radiofrequency Energy on Symptoms and Distensibility of the Gastro-Esophageal Junction in GERD. *Am J Gastroenterol.* 2012;107(2):222-30. PMID: 22108449
76. Coron E, Sebille V, Cadiot G, et al. Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. *Aliment Pharmacol Ther.* 2008;28(9):1147-58. PMID: 18616516
77. Perry KA, Banerjee A, Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech.* 2012;22(4):283-8. PMID: 22874675
78. Zerbib F, Sacher-Huvelin S, Coron E, et al. Randomised clinical trial: oesophageal radiofrequency energy delivery versus sham for PPI-refractory heartburn. *Aliment Pharmacol Ther.* 2020;52(4):637-45. PMID: 32656869
79. Kalapala R, Shah H, Nabi Z, et al. Treatment of gastroesophageal reflux disease using radiofrequency ablation (Stretta procedure): An interim analysis of a randomized trial. *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology.* 2017;36(5):337-42. PMID: 29030802
80. Triadafilopoulos G, DiBaise JK, Nostrant TT, et al. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc.* 2002;55(2):149-56. PMID: 11818914
81. Richards WO, Scholz S, Khaitan L, et al. Initial experience with the stretta procedure for the treatment of gastroesophageal reflux disease. *J Laparoendosc Adv Surg Tech A.* 2001;11(5):267-73. PMID: 11642661
82. DiBaise JK, Brand RE, Quigley EM. Endoluminal delivery of radiofrequency energy to the gastroesophageal junction in uncomplicated GERD: efficacy and potential mechanism of action. *Am J Gastroenterol.* 2002;97(4):833-42. PMID: 12003416
83. Triadafilopoulos G. Stretta: an effective, minimally invasive treatment for gastroesophageal reflux disease. *Am J Med.* 2003;115 Suppl 3A:192S-200S. PMID: 12928101
84. Vakil N, Sharma P. Review article: endoscopic treatments for gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2003;17(12):1427-34. PMID: 12823144
85. Houston H, Khaitan L, Holzman M, et al. First year experience of patients undergoing the Stretta procedure. *Surg Endosc.* 2003;17(3):401-4. PMID: 12436238
86. Noar MD, Lotfi-Emran S. Sustained improvement in symptoms of GERD and antisecretory drug use: 4-year follow-up of the Stretta procedure. *Gastrointest Endosc.* 2007;65(3):367-72. PMID: 17321232
87. Reymunde A, Santiago N. Long-term results of radiofrequency energy delivery for the treatment of GERD: sustained improvements in symptoms, quality of life, and drug use at 4-year follow-up. *Gastrointest Endosc.* 2007;65(3):361-6. PMID: 17321231
88. McClusky DA, 3rd, Khaitan L, Swafford VA, et al. Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) in patients with recurrent reflux after antireflux surgery: can surgery be avoided? *Surg Endosc.* 2007;21(7):1207-11. PMID: 17308947

89. Dundon JM, Davis SS, Hazey JW, et al. Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) does not provide long-term symptom control. *Surg Innov.* 2008;15(4):297-301. PMID: 18829607
90. Liu HF, Zhang JG, Li J, et al. Improvement of clinical parameters in patients with gastroesophageal reflux disease after radiofrequency energy delivery. *World J Gastroenterol.* 2011;17(39):4429-33. PMID: 22110270
91. Dughera L, Navino M, Cassolino P, et al. Long-Term Results of Radiofrequency Energy Delivery for the Treatment of GERD: Results of a Prospective 48-Month Study. *Diagn Ther Endosc.* 2011;2011:507157. PMID: 22110288
92. Ma L, Li T, Liu G, et al. Stretta radiofrequency treatment vs Toupet fundoplication for gastroesophageal reflux disease: a comparative study. *BMC gastroenterology.* 2020;20(1):162. PMID: 32460696
93. Noar M, Squires P, Noar E, et al. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. *Surg Endosc.* 2014;28(8):2323-33. PMID: 24562599
94. Fockens P, Cohen L, Edmundowicz SA, et al. Prospective randomized controlled trial of an injectable esophageal prosthesis versus a sham procedure for endoscopic treatment of gastroesophageal reflux disease. *Surg Endosc.* 2010;24(6):1387-97. PMID: 20198491
95. Deviere J, Costamagna G, Neuhaus H, et al. Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. *Gastroenterology.* 2005;128(3):532-40. PMID: 15765387
96. Feretis C, Benakis P, Dimopoulos C, et al. Endoscopic implantation of Plexiglas (PMMA) microspheres for the treatment of GERD. *Gastrointest Endosc.* 2001;53(4):423-6. PMID: 11275880
97. American Society of General Surgeons (ASGS). Position statement: Transoral fundoplication. [cited 11/14/2023]. 'Available from:' https://theasgs.org/position-statements/american-society-of-general-surgeons-asgs-position-statement-transoral-fundoplication/.
98. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008;135(4):1383-91, 91 e1-5. PMID: 18789939
99. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol.* 2022;117(1):27-56. PMID: 34807007
100. Slater BJ, Dirks RC, McKinley SK, et al. SAGES guidelines for the surgical treatment of gastroesophageal reflux (GERD). *Surg Endosc.* 2021;35(9):4903-17. PMID: 34279710
101. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Guidelines. May 2017 Clinical Spotlight Review: Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD). May 2017. [cited 11/14/2023]. 'Available from:' https://www.sages.org/publications/guidelines/endoluminal-treatments-for-gastroesophageal-reflux-disease-gerd/.

CODES

Codes	Number	Description
CPT	43192	Esophagoscopy; rigid, transoral; with directed submucosal injection(s), any substance

Codes	Number	Description
	43201	Esophagoscopy; flexible, transoral; with directed submucosal injection(s), any substance
	43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
	43236	Esophagogastroduodenoscopy, flexible, transoral, with direct submucosal injections, any substance
	43257	Esophagogastroduodenoscopy, flexible transoral; with deliver of thermal esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
	43499	Unlisted procedure, esophagus
HCPCS	None	

Date of Origin: *February 2001*

Regence

Medical Policy Manual Surgery, Policy No. 111

Gastric Electrical Stimulation

Effective: January 1, 2024

Next Review: April 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Gastric electrical stimulation (GES) is performed using an implantable device designed to treat chronic drug-refractory nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. Gastric electrical stimulation is also proposed as a treatment of obesity. The device may also be referred to as a gastric pacemaker or gastric pacing.

MEDICAL POLICY CRITERIA

I. Gastric electrical stimulation may be considered **medically necessary** in the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology when all of the following (A – C) Criteria are met:

   A. Significantly delayed gastric emptying as documented by standard scintigraphic imaging of solid food; and

   B. Patient is refractory or intolerant of 2 out of 3 classes of prokinetic medications and 2 out of 3 antiemetic medications. (see Appendices for classes); and

   C. Patient's nutritional status is sufficiently low that weight has decreased to 90 percent or less of normal body weight for a patient’s height and age in comparison with pre-illness weight.

II. The replacement of an existing gastric electrical stimulator and/or generator is considered **medically necessary** when the existing gastric electrical stimulator and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

III. Replacement of a gastric electrical stimulator and/or generator is considered **not medically necessary** when Criterion II. is not met.

IV. Gastric electrical stimulation for the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology is considered **not medically necessary** when Criterion I. is not met.

V. Gastric electrical stimulation is **investigational** for all other indications including but not limited to the treatment of obesity.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Prokinetic and Antiemetic Medications given and response
- Replacement and Revisions
    - Name and type of device requested
    - Documentation of specifically why the stimulator is no longer able to perform its basic function
    - Documentation that the current device cannot be repaired or adapted adequately to meet the patient's needs

CROSS REFERENCES

1. Bariatric Surgery, Surgery, Policy No. 58
2. Vagus Nerve Stimulation, Surgery, Policy No. 74

BACKGROUND

A subcutaneously implanted pulse generator delivers electrical stimulation to the stomach via intramuscular leads that are implanted on the outer surface of the greater curvature of the stomach either laparoscopically or during a laparotomy. Stimulation parameters are typically programmed at an "on time" (ON) (e.g., 0.1 second) alternating with an "off time" (OFF) (e.g., 5.0 seconds).

GASTRIC STIMULATION FOR THE TREATMENT OF INTRACTABLE NAUSEA AND VOMITING DUE TO GASTROPARESIS

Gastroparesis is a chronic disorder of gastric motility characterized by delayed emptying of a solid meal. Symptoms include bloating, distension, nausea, and vomiting. When severe and chronic, gastroparesis can be associated with dehydration, poor nutritional status, and poor glycemic control in diabetics. While most commonly associated with diabetes, gastroparesis is

also found in chronic pseudo-obstruction, connective tissue disorders, Parkinson disease, and psychological pathology. Idiopathic gastroparesis refers to symptoms of gastroparesis which are not associated with an identifiable cause. Treatment of gastroparesis includes prokinetic agents such as metoclopramide, and antiemetic agents such as metoclopramide, granisetron, or ondansetron. Severe cases may require enteral or total parenteral nutrition.

GASTRIC STIMULATION FOR THE TREATMENT OF OBESITY

GES has also been investigated as a treatment of obesity as a technique to increase a feeling of satiety with subsequent reduced food intake and weight loss. The exact mechanisms resulting in changes in eating behavior are uncertain but may be related to neurohormonal modulation and/or stomach muscle stimulation.

REGULATORY STATUS

The Enterra™ Therapy System (formerly named Gastric Electrical Stimulation [GES] System; manufactured by Medtronic) is the only device approved for treatment of chronic refractory gastroparesis. It received approval for marketing from the U.S. Food and Drug Administration (FDA) in 2000 through the humanitarian device exemption (HDE) process.[1] This process requires the manufacturer to provide adequate information for the FDA to determine that the device has “probable” benefit but does not pose an unreasonable or significant risk; it does not require data confirming the efficacy of the device. The HDE process is available for devices treating conditions that affect fewer than 4,000 Americans per year.

EVIDENCE SUMMARY

GASTRIC STIMULATION FOR THE TREATMENT OF INTRACTABLE NAUSEA AND VOMITING DUE TO GASTROPARESIS

Systematic Reviews

Several systematic reviews of studies of gastric electrical stimulation (GES) for gastroparesis have been published, the most recent and comprehensive of which is by Saleem (2022).[2-5]

Saleem identified 9 studies (7 RCTs; N=730) including a recent large (N=172) crossover study by Durcotte (2020). The primary outcome evaluated in this analysis was total symptom score (TSS). The included studies were deemed of moderate quality and low risk of bias. Analysis of the 7 blind RCTs found the TSS was significantly improved at the 4-day, 2-month, 4-month, and 12-month follow-up (mean difference [MD], -6.07; 95% confidence interval [CI], -4.5 to -7.65; p<0.00001) but not at all follow-up time points (not further defined). These studies had high heterogeneity (I2=70%) due to variable follow-up duration. The weekly vomiting frequency was not different between groups (MD, -1.76; 95% CI -6.15 to 2.63; p=0.43) when the blind RCTs were pooled; however, in the open trials, vomiting episodes were lower after GES (MD, 15.59; 95% CI 10.29 to 20.9; p<0.00001). The analysis is limited by the variety of scoring systems, variable time points of follow up, and relatively small sample sizes of the individual trials.

An older, but more inclusive meta-analysis, was published by Levinthal (2017).[2] To be included in the Levinthal review, studies had to include adults with established gastroparesis, report patient symptom scores and administer treatment for at least one week. Five randomized controlled trials (RCTs) and 13 non-RCTs meeting criteria were identified. Pooled analysis of data from the five RCTs (n=185 patients) did not find a statistically significant

difference in symptom severity when the GES was turned on versus off (standardized mean difference [SMD], 0.17; 95% confidence interval [CI], -0.06 to 0.40; p=0.15). Another pooled analysis did not find a statistically significant difference in nausea severity scores when the GES was on or off (SMD = -0.143; 95% CI, -0.50 to 0.22; p=0.45). In a pooled analysis of 13 open-label single-arm studies and data from open-label extensions of three RCTs, mean total symptom severity score decreased 2.68 (95% CI, 2.04 to 3.32) at follow-up from a mean of 6.85 (95% CI, 6.28 to 7.42) at baseline. The rate of adverse events in the immediate postoperative period (reported in seven studies) was 8.7% (95% CI, 4.3% to 17.1%). The in-hospital mortality rate within 30 days of surgery was 1.4% (95% CI, 0.8% to 2.5%), the rate of reoperations (up to 10 years of follow-up) was 11.1% (95% CI, 8.7% to 14.1%), and the rate of device removal was 8.4% (95% CI, 5.7% to 12.2%).

Randomized Controlled Trials

The data presented to the FDA documenting the “probable benefit” of the GES (Enterra™) system was based on a multicenter double-blind cross-over study referred to as the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS).[1] The study included 33 patients with intractable idiopathic or diabetic gastroparesis. The primary endpoint of the study was a reduction in vomiting frequency, as measured by patient diaries. In the initial phase of the study, all patients underwent implantation of the stimulator and were randomly and blindly assigned to stimulation ON or stimulation OFF for the first month, with crossover to OFF and ON during the second month. The baseline vomiting frequency was 47 episodes per month, which significantly declined in both ON and OFF groups to 23 and 29 episodes, respectively. However, there were no significant differences in the number of vomiting episodes between the two groups, suggesting a placebo effect.

After the first two months of therapy, patients were asked which month of the cross-over stimulation they preferred. Twenty-one of the 33 patients selected the ON mode as their preferred month, compared to 7 who preferred the OFF mode, and 5 who had no preference. The greater preference for ON stimulation suggested some short-term effect that was not placebo.

In a continuing open phase of the trial, the patients then received the stimulation consistent with their preference. However, by four months all patients had the device turned ON (it was not clear whether this phase was by preference or design). At 6 and 12 months follow-up, the mean number of vomiting episodes continued to decline, although only 15 patients were followed for a period of 12 months. Data regarding quality of life were also obtained at 6 and 12 months and showed improvement. At 6 months, there was a significant improvement in 2-hour gastric retention (from 80% retention to 60% retention), but not in 4-hour gastric retention. (Fifty percent gastric retention at two hours was considered the upper limits of normal.)

The results of the randomized portion of the study suggest a placebo effect. Therefore, long-term results of GES must be validated in a longer-term randomized trial. It is interesting to note that GES did not return gastric emptying to normal in the majority of the patients tested. In as much as the device is intended to improve gastric emptying, as a proof of principle, it would be interesting to investigate the correlation between the degree of gastric emptying and symptom improvement.

Ducrotte (2020) evaluated permanent GES (Enterra) in a cross-over trial. Patients (N=172) had refractory and chronic vomiting. After GES implantation, patients were randomized to receive stimulation or no stimulation then crossed over to the other treatment after 4 months. The

primary endpoints were vomiting score (range 0 to 4 where 0 is daily vomiting and 4 is no vomiting) and the Gastrointestinal Quality of Life Index. The median vomiting score with device on was 2 versus 1 with the device off (p<0.002); however, over 50% of patients reported similar vomiting scores during the on and off period. There was no difference between groups in the quality of life measure (73.3 on the on phase and 71.1 in the off; p=0.06). Delayed gastric emptying was not different in the on versus off period. Limitations of this trial include use of an unvalidated scale for the primary endpoint, inclusion of only refractory patients, and 4-month duration of treatment. Importantly, this trial was not limited to patients with gastroparesis.

In a 2003 update to WAVESS, Abell reported 12-month outcomes for all of the patients.[6] Statistically significant improvements were found for weekly vomiting frequency, total abdominal symptom score, and scintigraphic solid food emptying. At baseline the median vomiting frequency was 17.3 episodes per week with gastroparetic symptoms over a mean of 6.2 years. All patients had scintigraphic evidence of delayed gastric emptying at 2 and 4 hours, all patients were refractory to prokinetic and antiemetic medications, and 14 required some form of parenteral or enteral feedings. Results at the end of phase 1 (the blinded phase) showed a 50% decreased vomiting frequency for patients whose devices were ON compared to patients whose devices were OFF (p=0.05).

Symptom severity trended toward improvement in the ON versus OFF period, although these changes did not reach statistical significance in phase 1. In a second phase of the study all patients were switched to the ON position with 6- and 12- months follow-up. Vomiting at 12 months was compared to baseline; 72% for the combined group, 63% for diabetics with gastroparesis, and 83% for patients with idiopathic gastroparesis. Total symptom score improved significantly (p<0.05) at 6 and 12 months. Physical and mental quality of life scores improved significantly compared to baseline (p= less than 0.025). Baseline gastric retention was 78% at 2 hours. This decreased significantly with electrical stimulation to 65% at 6 months and 56% at 12 months for the combined group. The changes in 2-hour gastric emptying were not significant for the diabetic and idiopathic groups separately. Four-hour gastric emptying improved from 34% retention at baseline to 22% retention at 12 months. The difference was statistically significant for the combined group as well as the diabetic and idiopathic groups separately.

McCallum (2010) performed a multicenter prospective study to evaluate Enterra™ therapy in patients with chronic intractable nausea and vomiting from diabetic gastroparesis (DGP).[7] In this study, 55 patients with refractory DGP (5.9 years of DGP) were implanted with the Enterra™ system. After surgery, all patients had the stimulator turned ON for 6 weeks and then were randomly assigned to groups that had consecutive 3-month cross-over periods with the device ON or OFF. After this period, the device was turned ON in all patients and they were followed up unblinded for 4.5 months. During the initial 6-week phase with the stimulator turned ON, the median reduction in weekly vomiting frequency (WVF) compared with baseline was 57%. There was no difference in WVF between patients who had the device turned ON or OFF during the 3-month cross-over period. At 1 year, the WVF of all patients was significantly lower than baseline values (median reduction, 68%; P < 0.001). One of the patients had the device removed due to infection; 2 patients required surgical intervention due to lead-related problems.

In a later study, McCallum (2013) evaluated GES (Enterra™ system) in patients with chronic vomiting due to idiopathic gastroparesis in a randomized, double-blind crossover trial.[8] In this

study, 32 patients with nausea and vomiting associated with idiopathic gastroparesis, which was unresponsive or intolerant to prokinetic and antiemetic drugs, received Enterra™ implants and had the device turned on for 6 weeks. Subsequently, 27 of these patients were randomized to have the device turned on or off for 2 consecutive 3 month periods. Twenty five of these subjects completed the randomized phase; of note, 2 subjects had the device turned on early, 2 subjects had randomization assignment errors, and 1 subject had missing diaries. During the initial 6-week on period, all subjects demonstrated improvements in their WVF, demonstrating a median reduction of 61.2% compared with baseline (17.3 episodes/week at baseline vs 5.5 episodes/week at 6 week postimplant, p<0.001). During the on-off crossover phase, subjects demonstrated no significant differences between the on and off phase in the study's primary end point, median WVF (median 6.4 in the on phase vs 9.8 in the off phase; p=1.0). Among the 19 subjects who completed 12 months of follow up, there was an 87.1% reduction in median WVF compared with baseline (17.3 episodes/week at baseline vs 2 episodes/week at 12-month follow-up, p<0.001). Two subjects required surgical intervention for lead migration/dislodgement or neurostimulator migration.

Nonrandomized Studies

Samaan (2022) compared GES to laparoscopic gastrectomy in a retrospective, single-center analysis.[9] Overall, 130 refractory patients underwent GES while 51 received laparoscopic gastrectomy. Patients receiving GES were less likely to report symptom improvement compared with gastrectomy (odds ratio [OR], 0.16; 95% CI 0.048 to 0.532) over a mean follow-up period of 35 months. However, patients receiving gastrectomy had greater in-hospital morbidity (18% vs. 5%; p=0.017) and longer hospital stays (9 days vs. 3 days (p<0.001). The authors concluded that further study was needed to determine which patients might benefit from operative treatment of refractory gastroparesis.

Laine (2018) published a retrospective, multicenter analysis of patients with severe, medically refractory gastroparesis who received GES.[10] Fourteen patients (11 diabetic, 1 idiopathic, and 2 postoperative) treated in Finland between 2007 and 2015 were included; median follow-up was 3 years. Eight (57.1%) patients experience marked relief of gastroparesis symptoms, while 3 (21.4%) patients experience partial relief. There was a median weight gain of 5.1 kg in 11 (78.6%) patients after GES implantation, and, at last possible follow-up, 5 out of 10 (50%) patients were without medication for gastroparesis. The study was limited by its retrospective nature, small population size, and relatively short follow-up time.

Shada (2018) published a prospective study of patients with medically refractory gastroparesis who underwent implantation of GES between 2005 and 2016.[10] One hundred nineteen patients (64 diabetic, 55 idiopathic), with mean follow-up of 39.0 ± 32.0 months, were included in the analysis. Before GES placement, operatively placed feeding tubes were present in 22% of diabetic and 17% of idiopathic patients, however, after GES placement, 67% of feeding tubes were removed. Due to a perceived lack of benefit, 8 patients decided to have their GES device removed after a mean time of 36 ± 29 months. Also, there was significant improvement in GCSI scores for both diabetic (p=0.01) and idiopathic (p=0.003) subgroups at ≥2 years after implantation. The study was limited by its not all patients being administered the GCSI before GES, and a number of patients being lost to follow-up.

In 2016, Heckert reported on GES as a treatment for refractory symptoms of gastroparesis in 138 patients (65 diabetic, 68 idiopathic, and 5 other) with delayed gastric emptying at one-year follow-up (1.4 ± 1.0 years).[11] Patients reported their response to GES using the Clinical

Patient Grading Assessment Scale (CPGAS), of which, 75% of patients felt their symptoms had improved, and 25% felt their symptoms were the same or worsened (diabetics had a greater response than idiopathic patients). Symptom severity was assessed by analyzing Patient Assessment of GI Symptoms (PAGI-SYM) questionnaires, before insertion of GES and at the last follow-up visit. PAGI-SYM scores were improved for all symptoms, though the authors report nausea, early satiety and loss of appetite to have been most improved; and constipation, diarrhea, and abdominal distension to have been least improved. In this selected group of patients, the authors concluded GES to be beneficial in the majority of patients.

In 2013, Keller reported complication rates and need for a second surgery in 233 patients who had GES implantation surgery over a ten year period at a single institution.[12] Additional surgery was required in 58% of patients. The majority of reoperations were due to the following complications: nutritional access (45 patients, requiring 77 procedures), subcutaneous pocket issues (n = 21), gastroparetic symptoms (n = 11), mechanical issues (n = 9) and infection (n = 4). The study reported that patient BMI was predictive of additional surgeries, with 4.45 overall increased risk of pocket revision surgery. Although 70% of patients reported improved symptoms of pain, bloating and nausea, GES had a significantly high reoperation rate due to complications associated with the initial procedure.

In 2007, Anand reported on a study of 214 consecutive drug-refractory patients with the symptoms of gastroparesis (146 idiopathic, 45 diabetic, 23 after surgery).[13] A GES device was implanted in 156 patients. The remaining 58 patients, designated as the control group, were either on the waiting list for permanent implantation or consented to not receive a permanent implant. At last follow-up (median 4 years), most patients who received implants (135 of 156) were alive with intact devices, significantly reduced gastrointestinal symptoms, and improved health-related quality of life, with evidence of improved gastric emptying. Also, 90% of the patients had a response in at least 1 of 3 main symptoms. Most patients that explanted, usually for pocket infections, were later successfully reimplanted.

GES placement using minimally invasive surgical approaches has also been evaluated in several publications. Laparoscopy has been reported in at least two studies as a feasible approach in placement of GES for patients with medically refractory diabetic or idiopathic gastroparesis.[14, 15]

Several small case series and retrospective reviews have been reported, some with long-term outcomes up to 5 years.[14, 16-32] The data indicate that GES may be associated with improvements in gastrointestinal symptom scores, nutrition and quality-of-life for patients; these improvements were sustained over time. However, gastric emptying rates were mixed.

Adverse Events

In 2017, Bielefeldt analyzed the number, severity and type of voluntarily reported adverse events related to Enterra™ in the Manufacturer and User Device Experience (MAUDE) databank of the FDA.[33] Data were retrieved for 2001 through October 31, 2015, of which 1472 reports were abstracted. Thirty-six perioperative complication reports were reviewed; six were serious events, including three deaths (one due to cardiac arrest, two due to septic complications with resulting multi organ failure), one stroke, and one myocardial infarction complicated further by a pulmonary embolism. Overall, most of the reports were regarding patient concerns, local complications, or system failure. Limitations of these findings include reporting bias (the MAUDE data are voluntarily submitted), and report misclassification bias (MAUDE data sources vary from patient reports to published articles and inconsistencies in reporting have been found). Risk-

benefit could not directly be assessed given the nature of the MAUDE database, though the author cites other studies for outcomes measurement, most of which are included in the other sections of this evidence review. Overall, 35% of the reported adverse events prompted an additional surgery.

Section Summary

The evidence regarding the clinical utility of GES for gastroparesis due to intractable nausea and vomiting is limited to three small crossover RCTs. However, longer-term data suggest improvements in gastrointestinal symptom scores, nutrition, and quality-of-life scores, suggesting some benefit with GES treatment. Given the lack of alternative treatment options in this specific patient population, GES may be considered reasonable treatment of symptoms of gastroparesis.

GASTRIC STIMULATION FOR THE TREATMENT OF OBESITY

Systematic Review

In 2014, Cha published a review of 33 studies evaluating various methods of gastric stimulation as a treatment of obesity, including implantable GES.[34] The majority of included studies were small in nature with 24 studies evaluating 30 or fewer patients. In addition, many of the studies reported high dropout rates of more than 50% of patients at the end of the study follow-up period. A major limitation of the review was the inclusion of studies which did not include the treatment of obesity (i.e., BMI or weight loss) as a primary outcome measure. Furthermore, there were methodological difference in the patient inclusion criteria and most of the studies included in the review were limited by short-term follow-up of less than one year. The authors concluded that the level of evidence regarding GES as a treatment of obesity was low. Long-term RCTs which compare GES to other treatments of obesity and sham are needed in order to assess the safety and efficacy of GES in this population.

Randomized Controlled Trials

There is one published RCT on GES for the treatment of obesity. In 2009, Shikora reported on a randomized controlled, double-blind study (SHAPE trial) to evaluate GES for the treatment of obesity.[35] All 190 patients participating in the study received an implantable gastric stimulator and were randomized to have the stimulator turned on or off. All patients were evaluated monthly, participated in support groups and reduced their diet by 500-kcal/day. At 12-month follow-up, there was no difference in excess weight loss between the treatment group (weight loss of 11.8% +/- 17.6%) and the control group (weight loss of 11.7% +/- 16.9%) using intention-to-treat analysis (p=0.717).

Nonrandomized Studies

Additional, small studies – including one patient population with comorbidities of gastroparesis and morbid obesity – have reported positive outcomes in weight loss and maintenance of weight loss along with minimal complications.[36-41] However, due to lack of long-term outcomes from well-designed randomized clinical trials, conclusions cannot be made concerning the safety and efficacy of chronic gastric stimulation as a treatment for morbid obesity.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF GASTROENTEROLOGY[42]

In 2022, the American College of Gastroenterology updated practice guidelines on the management of gastroparesis.[43] and recommended that "Gastric electric stimulation (GES) may be considered for control of GP [gastroparesis] symptoms as a humanitarian use device (HUD) (conditional recommendation, low quality of evidence)."

The American College of Gastroenterology (ACG) published a clinical practice guideline on management of gastroparesis in 2013. The recommendations for this guideline were based on review of the evidence-base through 2011. The ACG concluded that GES treatment does not adequately address the clinical needs of these patients, but that, “GES may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Symptom severity and gastric emptying have been shown to improve in patients with diabetic gastroparesis (DG), but not in patients with idiopathic gastroparesis (IG) or postsurgical gastroparesis (PSG). (Conditional recommendation, moderate level of evidence.).”

SUMMARY

It appears that gastric electrical stimulation (GES) may improve intractable nausea and vomiting for patients with gastroparesis. Clinical guidelines based on research state GES may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Therefore, given the lack of treatment options in this very specific patient population, GES may be medically necessary in carefully selected patients with gastroparesis when policy Criteria are met. GES for the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology is considered not medically necessary when policy Criteria are not met.

There is limited evidence on the efficacy and safety gastric electrical stimulation for any other indication including but not limited to the treatment of obesity. There are no clinical practice guidelines that recommend the use of gastric electrical stimulation for any other indication. Therefore, the use of electrical gastric stimulation for all other indications including treatment for obesity are considered investigational.

In certain situations, a stimulator may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing gastric electrical stimulator may be considered medically necessary after the device has been placed.

In certain situations, a gastric electrical stimulator may no longer be able to perform its basic function due to damage or wear. When a gastric electrical stimulator is out of its warranty period and cannot be repaired adequately to meet the patient’s medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a gastric electrical stimulator may be considered medically necessary when device replacement Criteria are met.

When a gastric electrical stimulator is in its warranty period or can be repaired or adapted adequately to meet the patient’s medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a gastric electrical stimulator is considered not medically necessary when device replacement Criteria are not met.

REFERENCES

1. Enterra Therapy System FDA Summary of Safety and Effectiveness Data (SSED). [cited 5/23/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf/H990014b.pdf.
2. Levinthal DJ, Bielefeldt K. Systematic review and meta-analysis: Gastric electrical stimulation for gastroparesis. *Autonomic neuroscience : basic & clinical.* 2017;202:45-55. PMID: 27085627
3. Lal N, Livemore S, Dunne D, et al. Gastric Electrical Stimulation with the Enterra System: A Systematic Review. *Gastroenterology research and practice.* 2015;2015:762972. PMID: 26246804
4. Chu H, Lin Z, Zhong L, et al. Treatment of high-frequency gastric electrical stimulation for gastroparesis. *Journal of gastroenterology and hepatology.* 2012;27(6):1017-26. PMID: 22128901
5. Saleem S, Aziz M, Khan AA, et al. Gastric Electrical Stimulation for the Treatment of Gastroparesis or Gastroparesis-like Symptoms: A Systemic Review and Meta-analysis. *Neuromodulation.* 2022. PMID: 36464562
6. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology.* 2003;125(2):421-8. PMID: 12891544
7. Laine M, Siren J, Koskenpato J, et al. Outcomes of High-Frequency Gastric Electric Stimulation for the Treatment of Severe, Medically Refractory Gastroparesis in Finland. *Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society.* 2018;107(2):124-29. PMID: 29268656
8. McCallum RW, Sarosiek I, Parkman HP, et al. Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. *Neurogastroenterol Motil.* 2013;25(10):815-e636. PMID: 23895180
9. Samaan JS, Toubat O, Alicuben ET, et al. Gastric electric stimulator versus gastrectomy for the treatment of medically refractory gastroparesis. *Surgical endoscopy.* 2022;36(10):7561-68. PMID: 35338403
10. Shada A, Nielsen A, Marowski S, et al. Wisconsin's Enterra Therapy Experience: A multi-institutional review of gastric electrical stimulation for medically refractory gastroparesis. *Surgery.* 2018;164(4):760-65. PMID: 30072246
11. Heckert J, Sankineni A, Hughes WB, et al. Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center. *Digestive diseases and sciences.* 2016;61(1):168-75. PMID: 26280084
12. Keller DS, Parkman HP, Boucek DO, et al. Surgical outcomes after gastric electric stimulator placement for refractory gastroparesis. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(4):620-6. PMID: 23358845
13. Anand C, Al-Juburi A, Familoni B, et al. Gastric electrical stimulation is safe and effective: a long-term study in patients with drug-refractory gastroparesis in three regional centers. *Digestion.* 2007;75(2-3):83-9. PMID: 17519527
14. Timratana P, El-Hayek K, Shimizu H, et al. Laparoscopic gastric electrical stimulation for medically refractory diabetic and idiopathic gastroparesis. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(3):461-70. PMID: 23288718
15. Zehetner J, Ravari F, Ayazi S, et al. Minimally invasive surgical approach for the treatment of gastroparesis. *Surgical endoscopy.* 2013;27(1):61-6. PMID: 22752276

16. Abell T, Lou J, Tabbaa M, et al. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. *JPEN J Parenter Enteral Nutr.* 2003;27(4):277-81. PMID: 12903891
17. Forster J, Sarosiek I, Lin Z, et al. Further experience with gastric stimulation to treat drug refractory gastroparesis. *Am J Surg.* 2003;186(6):690-5. PMID: 14672781
18. van der Voort IR, Becker JC, Dietl KH, et al. Gastric electrical stimulation results in improved metabolic control in diabetic patients suffering from gastroparesis. *Exp Clin Endocrinol Diabetes.* 2005;113(1):38-42. PMID: 15662594
19. Lin Z, Forster J, Sarosiek I, et al. Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. *Diabetes Care.* 2004;27(5):1071-6. PMID: 15111523
20. Lin Z, Sarosiek I, Forster J, et al. Symptom responses, long-term outcomes and adverse events beyond 3 years of high-frequency gastric electrical stimulation for gastroparesis. *Neurogastroenterol Motil.* 2006;18(1):18-27. PMID: 16371079
21. Mason RJ, Lipham J, Eckerling G, et al. Gastric electrical stimulation: an alternative surgical therapy for patients with gastroparesis. *Arch Surg.* 2005;140(9):841-6; discussion 47-8. PMID: 16172292
22. Brody F, Vaziri K, Saddler A, et al. Gastric electrical stimulation for gastroparesis. *J Am Coll Surg.* 2008;207(4):533-8. PMID: 18926455
23. McKenna D, Beverstein G, Reichelderfer M, et al. Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. *Surgery.* 2008;144(4):566-72; discussion 72-4. PMID: 18847640
24. McCallum RW, Lin Z, Forster J, et al. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol.* 2011;9(4):314-19 e1. PMID: 21185396
25. Hou Q, Lin Z, Mayo MS, et al. Is symptom relief associated with reduction in gastric retention after gastric electrical stimulation treatment in patients with gastroparesis? A sensitivity analysis with logistic regression models. *Neurogastroenterol Motil.* 2012. PMID: 22497770
26. Gourcerol G, Huet E, Vandaele N, et al. Long term efficacy of gastric electrical stimulation in intractable nausea and vomiting. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver.* 2012;44(7):563-8. PMID: 22387288
27. Lahr CJ, Griffith J, Subramony C, et al. Gastric electrical stimulation for abdominal pain in patients with symptoms of gastroparesis. *The American surgeon.* 2013;79(5):457-64. PMID: 23635579
28. Teich S, Mousa HM, Punati J, et al. Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents. *Journal of pediatric surgery.* 2013;48(1):178-83. PMID: 23331812
29. Lu PL, Teich S, Di Lorenzo C, et al. Improvement of quality of life and symptoms after gastric electrical stimulation in children with functional dyspepsia. *Neurogastroenterol Motil.* 2013;25(7):567-e456. PMID: 23433238
30. Harrison NS, Williams PA, Walker MR, et al. Evaluation and Treatment of Gastric Stimulator Failure in Patients With Gastroparesis. *Surg Innov.* 2013;21:244-49. PMID: 24056201
31. Jayanthi NV, Dexter SP, Sarela AI. Gastric electrical stimulation for treatment of clinically severe gastroparesis. *J Minim Access Surg.* 2013;9:163-7. PMID: 24250062
32. Islam S, McLaughlin J, Pierson J, et al. Long-term outcomes of gastric electrical stimulation in children with gastroparesis. *Journal of pediatric surgery.* 2016;51(1):67-71. PMID: 26526207

33. Bielefeldt K. Adverse events of gastric electrical stimulators recorded in the Manufacturer and User Device Experience (MAUDE) Registry. *Autonomic neuroscience : basic & clinical.* 2017;202:40-44. PMID: 26850819
34. Cha R, Marescaux J, Diana M. Updates on gastric electrical stimulation to treat obesity: Systematic review and future perspectives. *World journal of gastrointestinal endoscopy.* 2014;6(9):419-31. PMID: 25228944
35. Shikora SA, Bergenstal R, Bessler M, et al. Implantable gastric stimulation for the treatment of clinically severe obesity: results of the SHAPE trial. *Surg Obes Relat Dis.* 2009;5:31-7. PMID: 19071066
36. Favretti F, De Luca M, Segato G, et al. Treatment of morbid obesity with the Transcend Implantable Gastric Stimulator (IGS): a prospective survey. *Obes Surg.* 2004;14(5):666-70. PMID: 15186636
37. Shikora SA. Implantable gastric stimulation for the treatment of severe obesity. *Obes Surg.* 2004;14(4):545-8. PMID: 15130236
38. Cigaina V, Hirschberg AL. Gastric pacing for morbid obesity: plasma levels of gastrointestinal peptides and leptin. *Obes Res.* 2003;11(12):1456-62. PMID: 14694209
39. De Luca M, Segato G, Busetto L, et al. Progress in implantable gastric stimulation: summary of results of the European multi-center study. *Obes Surg.* 2004;14 Suppl 1:S33-9. PMID: 15479588
40. D'Argent J. Gastric electrical stimulation as therapy of morbid obesity: preliminary results from the French study. *Obes Surg.* 2002;12 Suppl 1:21S-25S. PMID: 11969104
41. Sun Z, Rodriguez J, McMichael J, et al. Surgical treatment of medically refractory gastroparesis in the morbidly obese. *Surgical endoscopy.* 2015;29(9):2683-9. PMID: 25595741
42. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol.* 2013;108:18-37; quiz 38. PMID: 23147521
43. Camilleri M, Kuo B, Nguyen L, et al. ACG Clinical Guideline: Gastroparesis. *Am J Gastroenterol.* 2022;117(8):1197-220. PMID: 35926490

CODES

NOTES:

- The CPT coding manual indicates that procedures related to laparoscopic gastric stimulation electrodes for morbid obesity should be reported using code 43659 - Unlisted laparoscopy procedure, stomach
- HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
CPT	43647	Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum
	43648	Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum
	43659	Unlisted laparoscopy procedure, stomach
	43881	Implantation or replacement of gastric neurostimulator electrodes, antrum, open
	43882	Revision or removal of gastric neurostimulator electrodes, antrum, open
	43999	Unlisted procedure, stomach
	64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver

Codes	Number	Description
	64595	Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array
		Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient measurements) gastric neurostimulator pulse generator/transmitter; intraoperative, with programming
	95981	;subsequent, without programming
		;subsequent, with reprogramming
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C1883	Adaptor/Extension, pacing lead or neurostimular lead (implantable)
		Lead neurostimulator test kit (implantable)
	E0765	FDA approved nerve stimulator, with replaceable batteries, for treatment of nausea and vomiting
		Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	;non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	;non-rechargeable, includes extension

Appendix 1: Prokinetic Medications	
Class	**Common Examples**
Cholinergic Agonists	dexpanthenol (Ilopan®), bethanechol (Urecholine®)
Motolin receptor agonists	erythromycin
	metoclopramide (Reglan®)

Appendix 2: Antiemetic Medications	
Class	**Common Examples**
Antihistamines	diphenhydramine (Benadryl®), dimenhydrinate (Dramamine®), meclizine (Antivert®), hydroxyzine (Vistaril®), trimethobenzamide (Tigan®)
Serotonin ($5HT_3$) receptor antagonists	ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®)
Dopamine receptor antagonists	Metoclopramide (Reglan®), perphenazine (Trilafon®), prochlorperazine (Compazine®), promethazine (Phenergan®), thiethylperazine (Torecan®), cyclizine (Marezine®)

Date of Origin: *February 2001*

Regence

Medical Policy Manual Surgery, Policy No. 121

Transcutaneous Bone-Conduction and Bone-Anchored Hearing Aids

Effective: May 1, 2024

Next Review: March 2025
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

External bone-conduction hearing aids function by transmitting sound waves through the bone of the skull to the inner ear.

MEDICAL POLICY CRITERIA

Notes:

- This policy applies *only* to bone-conduction hearing aid systems that are bone anchored (also called bone-anchored hearing aids (BAHAs) or osseointegrated implants) or transcutaneous (non-surgical, secured by a Softband or other method). It does *not* apply to cochlear implants, which are addressed in a separate medical policy (see Cross References), or to intraoral bone-conduction hearing aids.
- Both bone-anchored and transcutaneous bone-conduction systems are hearing aids. There may be specific member benefit language addressing coverage of hearing aids. Any specific contract language supersedes medical policy. Unless otherwise specified, the contract language addressing coverage of hearing aids applies to both bone-conduction hearing aids and externally worn air-conduction hearing aids.

- Oregon HB 4104 Coverage of Hearing Loss Treatments (Oregon Hearing Mandate), effective January 1, 2019, requires coverage of medically necessary hearing aids, including specified replacement supplies, for Oregon members meeting age and educational enrollment requirements. This coverage is detailed in applicable contracts. Note that contract language rather than Criterion IV. may apply for Oregon members meeting the parameters of the Oregon Hearing Mandate.

I. **Unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s)** may be considered **medically necessary** as an alternative to air-conduction hearing aid(s) for conductive or mixed hearing loss when all of the following criteria (A.-D.) are met:

A. Patients who meet any of the following criteria:

1. Congenital or surgically induced malformations (e.g., atresia) of the external ear canal or middle ear; or
2. Chronic external otitis or otitis media; or
3. Tumors of the external canal and/or tympanic cavity; or
4. Dermatitis of the external canal.

B. A bone-conduction pure tone average threshold at 0.5, 1, 2, and 3 kHz no poorer than (i.e. threshold average of 0.5, 1, 2, and 3 kHz no higher than) one of the following (see Policy Guidelines):

1. 25 dB for ADHEAR; or
2. 45 dB for OBC, Ponto 3, Ponto 4, BONEBRIDGE, Baha4 and Baha5 devices; or
3. 55 dB for Ponto 3 Power, BAHA 5 Power, BAHA 6 Max, Osia, and Osia 2 devices; or
4. 65 dB for Ponto 3 SuperPower and BAHA 5 SuperPower devices; or
5. For a device not listed above, average threshold consistent with the device-specific FDA indication.

C. Meet one of the following age requirements:

1. 12 years or older for BONEBRIDGE, Osia, or Osia 2; or
2. 5 years or older for all other surgically implanted devices; or
3. Any age for non-surgically implanted devices; or
4. For a device not listed above, age consistent with the device-specific FDA indication (See Policy Guidelines).

D. Patients are to receive either:

1. A unilateral bone-conduction hearing aid; or
2. Bilateral bone-conduction hearing aids and have symmetrically conductive or mixed hearing loss (measured without augmentation) as defined by a difference between left- and right-side bone-conduction threshold of less than 10 dB on average measured at 0.5, 1, 2 and 3 kHz (and also 4 kHz for OBC,

Ponto Pro 3, and Otomag Alpha 1 [M]), or less than 15 dB at individual frequencies.

II. **A transcutaneous bone-conduction or bone-anchored hearing aid** may be considered **medically necessary** as an alternative to an air-conduction contralateral routing of signals (CROS) hearing aid in patients five years of age and older with single-sided sensorineural deafness and normal hearing in the other ear.

III. Other uses of transcutaneous bone-conduction or bone-anchored hearing aids, including but not limited to when Criterion I or II is not met and use in patients with bilateral sensorineural hearing loss, are considered **investigational**.

IV. **Implant replacement**, including **replacement parts or upgrades** to existing bone-anchored hearing aids and/or components, may be considered **medically necessary** when components are no longer functional, or for functional devices only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work.

V. **Implant replacement,** including **replacement parts or upgrades** to existing bone-anchored hearing aids and/or components are considered **not medically necessary** when Criterion IV. is not met, including but not limited to when requested for convenience or technology upgrade. Replacement parts or upgrades include, but are not limited to batteries, processors, headbands or Softbands. This criterion may not apply to Oregon members who meet the parameters of the Oregon Hearing Mandate (see applicable contracts for details).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

HEARING TESTS

Pure tone hearing tests measure the faintest level (hearing threshold) at which a tone can be heard at selected frequencies approximately 50% of the time. Lower thresholds represent better hearing.

Each ear is tested separately. The pure tone average threshold hearing level is calculated separately for each ear by averaging the hearing levels at each frequency. For example, if a patient's bone-conduction hearing threshold in the right ear at frequencies 0.5, 1, 2, and 3 kHz is 20, 20, 30, and 40 dB, respectively, the pure tone average for that ear is (20 + 20 + 30 + 40) divided by 4 = 27.5 dB.

Bone-conduction hearing is necessary for bone conduction hearing aids to provide value. The threshold required depends on the specific device, as listed in the policy criteria and in the FDA approval documentation. For example, given that lower thresholds represent better hearing, a bone-conduction pure tone average threshold of 40 dB would meet the criteria of no poorer than (*no higher than*) 45 dB (e.g. for the Ponto 3 device), while a bone-conduction pure tone average threshold of 50 dB would *not* meet the criteria of no poorer than (*no higher than*) 45 dB, but it would meet the criteria of no poorer than (*no higher than*) 55 dB (e.g. for the Ponto 3 Power device).

FDA APPROVAL

FDA-approved indications can be found by searching by device name in the FDA 510(k) Premarket Notification Database or the De Novo Database and viewing the Summary. Product codes for these devices include LXB, MAH, and PFO.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Audiology test results

CROSS REFERENCES

1. Cochlear Implant, Surgery Policy No. 8

BACKGROUND

Conventional external hearing aids can be generally subdivided into air-conduction hearing aids and bone-conduction hearing aids. Air-conduction hearing aids require the use of ear molds, which may be problematic in patients with chronic middle ear and ear canal infections, atresia of the external canal, or an ear canal that cannot accommodate an ear mold. In these patients, bone-conduction hearing aids may be an alternative.

External bone-conduction hearing aids historically were closely applied to the temporal bone with either a steel spring over the top of the head or with the use of a spring-loaded arm on a pair of spectacles. These devices may be associated with either pressure headaches or soreness. Partially implantable bone-conduction hearing aids have been investigated as an alternative, and external bone-conduction hearing aids applied with less or no pressure have also become available.

The bone-anchored hearing aid (BAHA) implant systems, also called osseointegrated devices, work by combining a vibrational transducer coupled directly to the skull via a percutaneous abutment that permanently protrudes through the skin from a small titanium implant anchored in the temporal bone. The system is based on the process of “osseointegration” through which living tissue integrates with titanium in the implant over a period of three to six months, allowing amplified and processed sound to be conducted via the skull bone directly to the cochlea. The lack of intervening skin permits the transmission of vibrations at a lower energy level than required for external bone-conduction hearing aids.

The BAHA device has been used successfully in children younger than five years in Europe and the United Kingdom. (The most recent [1999] update of the U.S. Food and Drug Administration [FDA] notification lists age less than five years as a contraindication.) A number of reports describe experience with preschool children or children with developmental issues that might interfere with maintenance of the device and skin integrity. A two-stage procedure is used in young children with the fixture placed into the bone at the first stage and, after three to six months to allow for osseointegration, a second procedure to connect the abutment through the skin to the fixture.

Baha sound processors can also be used with the Baha® Softband™. With this application there is no implantation surgery. The sound processor is attached to the head using either a hard or soft headband. The band can be adjusted to the individual's head size. The amplified sound is transmitted transcutaneously to the bones of the skull for transmission to the cochlea. These devices have been suggested as a bridge to bone anchor implantation in young children who are not eligible for the implant due to young age and/or bone strength/thickness not yet adequate. The recently approved ADHEAR device attaches with an adhesive and no headband is required.

Partially implantable magnetic bone conduction hearing systems, also referred to as transcutaneous bone-anchored systems, are an alternative to bone conduction hearing systems connected percutaneously via an abutment. With this technique, acoustic transmission occurs transcutaneously via magnetic coupling of the external sound processor and the internally implanted device components. The bone conduction hearing processor contains a magnet that adheres externally to magnets implanted in shallow bone beds with the bone conduction hearing implant. Since the processor adheres magnetically to the implant, there is no need for a percutaneous abutment. To facilitate greater transmission of acoustics between magnets, skin thickness may be reduced to 4-5 mm over the implant when it is surgically placed.

REGULATORY STATUS

The following *Baha® sound processors, currently marketed by Cochlear™ (formerly called Cochlear™ Americas), have received 510(k) clearance from the U.S. Food and Drug Administration (FDA) for use with the Baha auditory osseointegrated implant (hearing aid) systems (such as the Baha® Connect and Attract systems):

- Baha® 5 Sound Processor
- Baha® 5 SuperPower Sound Processor
- Baha® 5 Power Sound Processor
- Baha® 6 Max Sound Processor

The above devices are currently available from Cochlear™. However, predicate devices include the Baha®4, Cordelle II, Divino®, Intenso™ and BP100™.

*Note: These devices may be referred to as Cochlear™ Baha® systems or Cochlear osseointegrated implants, reflecting the manufacturer’s name. These devices are bone conduction hearing aids and *should not* be confused with cochlear implants which are prostheses that replace a damaged or absent cochlea in the inner ear. Cochlear implants are addressed in a separate medical policy (see Cross References).

The FDA approved the Cochlear™ Baha® system (initially approved under the trade name Branemark Bone-Anchored Hearing Aid [BAHA™] by Entific Medical Systems, Inc.) for use in children aged five years and older, and in adults, for the following indications:

- Patients who have conductive or mixed hearing loss and can still benefit from sound amplification;
- Patients with bilaterally symmetric conductive or mixed hearing loss, may be implanted bilaterally;
- Patients with sensorineural deafness in one ear and normal hearing in the other (i.e., single-sided deafness, SSD);
- Patients who are candidates for an air-conduction contralateral routing of signals (AC

CROS) hearing aid but who cannot or will not wear an AC CROS device.

Baha sound processors can also be used with the Baha® Softband and Baha® SoundArc. The Baha® Softband received FDA clearance in 2002 for use in children under the age of five years. The Baha® SoundArc received FDA clearance in 2017 for use in people of any age.

Subsequent bone conduction hearing systems (listed below) share similar indications as the Cochlear™ Baha® devices:

- OBC Bone Anchored Hearing Aid System (Oticon Medical)
- Sophono® (S) (Cochlear) (predicate device was Otomag [Sophono])
- Ponto Pro, Ponto Plus, Ponto Plus Power, Ponto 3, Ponto 3 Power, Ponto 3 SuperPower,Ponto 4 and Ponto 5 SuperPower processors (Oticon Medical), to be used with the Oticon or BAHA osseointegrated implant.

The MedEl ADHEAR device, which has no implantable components, received FDA 510(k) clearance with the Contact Mini (audiofon) and BAHA 5 (Cochlear) as predicate devices.

The following partially implantable magnetic bone conduction devices have received FDA 510(k) clearance:

- Sophono® (M) (Cochlear) (predicate device was Otomag Alpha [Sophono])
- Sophono™ Alpha 2 MPO™ (Medtronic)
- Baha® Attract (Cochlear®)

The BoneBridge™ (MedEl) partially implantable bone-conduction hearing aid received FDA approval via the de novo pathway in 2018.

The Osia™ (Cochlear) bone-conduction hearing aid received FDA 510(k) approval with BoneBridge™ as the predicate device in July 2019. The Osia™ 2 received FDA 510(k) approval with Osia™ as the predicate device in November 2019.

EVIDENCE SUMMARY

Hearing results of semi-implantable bone-conduction hearing aids may be compared either to 1) external bone-conduction hearing aids in patients with atresias who are unable to use external air-conduction hearing aids, or 2) external air-conduction hearing aids in patients who are unable to tolerate air-conduction hearing aids due to chronic infection. Reported studies have suggested that the bone-anchored hearing aid (BAHA) is associated with improved hearing outcomes compared to external bone-conduction hearing aids and equivalent outcomes compared to conventional air-conduction hearing aids.[1-4] However, given the objectively measured outcomes and the largely invariable natural history of hearing loss in individuals who would be eligible for an implantable bone-conduction device, a within-subjects comparison of hearing before and after device placement may be a reasonable study design.

UNILATERAL DEVICES

Systematic Review

In 2017 Kim conducted a systematic review on the efficacy of BAHAs in single-sided deafness, including 14 studies (n=296 patients). The reviewers reported that in the six studies that dealt with sound localization, no significant difference was found after the implantation. However,

twelve studies showed the benefits of BAHAs for speech discrimination in noise. Regarding subjective outcomes of using the prosthesis in patients with SSD (abbreviated profile of hearing aid benefit [APHAB] and the Glasgow hearing aid benefit profile [GHABP], etc.), improvements in quality of life were reported in the majority of studies.

This systematic review has indicated that BAHAs may successfully rehabilitate patients with SSD by alleviating the hearing handicap to a certain degree, which could improve patients' quality of life. This report has presented additional evidence of effective auditory rehabilitation for SSD and will be helpful to clinicians counseling patients regarding treatment options for SSD

In a 2015 Peters published a systematic review of the literature through April 7, 2014 on the use of BAHA devices with contralateral routing of sound systems for single-sided deafness (SSD).[5] Five[6-10] of the six studies that met inclusion criteria were rated as moderate to high directness of evidence and low to moderate risk of bias and, thus, were included in the review. Significant heterogeneity was found in the 91 total patients included. For speech perception in noise there was not consistent improvement with aided hearing over unaided hearing in all environments. All studies reported equal sound localization in the aided and unaided conditions, and quality of life measures were similar for the aided and unaided conditions. Interpretation of these outcomes was limited by the methodological limitations of the included studies, including the lack of RCTs, unclear inclusion criteria, small sample sizes, use in some studies of headband devices which have different bone conduction thresholds in the higher frequencies than implanted devices, clinical heterogeneity of included populations (e.g., duration of deafness, grade of hearing loss), unexplained missing data, and lack of long-term audiometric follow-up. The authors also noted that the lack of recent studies was surprising considering the recent advances in these devices and recommended high-quality studies on the clinical outcome of current devices.

Randomized Controlled Trials

No RCTs of unilateral BAHAs have been published.

Nonrandomized Studies

One retrospective study (Wazen 2021) compared results of BAHA implantation for SSD based on bone-conduction pure tone average (PTA) of the better-hearing ear.[11] Subjects were divided into three groups by bone conduction PTA of the better hearing ear, with the ranges of 0 to 20 dB, 21 to 40 dB, and 41 to 55 dB. All three groups showed statistically significant improvement in bone conduction PTA and quality of life.

Additionally, since publication of the Peters systematic review, the following prospective, interventional studies compared patient satisfaction with transcutaneous BAHA devices to CROS hearing aids for SSD.

Jakob (2021) compared long-term (one-year) results in patients with SSD who chose between a CROS, a BAHA, and a cochlear implant (CI) following a three-week test phase with CROS and a bone-anchored hearing system.[12] At the one-year follow up, study results showed an improvement in speech comprehension when speech was delivered to the deaf ear and noise to the hearing ear for the BAHA (p=0.008; median unaided=0%, median 12 m=40.59) and CI (p<0.001), but the CROS group had poorer speech comprehension compared to the unaided situation (median unaided=98.58%; median 12 m=64.62%, p=0.603). Localization error was

significantly reduced in the CI group after 12 months (median unaided 26.36°, median CI 12 m=15.43°; p<0.001) compared to the unaided conditions. No differences in localization error were found for the BAHA or CROS groups.

den Besten (2019) assessed 54 adults with SSD, each of whom underwent a trial with the Baha Softband before a trial of the percutaneous, partially implantable Baha Attract device.[13] No statistically significant difference in audiological outcomes was seen between the two devices (p>0.05). At a six-month follow-up after implantation, patients reported numbness (20%) and slight pain/discomfort (38%) associated with the device.

Choi (2019) compared the performance of contralateral routing of signal (CROS)/bilateral routing of signal (BiCROS) and soft-band bone-anchored hearing aid (BAHA) devices in 21 patients with unilateral sensorineural hearing loss.[14] All participants were naïve to hearing devices. Sound localization, speech perception, psychoacoustic performance, and subjective assessments were analyzed. The subjects were assessed with each device and in the unaided condition. Sound localization was not improved in the soft-band BAHA condition and was significantly impaired with the CROS/BiCROS. Both devices significantly improved speech-in-noise perception when targeted to the impaired ear side. With regard to psychoacoustic performance, temporal resolution was significantly decreased with the BAHA compared to the unaided condition and CROS/BiCROS. There were no significant differences reported for preference between devices or subjective assessments of background noise or sound quality.

In 2017, Snapp reported a prospective single-center study of 27 patients with unilateral severe-profound sensorineural hearing loss who had either a CROS (n=13) or transcutaneous BAHA (n=14) device.[15] Mean device use was 66 months for the BAHAs and 34 months for CROS devices. Both BAHA and CROS groups had significant improvement in speech-in-noise performance, but neither showed improvement in localization ability. There were no differences between the devices for subjective measures of posttreatment residual disability or satisfaction as measured by the Glasgow Hearing Aid Benefit Profile (GHABP).

Leterme (2015) assessed 24 adults with SSD, 18 of whom were evaluated with trials of both hearing aids with CROS and bone conduction–assisted hearing using the Baha Softband.[16] Most patients (72%), after completing trials of both devices, preferred the BAHA device to hearing aid with CROS. Glasgow Benefit Index and Abbreviated Profile of Hearing Aid Benefit (APHAB) scores did not differ significantly between devices. Sixteen of the 18 subjects elected to undergo implantation of a percutaneous BAHA device. In general, hearing improvement with the Baha Softband trial correlated with hearing improvements following device implantation.

BILATERAL DEVICES

Use of bilateral devices has been evaluated in nonrandomized studies of patients with conductive or mixed hearing losses. In general, bilateral BAHAs seem to provide additional objective and subjective benefit compared with unilateral BAHAs.

Systematic Reviews

Heath (2022) conducted a systematic review (SR) of studies that compared outcomes between bilateral and unilateral BAHA for patients with no benefit from conventional hearing aids.[17] A total of 14 articles were included; all studies were retrospective with the exception of one case report, and all studies had a substantial risk of bias. A meta-analysis was not performed, but descriptive comparison found that bilateral BAHA were associated with greater improvement in

hearing thresholds, understanding speech, and localization. Unilateral BAHA were more effective when noise was one-sided. All studies reported improvement in quality of life.

A systematic review by the Health Technology Assessment Program was published in 2011 on the use of bone-anchored hearing aids (BAHAs) for bilateral hearing impairment.[18, 19]The authors noted that the quality of available studies on the use of BAHAs is weak. No studies with control groups were identified for the review. Cohort pre-post studies and cross-sectional comparative studies demonstrated improvements in hearing with use of BAHAs over conventional bone-conduction hearing aids or unaided hearing. However, whether improvements in hearing with BAHAs are greater than air-conduction hearing aids is uncertain. Additionally, bilateral use of BAHAs improved hearing outcomes in some patients over unilateral use, but the evidence was uncertain. Implant loss was noted to be between 6.1% and 19.4%. The authors noted hearing-specific quality of life improved, but overall quality of life did not differ.

In 2012 Janssen reported similar findings in a systematic review that assessed the outcomes of bilateral versus unilateral BAHA for individuals with bilateral permanent conductive hearing loss (CHL).[20] Their search strategy included studies of all languages published between 1977 and July 2011. Studies were included if subjects of any age had permanent bilateral CHL and bilateral implanted BAHAs. Outcome measures of interest were any subjective or objective audiologic measures, quality of life indicators, or reports of adverse events. Eleven studies met their inclusion criteria. All 11 studies were observational. There were a total of 168 patients in the 11 studies, 155 of whom had BAHAs and 146 of whom had bilateral BAHAs. In most studies, comparisons between unilateral and bilateral BAHA were intra-subject. Patients ranged from 5 to 83 years of age; 46% were male, and 54% were female. Heterogeneity of the methodologies between studies precluded meta-analysis, therefore a qualitative review was performed. Results from three studies were excluded from synthesis because their patients had been included in multiple publications. Adverse events were not an outcome measure of any of the included studies. In general, bilateral BAHA was observed to provide additional objective and subjective benefit compared to unilateral BAHA. For example, the improvement in tone thresholds associated with bilateral BAHA ranged from 2 to 15dB, the improvement in speech recognition patterns ranged from 4 to 5.4dB, and the improvement in the Word Recognition Score ranged from 1 to 8%. However, these results were based on a limited number of small observational studies consisting of heterogeneous patient groups that varied in age, severity of hearing loss, etiology of hearing loss, and previous amplification experience.

Randomized Controlled Trials

No RCTs of bilateral BAHAs have been published.

Nonrandomized Studies

No new studies have been published since the most recent systematic review.

BAHA IN CHILDREN UNDER AGE FIVE YEARS

Nonrandomized Studies

The literature on the use of these devices in children consists of a review article and several nonrandomized studies.

The largest series in children under five years identified for this review, described by Amonoo-

Kuofi in 2015, which included 24 children identified from a single center's prospectively maintained database.[21] Most patients underwent a 2-stage surgical approach. The largest proportion of patients (52%) received the implant for isolated microtia, followed by Goldenhar syndrome (16%). Following implantation, 13 patients (54%) had grade 2 or 3 local reactions on the Holgers Scale (redness, moistness, and/or granulation tissue) and 7 (29%) had grade 4 local reactions on the Holgers Scale (extensive soft-tissue reaction requiring removal of the abutment). Quality of life scores (Glasgow Children's Benefit Inventory [GCBI]; scoring range, -100 to 100) were obtained in 18 subjects/parents with a finale mean score change of +40 points. Audiologic testing indicated that the average performance of the device fell within the range of normal auditory perception in noisy and quiet environments.

Marsella (2012) reported on their center's experience with pediatric BAHA in all 47 children implanted, seven of which were younger than five years of age.[22] The functional gain was significantly better with BAHA than with conventional bone-conduction hearing aids. There was no significant difference in terms of functional outcome between the seven patients younger than age five and the rest of the patient cohort. Based on these findings, the study authors suggested that implantation of children at an age younger than five years can be conducted safely and effectively in such settings. However, the conclusions from this study were limited by the small number of children younger than five years of age and the limited power to detect a difference between younger and older children.

A 2008 review article noted that for children younger than age five years, other solutions (such as a bone conductor with transcutaneous coupling) should be utilized.[23] This recommendation is in agreement with the FDA clearance of the osseointegration implant only for children five years of age and older, and adults.

McDermott (2008) reported on the role of BAHAs in children with Down syndrome in a retrospective case analysis and postal survey of complication rates and quality of life outcomes for 15 children aged 2 to 15 years.[24] All patients were using their BAHA devices after a follow-up of 14 months. No fixtures were lost, and skin problems were encountered in three patients. All 15 patients had improved social and physical functioning as a result of better hearing.

Davids (2007) at the University of Toronto provided BAHA devices to children less than five years of age for auditory and speech-language development and retrospectively compared surgical outcomes for a study group of 20 children five years or younger and a control group of 20 older children.[25] Children with cortical bone thickness greater than 4 mm underwent a single-stage procedure. The interstage interval for children having 2-stage procedures was significantly longer in the study group to allow implantation in younger patients without increasing surgical or postoperative morbidity. Two traumatic fractures occurred in the study group versus four in the older children. Three younger children required skin site revision. All children were wearing their BAHA devices at the time of writing.

BAHA SOFTBAND AND ADHESIVE HEARING DEVICE USE IN CHILDREN

Nonrandomized Studies

The current evidence consists of small retrospective studies and comparative studies. Externally worn AOD sound processors appears to consistently be beneficial for children under age five years with bilateral aural atresia who are too young to receive an implantable device.[26-28]

A 2014 report compared use of the Softband in 16 children (ages ranging from three months to

six years) with bilateral aural atresia to 29 normal-hearing children (ages ranging from eight months to six years).[29] Auditory development was assessed at baseline, six months, and 12 months. The full text of the article was not available and the abstract did not provide data from the normal-hearing children for comparison. The authors concluded that the Softband was a suitable bridge to surgical implantation in infants and young children with bilateral atresia.

Ramakrishnan used the Glasgow Benefit Inventory (GBI) and Listening Situation Questionnaire to report quality of life findings in a retrospective cross-sectional survey administered to parents of 22 children (n=109 total participants), some with skull and congenital/chromosomal abnormalities from inherited syndromes that involve unilateral (hemifocal microsomia) or bilateral hearing impairment (Treacher-Collins Syndrome, n=4 of 22) due to microtia or aural atresia.[30] The youngest child utilizing an externally worn BAHA with Softband was six months of age. Overall, parents reported short-term satisfaction in the mean GBI scores for the children after three months of implanted BAHA or externally worn BAHA with Softband use. Despite the heterogeneous etiology of children in the study population, the authors suggest that the utility of BAHAs for children with syndromes and craniofacial anomalies is poorly recognized, resulting in delays in aid fitting and therefore in early hearing rehabilitation. In such cases, surgical reconstruction of the ear canal and middle-ear defects is not only technically challenging but also plagued by poor results (with a high rate of ear canal restenosis and limited functional hearing benefit). Hence, alternative treatment options such as Softband and BAHA may be of considerable benefit.

In 2010 Christensen reported on a retrospective chart review of 10 children (ages 6 months to 16 years) with bilateral conductive hearing loss.[31] Participants had been initially fit with a traditional bone-conduction hearing aid, then progressed first to the externally worn AOS with the Softband, then to the implanted BAHA. Functional gain was measured at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz for each device. Both the external AOS and the implanted BAHA provided statistically significantly higher functional gain than the conventional BCHAs.

A number of the same authors for the Christensen study also reported the results of a retrospective chart review of 25 children aged 6 months to 18 years with craniofacial disorders and bilateral conductive hearing loss.

It is unknown whether some of the children in the 2010 study were also included in these results. The focus of this study was on functional as measure by comparison of aided (using the Baha Softband) and unaided soundfield audiometric thresholds. Soundfield thresholds were improved with the Baha amplification, with over 80% of the thresholds meeting significant target levels. The authors concluded that this demonstrated the benefit of the Baha for children with bilateral congenital conductive hearing loss.

Hol (2008) evaluated the validity of a BAHA with Softband (fitted unilaterally and bilaterally) in two young children with severe bilateral conductive hearing loss due to CAA.[32] In a small multicenter comparative study, 12 children (including the two children in the Hol, 2005 study) with bilateral CAA with a pure conductive hearing loss of around 60 dB HL were fitted with the BAHA with Softband.[33] These children were retrospectively compared to a reference group of eight children selected from a database of those who had a conventional bone conduction hearing aid for bilateral CAA. The authors reported the mean aided hearing threshold of the children with the BAHA with Softband compared to the reference group was 27 dB HL, ± 6 dB HL to 25 dB HL ± 6 dB HL, respectively. Further results compared psychological and language development in 5 of the 12 children available from the BAHA with Softband group.

ADVERSE EFFECTS OF BAHAS

Systematic Reviews

Hernández (2021) reported a retrospective chart review the frequency of cutaneous complications due to surgically implanted BAHAs.[34] Of the 88 patients identified (a total of 104 devices) with a minimum of six months of follow-up, 49 (55.7%) developed at least one episode of inflammatory or infectious skin reaction at the surgical incision site (mostly mild in severity), while 47 (53.4%) reported pain at the surgical site unrelated to clinically evident infection at some point during the follow-up.

Schwab (2020) completed a systematic review of adverse events associated with bone-conduction and middle-ear implants.[35] The 10 most frequently reported adverse events for bone conduction hearing implants included skin reactions (Holgers grade 1 to 3), skin revision surgery due to overgrowth or cellulitis, minor soft tissue/skin overgrowth, skin infection, surgical revision, reimplantation, failure to osseointegrate, and minor skin complications.

In 2016, Verheij published a systematic review on complications of tissue preservation surgical techniques with percutaneous BAHA devices including 18 studies with 381 devices.[36] The implantation techniques reported in the studies were as follows: punch method, four studies (81 implants); linear incision technique without soft tissue reduction, 13 studies (288 implants); and Weber technique, one study (12 implants). Indications for surgery were SSD (n=68), sensorineural hearing loss (n=4), mixed hearing loss (n=65), or CHL (n=66). The Holgers classification was used to grade soft tissue reactions (grade 0, no reaction; grade 2, red and moist tissue; grade 3, granulation tissue; grade 4, removal of skin-penetrating implant necessary due to infection). The incidence of Holgers 3 was 2.5% with the punch technique, 5.9% with the linear incision technique, and 0% with the Weber technique. Holgers 4 was reported in one patient implanted with the linear incision technique.

In 2014 Mohamad performed a systematic review focusing on the association between surgical technique and skin complications following BAHA implantation. Thirty randomized controlled trials and retrospective studies were included, which highlighted that the most common surgical techniques identified were full-thickness skin graft, dermatome and linear incision. The investigators reported that dermatome technique is associated with higher rate of skin complications and the use of a linear incision technique is associated with lower skin complications. However, the investigators concluded that the data to support these conclusions in limited and that higher quality studies are needed.[37]

In 2103 Kiringoda reported on a meta-analysis of complications related to BAHA devices. Included in the meta-analysis were 20 studies that evaluated complication in 2134 adult and pediatric patients who received a total of 2310 BAHA devices.[38] The quality of available studies was considered poor and lacking in uniformity. The most common complications related to BAHA devices were minor skin reactions. Holgers Grade 2 to 4 skin reactions were reported to occur from 2.4% to 38.1% in all studies. Zero to 18% of implants failed osseointegration in adult and mixed population studies while 0% to 14.3% failed osseointegration in pediatric population studies. Adult and mixed population studies reported revision surgery was required in 1.7% to 34.5% of cases while pediatric population studies reported required revision surgery in 0.0% to 44.4% of cases. Implant loss occurred in 1.6% to 17.4% in adult and mixed population studies and from 0.0% to 25% in pediatric studies.

Nonrandomized Studies

In 2016, Roplekar compared skin-related complications of the traditional skin flap method to the linear incision method performed by a single surgeon in 117 patients with at least one year of follow-up.[39] Twenty-one (24%) patients experienced skin-related complications in the skin flap group (12 skin overgrowths, eight wound infections, one numbness) and three (10%) patients experienced complications in the linear incision group (three wound infections).

Four 2014 retrospective studies reported specific complication rates related to BAHA implants. The rate of skin reaction (e.g., skin overgrowth, inflammation) ranged from 6% to 22%. Implant loss was 10-18% and were spontaneous while others required removal; the primary reasons for implant loss were loss of osseointegration, trauma, and soft tissue reactions or discomfort. In addition, a number of small studies reported the safety outcomes of various techniques for surgically implanting BAHA devices. These included skin flap versus full-thickness skin graft implantation[40], non-skin-thinning technique versus either flap or dermatome implantation[41], and techniques related to implant size[42, 43].

Section Summary: Safety and Adverse Events Related to BAHA Devices

The quality of available data for adverse events is generally poor with high heterogeneity. The most frequently reported complication from surgical procedures for BAHA insertion are adverse skin reactions, with an incidence of Holgers grade 2 to 4 reactions ranging from less than 2% to more than 34%, and implant loss ranging from less than 2% to more than 17%. There is some evidence of improvement in complication rates and severity with newer surgical techniques such as linear incision.

PARTIALLY IMPLANTABLE MAGNETIC BONE CONDUCTION HEARING AIDS

A small body of literature addresses outcomes associated with transcutaneous, partially implantable bone-anchored devices. The majority of studies use a within-subjects comparison of hearing thresholds with and without the device. The indications for partially implantable systems are the same as those for transcutaneous bone-anchored devices.

Systematic Reviews

Gutierrez (2024) published a SR comparing quality of life (QOL) outcomes of percutaneous and transcutaneous bone conduction devices (pBCD and tBCD, respectively).[44] A total of 52 articles with 1,469 patients were included. Six hundred eighty-nine patients were implanted with pBCDs, and the remaining 780 were implanted with tBCDs. Average Glasgow Benefit Inventory scores for the tBCD group (33.0, 95% confidence interval [22.7-43.3]) were significantly higher than the pBCD group (30.9 [25.2-36.6]) (Δ2.1 [1.4-2.8], $p < 0.0001$). Mean Glasgow Children's Benefit Inventory scores (Δ3.9 [2.0-5.8], $p = 0.0001$) and mean gain in Abbreviated Profile of Hearing Aid Benefit scores (Δ5.6 [4.8-6.4], $p < 0.0001$) were significantly higher among patients implanted with tBCDs than those implanted with pBCDs. Patients implanted with tBCDs also had significantly higher gains on the Speech (Δ1.1 [0.9-1.3], $p < 0.0001$), Spatial (Δ0.8 [0.7-0.9], $p < 0.0001$), and Qualities of Hearing (Δ1.2 [1.1-1.3], $p < 0.0001$) portions of the Speech, Spatial, and Qualities of Hearing Scale than those implanted with pBCDs. The authors conclude that patients implanted with transcutaneous devices had better QOL outcomes than those implanted with percutaneous devices.

Bezdjian (2017) published a systematic review of noncomparative studies that assessed outcomes and adverse events in patients with Sophono implants.[45] Thirteen articles were assessed for directness of evidence (DoE) and risk of bias (RoB) using predetermined criteria. Of these, eight studies (including 86 patients; 79.1% children) were considered to have high

enough quality for data extraction. These studies all had medium or low risk of bias and high directness of evidence. A pooled analysis of all studies showed an average unaided pure tone average of 63.70 dB and an aided pure tone average of 31.60 dB. Four studies reported unaided and aided sound reception thresholds in raw dB scores. A pooled analysis of these studies showed a mean unaided score of 66.90 dB and a mean aided score of 33.34. No intra-operative complications were reported and 29% of patients reported post-operative complications. Of these, three were serious adverse events. No implant loss occurred, except in one patient who requested explantation due to severe headaches. While there were improvements in auditory functions, no statistical analyses were reported.

In 2016, Dimitriadis reported on a systematic review of observational studies of the BAHA Attract device including 10 studies (total n=89 patients; range, 1 to 27 patients).[46] Seventeen (19%) of the patients were children, of whom five had unilateral sensorineural hearing loss and 4 had CHL. Of the 27 (45%) adults, 22 had unilateral sensorineural hearing loss and 11 (18%) had bilateral mixed hearing loss. Audiologic and functional outcome measures and the timing of testing varied greatly in the studies. Summary measures were not reported. In general, audiologic and functional outcomes measured pre- and postimplantation showed improvement, although statistical comparisons were lacking in some studies.

Randomized Studies

Gawecki (2022) completed a small randomized study that compared patients who received the Osia system (n=4) or the Baha Attract system (n=4) for bilateral mixed hearing loss.[47] After implantation, the mean gain in PTA was 42.8 ± 4.9 dB in the Osia group and 38.8 ± 8.5 dB in the Baha group. Patient ratings of hearing quality were better in the Osia group based on subjective Likert scores of sound loudness, sound distinctness, and hearing of own voice. Patient reported voice quality scores for reverberation were similar in the Osia and Baha groups. Both groups reported improved quality of life based on global Abbreviated Profile of Hearing Aid Benefit scores but there was a numerically larger improvement in the Osia group. Results for the Speech, Spatial and Qualities of Hearing Scale improved in both groups and were slightly better in the Baha group. The authors concluded that larger studies with longer follow-up are needed to evaluate differences in outcomes between these two systems.

Nonrandomized Studies

Kim (2022) compared the effects of the Osia system with the Baha Attract and Bonebridge systems in 67 patients with CHL or mixed hearing loss or single-sided deafness (SSD).[48] Patients who received the Osia system (n=17) were prospectively recruited and retrospectively compared with patients who received the Baha Attract or Bonebridge systems (n=50). Effective gains in bone conduction threshold at 2 kHz were 11.1 ± 14.9 dB in the Osia group compared to -2.7 ± 12.6 dB in the Baha Attract and Bonebridge group (combined) among patients with CHL or mixed hearing loss (p=0.01). Among patients with SSD, average functional gains at 4 kHz were 37.5 ± 8.9 dB in the Osia group, 21.7 ± 15.7 dB in the Baha Attract group, and 29.0 ± 13.0 dB in the Bonebridge group.

Iseri (2015) described a retrospective, single-center study from Turkey comparing 21 patients treated with a transcutaneous, fully implantable BAHA with 16 patients treated with a percutaneous device (the BAHA Attract).[49] Groups were generally similar at baseline, with most individuals undergoing BAHA placement for chronic otitis media. Operating time was longer in patients treated with the transcutaneous partially implantable devices (46 minutes vs 26 minutes, p<0.05). Three patients treated with percutaneous devices had Holger grade 2

skin reactions, and two had stopped using their devices. Mean thresholds for frequencies 0.5 to 4.0 kHz were 64.4 dB without the BAHA and 31.6 dB with the BAHA in the percutaneous device group, and 58.3 dB without the BAHA and 27.2 dB with the BAHA in the transcutaneous device group. Frequency-specific threshold hearing gains did not differ significantly between groups. Mean hearing gain measured by speech reception threshold was statistically significantly smaller in the percutaneous group (24 dB vs 36.7 dB, p=0.02).

There have been other, small nonrandomized studies that have assessed the outcomes of the BAHA Attract device, in comparison with other devices, or in single-center observational studies.[50-52] In addition, one case series of 34 patients has reported on complications of the BAHA attract device, where only three patients reported moderate to severe complications, two of which required removal of the magnet.[53]

In 2015, Denoyelle reported on a prospective trial of the Sophono device in children ages 5 to 18 years with uni- or bilateral congenital aural atresia with complete absence of the external auditory canal with pure CHL.[54] The study included a within-subject comparison of hearing results with the Sophono devices to those obtained with the Baha Softband preoperatively. All 15 patients enrolled were implanted (median age, 97 months). At six-month follow-up, mean aided AC pure-tone audiometry was 33.49 (mean gain, 35.53 dB), with a mean aided sound reception threshold of 38.2 (mean gain, 33.47 dB). The difference in AC pure tone average (PTA) between the Baha Softband and the Sophono device was 0.6 dB (confidence interval upper limit, 4.42 dB), which met the study's prespecified noninferiority margin. Adverse effects were generally mild, including skin erythema in two patients, which improved by using a weaker magnet, and brief episodes of pain or tingling in three patients.

The Otomag Sophono system has been studied in a number of very small (n=5 to 12) nonrandomized studies in pediatric patients.[50, 51, 55-61]

Similarly, the Bonebridge partially implantable system has also been studied in a number of small (n=5 to 44) case series, summarized in table 1.[62-68]

Table 1. Case Series Evaluating the Bonebridge Implant

Study	N	Patient Population	Main Hearing Results	Safety Outcomes
Seiwerth (2021)[69]	31	• Seven cases age <16 • 30 unilateral implantations • 1 bilateral implantation	• Mean sound-field threshold improvement at three and six months: 27 and 26 dB • WRS in quiet improved from 11% preoperatively to 74% three months postoperatively • Speech reception threshold in noise improved from -1.01 dB unaided to -2.69 dB best-aided	Not reported
Garcier (2021)[70]	24	• Adults with mixed hearing loss	• Average prosthetic gain in chronic otitis media vs. other etiologies: 43±4.8 dB and 50 ± 7.2, respectively • Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire global score	No major complications. Local pain on the analogue visual scale was 3.23 ± 3.2 (n = 16

Study	N	Patient Population	Main Hearing Results	Safety Outcomes
			improved: 32 ± 10.2%	reporting) and manipulation difficulties were 3.1 ± 3.69
Bravo-Torres (2018)[71]	15	• Pediatric patients with bilateral CHL (microtia associated with external auditory canal atresia)	• Aided sound-field threshold improvement: 25.2 dB	Minor feedback (4), broken processors (4), mild skin redness (2) with one-month follow-up
Schmerber (2017)[72]	25	• SSD (n=12) • Bilateral CHL (n=7) • Bilateral mixed HL (n=6)	• SSD, in 5/7 patients speech reception threshold in noise lower with Bonebridge activated • CHL and mixed, average functional gain: 26 dB HL; mean % of speech recognition in quiet improved from 74% unaided to 95% aided	No complications, device failures, revision surgery, or skin injury reported with one year follow-up
Rahne (2015)[67]	11	• SSD (n=6; 1 sensorineural, 3 mixed, 2 conductive) • Bilateral CHL (n=2) • Bilateral mixed HL or mixed/sensorineural (n=3)	• Aided sound-field threshold improvement: 33.4 dB • WRS improved from mean of 10% unaided to 87.5% aided	One case of chronic fibrosing mastoiditis requiring mastoidectomy and antrotomy; no other complications
Laske (2015)[68]	9	• Adults with SSD and normal contralateral hearing	• Speech discrimination signal-to-noise improvement for aided vs unaided condition, sound presented to aided ear: 1.7 dB • Positive improvements on quality-of life questions	Not reported
Riss (2014)[62]	24	• Combined HL (n=9) • EAC atresia (n=12) • SSD (n=3)	• Average functional gain: 28.8 dB • Monosyllabic word scores at 65-dB sound pressure increased from 4.6 to 53.7 percentage points	Not reported
Manrique (2014)[63]	5	• Mixed HL (n=4) • SSD (n=1)	• PTA improvement: 35.62 dB (p=0.01) • Disyllabic word discrimination improvement: 20% (p=0.016)	No perioperative complications reported

Study	N	Patient Population	Main Hearing Results	Safety Outcomes
Ihler (2014)[64]	6	• Mixed HL (n=4) • CHL (n=2)	• PTA functional gain (average, 0.5-4.0 kHz): 34.5 dB • Speech discrimination at 65 dB improvement: o In quiet: 63.3 percentage points o In noise: 37.5 percentage points	Prolonged wound healing in one case
Desmet (2014)[65]	44	• All unilaterally deaf adults	• Statistically significant improvement on APHAB and SHHIA	Not reported

APHAB: Abbreviated Profile of Hearing Aid Benefit; CHL: conductive hearing loss; EAC: external auditory canal; HL: hearing loss; PTA: pure-tone average; SHHIA: Short Hearing Handicap Inventory for Adults; SSD: single-sided deafness; WRS: Word Recognition Score.

Section Summary: Partially Implantable Magnetic BAHA Devices

Studies of transcutaneous, partially implantable BAHAs have typically used a retrospective within-subjects comparison of hearing thresholds with and without the device, although there have been two small (27 and 15 participants) prospective studies. There was heterogeneity in the audiologic and functional outcome measures used in the studies and the timing of testing. Studies of partially implantable BAHAs have generally demonstrated within-subjects improvements in hearing.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY

In 2021, the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) updated its consensus-based position statement on the use of bone conduction hearing devices.[73] It considers bone conduction hearing devices (BCHD) appropriate, and in some cases preferred, for the treatment of conductive and mixed hearing loss. BCHD may also be indicated in select patients with single-sided deafness. BCHD include semi-implantable bone conduction devices utilizing either a percutaneous or transcutaneous attachment, as well as bone conduction oral appliances and scalp-worn devices. The recommendation for BCHD should be determined by a qualified otolaryngology-head and neck surgeon. The statement indicates that the procedure should be performed by a qualified otolaryngologist-head and neck surgeon with devices which have been Food and Drug Administration (FDA)-approved, and "should adhere to the restrictions and guidelines specified by the appropriate governing agency, such as the Food and Drug Administration in the United States."

SUMMARY

There is enough research to show that unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s) improve net health outcomes when used as an alternative to air-conduction hearing aids in select patients. Clinical guidelines based on research recommend bone conduction hearing devices for the treatment of conductive or

mixed hearing loss and single-sided deafness. In addition, a binaural hearing benefit may be provided for patients with single-sided sensorineural deafness by the routing of signals to the hearing ear. Therefore, use of these devices is considered medically necessary for patients who meet the policy criteria.

There is not enough research to show that unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s) improve health outcomes for patients who do not meet the policy criteria, including but not limited to patients not meeting the age requirements and patients with bilateral sensorineural hearing loss. In addition, there are no evidence-based clinical practice guidelines that recommend these devices for patients who do not meet the criteria. Therefore, these devices are considered investigational for patients who do not meet the policy criteria.

Implant replacement, including replacement parts or upgrades, may be considered medically necessary only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work; or when components are no longer functional.

Implant replacement, including replacement parts or upgrades to existing bone-anchored hearing aid components (for example, batteries, processor, headband or Softband) are considered not medically necessary when criteria are not met, including when requested for convenience or to upgrade to newer technology when the current components remain functional.

REFERENCES

1. Snik AF, Mylanus EA, Cremers CW. The bone-anchored hearing aid compared with conventional hearing aids. Audiologic results and the patients' opinions. *Otolaryngol Clin North Am.* 1995;28(1):73-83. PMID: 7739870
2. Wazen JJ, Caruso M, Tjellstrom A. Long-term results with the titanium bone-anchored hearing aid: the U.S. experience. *Am J Otol.* 1998;19(6):737-41. PMID: 9831146
3. van der Pouw CT, Snik AF, Cremers CW. The BAHA HC200/300 in comparison with conventional bone conduction hearing aids. *Clin Otolaryngol Allied Sci.* 1999;24(3):171-6. PMID: 10384840
4. Granstrom G, Tjellstrom A. The bone-anchored hearing aid (BAHA) in children with auricular malformations. *Ear Nose Throat J.* 1997;76(4):238-40, 42, 44-7. PMID: 9127523
5. Peters JP, Smit AL, Stegeman I, et al. Review: Bone conduction devices and contralateral routing of sound systems in single-sided deafness. *The Laryngoscope.* 2015;125(1):218-26. PMID: 25124297
6. Wazen JJ, Spitzer JB, Ghossaini SN, et al. Transcranial contralateral cochlear stimulation in unilateral deafness. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2003;129:248-54. PMID: 12958575
7. Arndt S, Aschendorff A, Laszig R, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2011;32(1):39-47. PMID: 21068690

8. Hol MK, Kunst SJ, Snik AF, et al. Pilot study on the effectiveness of the conventional CROS, the transcranial CROS and the BAHA transcranial CROS in adults with unilateral inner ear deafness. *Eur Arch Otorhinolaryngol.* 2010;267(6):889-96. PMID: 19904546
9. Hol MK, Bosman AJ, Snik AF, et al. Bone-anchored hearing aids in unilateral inner ear deafness: an evaluation of audiometric and patient outcome measurements. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2005;26:999-1006. PMID: 16151349
10. Lin LM, Bowditch S, Anderson MJ, et al. Amplification in the rehabilitation of unilateral deafness: speech in noise and directional hearing effects with bone-anchored hearing and contralateral routing of signal amplification. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2006;27:172-82. PMID: 16436986
11. Wazen JJ, Ortega C, Nazarian R, et al. Expanding the indications for the bone anchored hearing system (BAHS) in patients with single sided deafness. *Am J Otolaryngol.* 2021;42(3):102864. PMID: 33476970
12. Jakob TF, Speck I, Rauch AK, et al. Bone-anchored hearing system, contralateral routing of signals hearing aid or cochlear implant: what is best in single-sided deafness? *Eur Arch Otorhinolaryngol.* 2021. PMID: 33566175
13. den Besten CA, Monksfield P, Bosman A, et al. Audiological and clinical outcomes of a transcutaneous bone conduction hearing implant: Six-month results from a multicentre study. *Clin Otolaryngol.* 2019;44(2):144-57. PMID: 30358920
14. Choi JE, Ma SM, Park H, et al. A comparison between wireless CROS/BiCROS and soft-band BAHA for patients with unilateral hearing loss. *PLoS One.* 2019;14(2):e0212503. PMID: 30789931
15. Snapp HA, Holt FD, Liu X, et al. Comparison of Speech-in-Noise and Localization Benefits in Unilateral Hearing Loss Subjects Using Contralateral Routing of Signal Hearing Aids or Bone-Anchored Implants. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2017;38(1):11-18. PMID: 27846038
16. Leterme G, Bernardeschi D, Bensemman A, et al. Contralateral routing of signal hearing aid versus transcutaneous bone conduction in single-sided deafness. *Audiol Neurootol.* 2015;20:251-60. PMID: 26021779
17. Heath E, Dawoud MM, Stavrakas M, et al. The outcomes of bilateral bone conduction hearing devices (BCHD) implantation in the treatment of hearing loss: A systematic review. *Cochlear Implants Int.* 2022;23(2):95-108. PMID: 34852723
18. Colquitt JL, Loveman E, Baguley DM, et al. Bone-anchored hearing aids for people with bilateral hearing impairment: a systematic review. *Clin Otolaryngol.* 2011;36(5):419-41. PMID: 21816006
19. Colquitt JL, Jones J, Harris P, et al. Bone-anchored hearing aids (BAHAs) for people who are bilaterally deaf: a systematic review and economic evaluation. *Health Technol Assess.* 2011;15(26):1-200, iii-iv. PMID: 21729632
20. Janssen RM, Hong P, Chadha NK. Bilateral bone-anchored hearing aids for bilateral permanent conductive hearing loss: a systematic review. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2012;147(3):412-22. PMID: 22714424

21. Amonoo-Kuofi K, Kelly A, Neeff M, et al. Experience of bone-anchored hearing aid implantation in children younger than 5 years of age. *Int J Pediatr Otorhinolaryngol.* 2015;79(4):474-80. PMID: 25680294
22. Marsella P, Scorpecci A, Pacifico C, et al. Pediatric BAHA in Italy: the "Bambino Gesu" Children's Hospital's experience. *Eur Arch Otorhinolaryngol.* 2012;269(2):467-74. PMID: 21739094
23. Snik A, Leijendeckers J, Hol M, et al. The bone-anchored hearing aid for children: recent developments. *Int J Audiol.* 2008;47(9):554-9. PMID: 18821224
24. McDermott AL, Williams J, Kuo MJ, et al. The role of bone anchored hearing aids in children with Down syndrome. *Int J Pediatr Otorhinolaryngol.* 2008;72(6):751-7. PMID: 18433885
25. Davids T, Gordon KA, Clutton D, et al. Bone-anchored hearing aids in infants and children younger than 5 years. *Arch Otolaryngol Head Neck Surg.* 2007;133(1):51-5. PMID: 17224524
26. Zarowski AJ, Verstraeten N, Somers T, et al. Headbands, testbands and softbands in preoperative testing and application of bone-anchored devices in adults and children. *Adv Otorhinolaryngol.* 2011;71:124-31. PMID: 21389712
27. Dun CA, de Wolf MJ, Mylanus EA, et al. Bilateral bone-anchored hearing aid application in children: the Nijmegen experience from 1996 to 2008. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2010;31(4):615-23. PMID: 20393374
28. Priwin C, Jonsson R, Hultcrantz M, et al. BAHA in children and adolescents with unilateral or bilateral conductive hearing loss: a study of outcome. *Int J Pediatr Otorhinolaryngol.* 2007;71:135-45. PMID: 17092570
29. Fan Y, Zhang Y, Wang S, et al. Auditory development after placement of bone-anchored hearing aids Softband among Chinese Mandarin-speaking children with bilateral aural atresia. *Int J Pediatr Otorhinolaryngol.* 2014;78(1):60-4. PMID: 24290950
30. Ramakrishnan Y, Marley S, Leese D, et al. Bone-anchored hearing aids in children and young adults: the Freeman Hospital experience. *J Laryngol Otol.* 2011;125(2):153-7. PMID: 20849670
31. Christensen L, Smith-Olinde L, Kimberlain J, et al. Comparison of traditional bone-conduction hearing AIDS with the Baha system. *Journal of the American Academy of Audiology.* 2010;21(4):267-73. PMID: 20388452
32. Hol MK, Cremers CW, Coppens-Schellekens W, et al. The BAHA Softband. A new treatment for young children with bilateral congenital aural atresia. *Int J Pediatr Otorhinolaryngol.* 2005;69:973-80. PMID: 15911017
33. Verhagen CV, Hol MK, Coppens-Schellekens W, et al. The Baha Softband. A new treatment for young children with bilateral congenital aural atresia. *Int J Pediatr Otorhinolaryngol.* 2008;72:1455-9. PMID: 18667244
34. Hernández S, Ospina JC, Gutiérrez-Gómez E, et al. Long term cutaneous complications related to bone conduction hearing implants. A retrospective study (2004-2018). *Auris Nasus Larynx.* 2021. PMID: 33531159
35. Schwab B, Wimmer W, Severens JL, et al. Adverse events associated with bone-conduction and middle-ear implants: a systematic review. *Eur Arch Otorhinolaryngol.* 2020;277(2):423-38. PMID: 31749056
36. Verheij E, Bezdjian A, Grolman W, et al. A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices. *Otology & neurotology : official publication of the American Otological Society,*

American Neurotology Society [and] European Academy of Otology and Neurotology. 2016;37(7):829-37. PMID: 27273402
37. Mohamad S, Khan I, Hey SY, et al. A systematic review on skin complications of bone-anchored hearing aids in relation to surgical techniques. *Eur Arch Otorhinolaryngol.* 2014. PMID: 25503356
38. Kiringoda R, Lustig LR. A meta-analysis of the complications associated with osseointegrated hearing aids. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2013;34(5):790-4. PMID: 23739555
39. Roplekar R, Lim A, Hussain SS. Has the use of the linear incision reduced skin complications in bone-anchored hearing aid implantation? *J Laryngol Otol.* 2016;130(6):541-4. PMID: 27160014
40. Fontaine N, Hemar P, Schultz P, et al. BAHA implant: implantation technique and complications. *European annals of otorhinolaryngology, head and neck diseases.* 2014;131(1):69-74. PMID: 23835074
41. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35(8):1480-5. PMID: 24770406
42. Nelissen RC, Stalfors J, de Wolf MJ, et al. Long-term stability, survival, and tolerability of a novel osseointegrated implant for bone conduction hearing: 3-year data from a multicenter, randomized, controlled, clinical investigation. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35(8):1486-91. PMID: 25080037
43. Singam S, Williams R, Saxby C, et al. Percutaneous bone-anchored hearing implant surgery without soft-tissue reduction: up to 42 months of follow-up. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35(9):1596-600. PMID: 25076228
44. Gutierrez JA, 3rd, Shannon CM, Nguyen SA, et al. Comparison of Quality of Life Outcomes for Percutaneous Versus Transcutaneous Implantable Hearing Devices: A Systematic Review and Meta-analysis. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2024;45(3):e129-e36. PMID: 38270194
45. Bezdjian A, Bruijnzeel H, Daniel SJ, et al. Preliminary audiologic and peri-operative outcomes of the Sophono transcutaneous bone conduction device: A systematic review. *Int J Pediatr Otorhinolaryngol.* 2017;101:196-203. PMID: 28964294
46. Dimitriadis PA, Farr MR, Allam A, et al. Three year experience with the cochlear BAHA attract implant: a systematic review of the literature. *BMC ear, nose, and throat disorders.* 2016;16:12. PMID: 27733813
47. Gawęcki W, Gibasiewicz R, Marszał J, et al. The evaluation of a surgery and the short-term benefits of a new active bone conduction hearing implant - the Osia®. *Braz J Otorhinolaryngol.* 2022;88(3):289-95. PMID: 32713797
48. Kim Y, Choe G, Oh H, et al. A comparative study of audiological outcomes and compliance between the Osia system and other bone conduction hearing implants. *Eur Arch Otorhinolaryngol.* 2022. PMID: 36318324
49. Iseri M, Orhan KS, Tuncer U, et al. Transcutaneous bone-anchored hearing aids versus percutaneous ones: multicenter comparative clinical study. *Otology & neurotology :*

official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2015;36(5):849-53. PMID: 25730451
50. Powell HR, Rolfe AM, Birman CS. A Comparative Study of Audiologic Outcomes for Two Transcutaneous Bone-Anchored Hearing Devices. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2015;36:1525-31. PMID: 26375976
51. Baker S, Centric A, Chennupati SK. Innovation in abutment-free bone-anchored hearing devices in children: Updated results and experience. *Int J Pediatr Otorhinolaryngol.* 2015;79(10):1667-72. PMID: 26279245
52. Carr SD, Moraleda J, Procter V, et al. Initial UK Experience With a Novel Magnetic Transcutaneous Bone Conduction Device. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2015;36(8):1399-402. PMID: 26196208
53. Reddy-Kolanu R, Gan R, Marshall AH. A case series of a magnetic bone conduction hearing implant. *Annals of the Royal College of Surgeons of England.* 2016;98(8):552-53. PMID: 27490984
54. Denoyelle F, Coudert C, Thierry B, et al. Hearing rehabilitation with the closed skin bone-anchored implant Sophono Alpha1: results of a prospective study in 15 children with ear atresia. *Int J Pediatr Otorhinolaryngol.* 2015;79(3):382-7. PMID: 25617189
55. Siegert R. Partially implantable bone conduction hearing aids without a percutaneous abutment (Otomag): technique and preliminary clinical results. *Adv Otorhinolaryngol.* 2011;71:41-6. PMID: 21389703
56. Hol MK, Nelissen RC, Agterberg MJ, et al. Comparison between a new implantable transcutaneous bone conductor and percutaneous bone-conduction hearing implant. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2013;34(6):1071-5. PMID: 23598702
57. O'Niel MB, Runge CL, Friedland DR, et al. Patient Outcomes in Magnet-Based Implantable Auditory Assist Devices. *JAMA Otolaryngol Head Neck Surg.* 2014. PMID: 24763485
58. Centric A, Chennupati SK. Abutment-free bone-anchored hearing devices in children: initial results and experience. *Int J Pediatr Otorhinolaryngol.* 2014;78(5):875-8. PMID: 24612554
59. Marsella P, Scorpecci A, Vallarino MV, et al. Sophono in Pediatric Patients: The Experience of an Italian Tertiary Care Center. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2014;151:328-32. PMID: 24714216
60. Magliulo G, Turchetta R, Iannella G, et al. Sophono Alpha System and subtotal petrosectomy with external auditory canal blind sac closure. *Eur Arch Otorhinolaryngol.* 2015;272(9):2183-90. PMID: 24908070
61. Nelissen RC, Agterberg MJ, Hol MK, et al. Three-year experience with the Sophono in children with congenital conductive unilateral hearing loss: tolerability, audiometry, and sound localization compared to a bone-anchored hearing aid. *Eur Arch Otorhinolaryngol.* 2016;273:3149-56. PMID: 26924741
62. Riss D, Arnoldner C, Baumgartner WD, et al. Indication criteria and outcomes with the Bonebridge transcutaneous bone-conduction implant. *The Laryngoscope.* 2014;124(12):2802-6. PMID: 25142577

63. Manrique M, Sanhueza I, Manrique R, et al. A new bone conduction implant: surgical technique and results. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35:216-20. PMID: 24448280
64. Ihler F, Volbers L, Blum J, et al. Preliminary functional results and quality of life after implantation of a new bone conduction hearing device in patients with conductive and mixed hearing loss. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35:211-5. PMID: 24448279
65. Desmet J, Wouters K, De Bodt M, et al. Long-term subjective benefit with a bone conduction implant sound processor in 44 patients with single-sided deafness. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2014;35(6):1017-25. PMID: 24751733
66. Iseri M, Orhan KS, Kara A, et al. A new transcutaneous bone anchored hearing device - the Baha(R) Attract System: the first experience in Turkey. *Kulak burun bogaz ihtisas dergisi : KBB = Journal of ear, nose, and throat.* 2014;24(2):59-64. PMID: 24835899
67. Rahne T, Seiwerth I, Gotze G, et al. Functional results after Bonebridge implantation in adults and children with conductive and mixed hearing loss. *Eur Arch Otorhinolaryngol.* 2015;272:3263-9. PMID: 25425039
68. Laske RD, Roosli C, Pfiffner F, et al. Functional Results and Subjective Benefit of a Transcutaneous Bone Conduction Device in Patients With Single-Sided Deafness. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2015;36(7):1151-6. PMID: 26111077
69. Seiwerth I, Fröhlich L, Schilde S, et al. Clinical and functional results after implantation of the bonebridge, a semi-implantable, active transcutaneous bone conduction device, in children and adults. *Eur Arch Otorhinolaryngol.* 2021. PMID: 33674927
70. Garcier M, Lavedrine A, Gagneux C, et al. Bone-Anchored and Closed Skin Bonebridge Implant in Adults: Hearing Performances and Quality of Life. *Audiol Neurootol.* 2021:1-7. PMID: 33662952
71. Bravo-Torres S, Der-Mussa C, Fuentes-Lopez E. Active transcutaneous bone conduction implant: audiological results in paediatric patients with bilateral microtia associated with external auditory canal atresia. *Int J Audiol.* 2018;57(1):53-60. PMID: 28857620
72. Schmerber S, Deguine O, Marx M, et al. Safety and effectiveness of the Bonebridge transcutaneous active direct-drive bone-conduction hearing implant at 1-year device use. *Eur Arch Otorhinolaryngol.* 2017;274(4):1835-51. PMID: 27475796
73. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Bone Conduction Hearing Devices. 2021. [cited 3/14/2024]. 'Available from:' http://www.entnet.org/content/position-statement-bone-conduction-hearing-devices.

CODES

NOTE: The following CPT codes describe semi-implantable electromagnetic bone conduction hearing aids:

Codes	Number	Description
CPT	69710	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone*

Codes	Number	Description
	69711	Removal or repair of electromagnetic bone conduction hearing device in temporal bone

*****The Audiant™ bone conductor is a type of electromagnetic bone conduction hearing device. While this product is no longer actively marketed, patients with existing Audiant devices may require replacement, removal, or repair.

	69714	Implantation, osseointegrated implant, skull; with percutaneous attachment to external speech processor **
	69716	Osseointegrated implant insertion with magnetic transcutaneous attachment to a speech processor
	69717	Revision (including removal of existing device), osseointegrated implant, skull; with percutaneous attachment to external speech processor
	69719	Revision or replacement (including removal of existing device), osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, within the mastoid and/or involving a bony defect less than 100 sq mm surface area of bone deep to the outer cranial cortex
	69726	Removal, entire osseointegrated implant, skull; with percutaneous attachment to external speech processor
	69727	Removal, entire osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, within the mastoid and/or involving a bony defect less than 100 sq mm surface area of bone deep to the outer cranial cortex
	69728	Removal, entire osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside the mastoid and involving a bony defect greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex
	69729	Implantation, osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside of the mastoid and resulting in removal of greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex
	69730	Replacement (including removal of existing device), osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside the mastoid and involving a bony defect greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex
	92622	Diagnostic analysis, programming, and verification of an auditory osseointegrated sound processor, any type; first 60 minutes
	92623	Diagnostic analysis, programming, and verification of an auditory osseointegrated sound processor, any type; each additional 15 minutes (List separately in addition to code for primary procedure)

**These codes describe implantation of the Baha®, Ponto™, and similar devices.

HCPCS	L8621	Zinc air battery for use with cochlear implant device and auditory osseointegrated sound processors, replacement, each
	L8624	Lithium ion battery for use with cochlear implant device or auditory osseointegrated device speech processor, ear level, replacement each
	L8625	External recharging system for battery for use with cochlear implant or auditory osseointegrated device, replacement only, each
	L8690	Auditory osseointegrated device, includes all internal and external components***
	L8691	Auditory osseointegrated device, external sound processor, excludes transducer/actuator, replacement only, each

Codes	Number	Description
	L8692	Auditory osseointegrated device, external sound processor, used without osseointegration, body worn, includes headband or other means of external attachment
	L8693	Auditory osseointegrated device abutment, any length, replacement only
	L8694	Auditory osseointegrated device, transducer/actuator, replacement only, each

***These codes describe the Baha®, Ponto™, and similar devices.

Date of Origin: *July 2003*

Regence

Medical Policy Manual Surgery, Policy No. 132

Cryosurgical Ablation of Miscellaneous Solid Tumors Outside of the Liver

Effective: February 1, 2024

Next Review: November 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Cryoablation kills cells by freezing the tissue using a coolant that is circulated via a probe inserted into the tumor.

MEDICAL POLICY CRITERIA

Note: This policy does not address liver tumors (primary or metastatic). See Cross References.

I. Cryosurgical ablation may be considered **medically necessary** for the treatment of any of the following indications:
   A. Malignant dermatologic tumors
   B. Uveal melanoma
   C. Kidney tumors
   D. Prostate tumors
   E. Cervical intraepithelial neoplasia

F. Lung cancer when either of the following criteria is met:

1. For non-small cell lung cancer when the patient has early-stage (Stage I, and selected node negative Stage IIA) non-small cell lung cancer; or
2. The patient requires palliation for a central airway obstructing lesion.

II. Cryosurgical ablation is considered **investigational** as a treatment for all solid tumors not meeting Criterion I, including desmoid tumors and malignant or benign tumors of the breast (including fibroadenoma), pancreas, and bone; and for metastases outside of the liver or prostate.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical
- Treatment plan including treatment area.

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE), Medicine, Policy No. 140
2. Radiofrequency Ablation (RFA) of Tumors Other than Liver, Surgery, Policy No. 92
3. Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation, Surgery, Policy No. 139
4. Microwave Tumor Ablation, Surgery, Policy No. 189
5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204
6. Focal Laser Ablation of Prostate Cancer, Surgery, Policy No. 222

BACKGROUND

Cryosurgical ablation (also called cryosurgery, cryotherapy, or cryoablation) kills cells (cancerous and normal) by freezing target tissues, most often by inserting a probe into the tumor through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The goals of cryosurgery may include the following:

- Destruction or shrinkage of tumor tissue
- Controlling local tumor growth and preventing recurrence
- Palliating symptoms
- Extending survival duration for patients with certain tumors.

Potential complications associated with cryosurgery in any organ include the following:

- Hypothermic damage to normal tissue adjacent to the tumor (e.g., nerve damage)
- Structural damage along the probe track
- Secondary tumors if cancerous cells are seeded during probe removal.

REGULATORY STATUS

There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear, nose and throat. Examples include:

- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical;
- IceRod® CX, IcePearl® 2.1 CX and IceFORCE® 2.1 CX Cryoablation Needles by Galil Medical;
- IceSense3™, ProSense™, and MultiSense Systems (IceCure Medical);
- SeedNet™ System by Galil Medical;
- Visica® System by Sanarus Medical;
- Visual-ICE® Cryoablation System by Galil;
- ERBECRYO 2® Cryosurgical Unit, ERBE USA Incorporated

EVIDENCE SUMMARY

In order to understand the impact of cryosurgical ablation on local or distant tumor recurrence and disease-free and overall survival in patients with solid tumors, randomized trials are needed that compare this technique with current standard treatments. The standard treatment for most solid tumors is surgical resection. For unresectable solid tumors, alternatives to resection depend on the tumor type and location, and may include thermal ablation, percutaneous ethanol injection, chemoembolization, chemotherapy, and radiation therapy.

Despite the weaknesses in the published clinical evidence, cryosurgical ablation has become a recognized standard of care for tumors of the kidney, liver (addressed in Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204), prostate, and carefully selected patients with tumors of the lung.[1-51]

The following literature appraisal focuses on the investigational indications noted in medical policy criteria above.

BREAST TUMORS

The standard treatment for breast cancer is surgical excision by lumpectomy or mastectomy, with or without adjuvant radiation therapy, chemotherapy, and/or hormone therapy. Fibroadenomas, benign tumors of the breast, generally do not require treatment. If treated, they are typically surgically excised.

Systematic Reviews

One systematic review, by Zhao (2010), was found that included cryoablation along with other minimally-invasive thermal ablation techniques (i.e., radiofrequency, microwave, cryoablation and high-intensity focused ultrasound) for treatment of early-stage breast cancer.[52] Zhao reported that studies on cryoablation for breast cancer were primarily limited to pilot and feasibility studies conducted in the research setting. A wide range of 36-83% was reported for complete ablation of tumors. The authors concluded that, while promising, large randomized

controlled trials are needed to further evaluate patient selection criteria, techniques to ensure complete tumor ablation, and long-term outcomes compared with surgical excision of breast tumors.

Randomized Controlled Trials

There are no prospective, randomized controlled trials comparing survival and recurrence rates following cryoablation of breast tumors with surgical excision or, for unresectable tumors, with nonoperative therapies.

Nonrandomized Studies

The remaining nonrandomized evidence does not permit reliable conclusions concerning the impact of cryosurgical ablation on breast cancer survival or recurrence due to a number of methodological limitations, including: heterogeneous or unreported patient selection criteria, the use of varied cryoablation techniques, nonrandomized allocation of treatment, lack of an appropriate surgical excision control group for comparison, small subject population, and limited data on long-term outcomes.[53-66]

PULMONARY TUMORS

Systematic Reviews

Lee (2011) conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors.[67] Included in the review were 15 case studies and one comparative observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with comorbid conditions and poor general health who would not be considered surgical candidates. Complications occurred in 11.1% of patients (10 studies) and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes. One published review reported the outcomes of 15 case series and one comparative observational study for endoscopic cryotherapy of endobronchial tumors. Most studies were for inoperable, advanced lung and bronchial cancers. A critical analysis of the studies was not provided. However, the authors noted the significant limitations in the available evidence due to lack of control groups, lack of random treatment allocation, and heterogeneity in study methodologies, participants' characteristics (e.g., comorbid conditions, general health, cancer grade), treatment protocols, operative techniques, and outcome measures. Complications occurred in 11.1% of patients from ten studies and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes. Because the studies in the review did not include control groups or compare outcomes of cryosurgery to alternative strategies for managing similar patients, no conclusions can be made on the net health outcomes of cryosurgery for lung cancer.

Randomized Controlled Trials

One preliminary randomized trial studied 36 female patients with NSCLC who also had epidermal growth factor receptor gene mutations.[68] All patients received six months treatment

with molecular target therapy gefitinib, an epidermal growth factor receptor-tyrosine kinase inhibitor. Patients were randomized to either an experimental group and underwent cryoablation prior to receiving gefitinib, or to a control group in which cryoablation was not performed. At one-year follow-up, the survival rate in the cryoablation group was significantly higher than that of the control group. The findings of this preliminary study suggest that cryoablation may improve the effects of gefitinib in this patient population. Additional larger, long-term randomized trials are needed to validate these findings.

Nonrandomized Studies

The Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE) study assessed the safety and local recurrence-free survival after cryoablation for treatment of pulmonary metastases. Callstrom (2020) published this multicenter, prospective, single-arm, phase 2 study in 128 patients with 224 lung metastases ≤3.5 cm.[69] Median tumor size was 1.0 cm. Local recurrence-free response was 85.1% at 12 months and 77.2% at 24 months. Secondary local recurrence-free response after retreatment with cryoablation for recurrent tumors was 91.1% at 12 months and 84.4% at 24 months. Overall survival at 12 and 24 months was 97.6% and 86.6%, respectively.

The ECLIPSE trial is prospective, multicenter trial of cryoablation for metastatic disease in the lungs, interim results at one-year follow-up were published in 2015.[70] The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with cryoablation and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and one-year OS was 97.5% (39/40). There were no significant changes in quality of life over the 12-month study. The most common adverse event was pneumothorax requiring chest tube insertion in 18.8% (9/48 procedures). Five-year results of the trial were published by de Baère (2021), which reported disease-specific survival rates of 74.8% at three years and 55.3% at five years.[70] Five-year overall survival was 46.7% and there was no significant difference in quality-of-life measures.

BONE TUMORS

Systematic Reviews

Khanmohammadi (2023) published a systematic review of cryoablation for the palliation of painful bone metastases.[71] The review included 15 studies (n=376): ten case series and five prospective interventional studies. Of these, six were scored as “good,” six as “fair,” and three as “poor” according to the NIH Study Quality Assessment Tools. A total of 436 metastatic lesions were treated, mostly in the spine, pelvic bone, and ribs. All of the studies reported a statistically significant reduction in pain between one day and six months following the procedure.

A systematic review by Sagoo (2022) assessed percutaneous cryoablation of spinal metastases.[72] Eight studies, seven of which were retrospective, were included in the review, with a total of 148 patients and 187 treated lesions (3 cervical, 74 thoracic, 37 lumbar, and 17 sacrococcygeal). At one-month follow-up, the pooled mean difference in pain scores (1-10 scale) was 5.03 (95% confidence interval [CI] 4.24 to 5.82). Reported tumor control rates varied from 60% to 100% and complications were reported in 12 patients, three of which were grade III-V.

Lindquester (2020) published a systematic review evaluating percutaneous thermal ablation technologies for osteoid osteoma, which included 36 case-series (total n=1,798).[73] While the authors stated that the studies were evaluated for quality, the results of such an evaluation were not included in the publication. An overall success rate of 91.9% was reported, which included both technical and clinical success of the procedure as well as freedom from recurrence during follow-up, however median length of follow-up in these studies was not reported. The overall complication rate was 2.5% (95% CI 1.9% to 3.3%). No significant differences were found between radiofrequency and cryoablation, but only three of the 36 studies included cryoablation; most (32 studies) were for radiofrequency ablation.

Nonrandomized Studies

Cazzato (2022) published a review of 74 patients with spinal metastases who underwent cryoablation treatment at two academic medical centers.[74] Of these, 21 patients underwent treatment for curative purposes while 53 were treated for palliative purposes. Cryoablation was associated with a reduction in pain among those who presented with painful lesions. Local tumor control was achieved in 21 patients undergoing cryoablation with curative intent (mean follow-up of 25.9 ± 21.2 months).

Jennings (2021) reported on a multicenter, single-arm prospective study of 66 patients with metastatic bone disease who were treated with cryoablation, all of whom were not candidates for or had not benefited from standard therapy.[75] The primary endpoint was the change in pain score from baseline to week eight and patients were followed for 24 weeks. The mean decrease in pain score from baseline to week eight was 2.61 points (95% CI 3.45 to 1.78). Pain scores decreased further after the primary endpoint and reached clinically meaningful levels (more than a two-point decrease) after week eight. This study was limited by its lack of a comparator, potential for selection bias, and lack of blinding combined with subjective outcome measures.

Callstrom (2013) reported on 61 patients treated with cryoablation for pain from 69 tumors (size 1 to 11 cm) metastatic to the bone. Before treatment, patients rated their pain with a 4+ on a 1-to-10 scale using the Brief Pain Inventory, with a mean score of 7.1 for worst pain in a 24-hour period. The mean pain score gradually decreased after cryoablation to 1.4 ($p<0.001$) at 24 weeks for worst pain in a 24-hour period. A major complication of osteomyelitis was experienced by one (2%) patient.

Meller (2008) retrospectively analyzed a single-center experience with 440 bone tumor cryosurgery procedures performed between 1988 and 2002, two-thirds of them for primary benign-aggressive and low-grade malignant lesions, and one-third for primary high-grade and metastatic bone tumors.**[76]** At a median follow-up of seven years (range 3 to 18 years), the overall recurrence rate was 8%. Based on their data, the authors suggested that the ideal case for cryosurgery is a young adult with involvement of long bone, a benign-aggressive or low-grade malignant bone tumor, a good cavity with greater than 75%-thick surrounding walls, no or minimal soft-tissue component, and at least ±1 cm of subchondral bone left near a joint surface after curettage and burr drilling.

OTHER TUMORS

Cryoablation for the treatment of other solid tumors has not been well-studied.

Systematic Reviews

Keane (2014) reported on a systematic review of ablation therapies, including cryoablation, for locally advanced pancreatic cancer.[77] The review noted studies have demonstrated ablative therapies, including cryoablation, are feasible but larger studies are needed. No conclusions could be made on whether ablation resulted in better oncologic outcomes than best supportive care.

Tao (2012) reported on a systematic review of cryoablation for pancreatic cancer.[78] The authors identified 29 studies from the literature search and included five of these studies in the review. The five studies were all case series and considered to be of low quality. Adverse events, when mentioned in the studies, included delayed gastric emptying (0% to 40.9% in three studies), pancreatic leak (0% to 6.8% in four studies), biliary leak (0% to 6.8% in three studies), and one instance of upper gastrointestinal hemorrhage. Pain relief was reported in three studies and ranged from 66.7% to 100%. Median survival times reported in three studies ranged from 13.4 to 16 months. One-year total survival rates reported in two studies were 57.5% and 63.6%.

Nonrandomized Studies

The remaining published literature is limited to case series and retrospective reviews.[79-89] As discussed above, these studies do not permit reliable conclusions concerning the impact of cryoablation on health outcomes.

PRACTICE GUIDELINE SUMMARY

Clinical practice guidelines from U.S. professional associations consistently list cryoablation as a treatment option for uveal melanoma, certain NSCLC tumors, and for tumors of the kidney or prostate.[90-96]

No clinical practice guidelines or position statements based on research from U.S. professional societies were identified that specifically recommend cryoablation for the treatment of solid tumors other than those listed above, though some refer more generally to ablation procedures.[97 98]

SUMMARY

Cryosurgical ablation has become a recognized standard of care in the management of tumors of the skin, kidney and prostate, uveal melanoma, cervical intraepithelial neoplasia, and carefully selected patients with lung tumors. Therefore, this technique may be considered medically necessary in the treatment of these tumors when criteria are met.

There is not enough research to show that cryosurgical ablation can improve health outcomes for patients with solid tumors that do not meet policy criteria, including malignant or benign tumors of the breast (including fibroadenoma), pancreas, and bone; and for metastases outside of the liver or prostate. Therefore, cryosurgical ablation for these indications is considered investigational.

REFERENCES

1. Kunkle DA,Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass : a meta-analysis. *Cancer.* 2008;113(10):2671-80. PMID: 18816624
2. Long L,Park S. Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty. *J Endourol.* 2009;23(3):421-6. PMID: 19260799
3. Laguna MP, Beemster P, Kumar V, et al. Perioperative morbidity of laparoscopic cryoablation of small renal masses with ultrathin probes: a European multicentre experience. *Eur Urol.* 2009;56(2):355-61. PMID: 19467771
4. Gill IS, Remer EM, Hasan WA, et al. Renal cryoablation: outcome at 3 years. *J Urol.* 2005;173(6):1903-7. PMID: 15879772
5. Niu R, Yan TD, Zhu JC, et al. Recurrence and survival outcomes after hepatic resection with or without cryotherapy for liver metastases from colorectal carcinoma. *Ann Surg Oncol.* 2007;14(7):2078-87. PMID: 17473951
6. Seifert JK, Springer A, Baier P, et al. Liver resection or cryotherapy for colorectal liver metastases: a prospective case control study. *Int J Colorectal Dis.* 2005;20(6):507-20. PMID: 15973545
7. Ruers TJ, Joosten JJ, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol.* 2007;14(3):1161-9. PMID: 17195903
8. Joosten J, Jager G, Oyen W, et al. Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. *Eur J Surg Oncol.* 2005;31(10):1152-9. PMID: 16126363
9. Kornprat P, Jarnagin WR, DeMatteo RP, et al. Role of intraoperative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. *Arch Surg.* 2007;142(11):1087-92. PMID: 18025338
10. Si T, Guo Z,Hao X. Combined cryoablation and GM-CSF treatment for metastatic hormone refractory prostate cancer. *J Immunother.* 2009;32(1):86-91. PMID: 19307997
11. Onik G, Vaughan D, Lotenfoe R, et al. The "male lumpectomy": focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. *Urol Oncol.* 2008;26(5):500-5. PMID: 18774463
12. Langenhuijsen JF, Broers EM,Vergunst H. Cryosurgery for prostate cancer: an update on clinical results of modern cryotechnology. *Eur Urol.* 2009;55(1):76-86. PMID: 18789572
13. Eisenberg ML,Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. *Urology.* 2008;72(6):1315-8. PMID: 18597824
14. Ng CK, Moussa M, Downey DB, et al. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. *J Urol.* 2007;178(4 Pt 1):1253-7; discussion 57. PMID: 17698104
15. Van Poppel H, Becker F, Cadeddu JA, et al. Treatment of localised renal cell carcinoma. *Eur Urol.* 2011;60(4):662-72. PMID: 21726933
16. Chou R, Dana T, Bougatsos C, et al. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. Rockville (MD). 2011. PMID: 22171386
17. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU international.* 2012;109 Suppl 1:22-9. PMID: 22239226

18. Williams SB, Lei Y, Nguyen PL, et al. Comparative effectiveness of cryotherapy vs brachytherapy for localised prostate cancer. *BJU international.* 2012;110(2 Pt 2):E92-8. PMID: 22192688
19. Mouraviev V, Spiess PE,Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. *Eur Urol.* 2012;61(6):1204-11. PMID: 22421081
20. Nabi G, Cleves A,Shelley M. Surgical management of localised renal cell carcinoma. *Cochrane Database Syst Rev.* 2010(3):CD006579. PMID: 20238346
21. O'Malley RL, Berger AD, Kanofsky JA, et al. A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. *BJU international.* 2007;99(2):395-8. PMID: 17092288
22. Long CJ, Kutikov A, Canter DJ, et al. Percutaneous vs surgical cryoablation of the small renal mass: is efficacy compromised? *BJU international.* 2011;107(9):1376-80. PMID: 21062399
23. Klatte T, Grubmuller B, Waldert M, et al. Laparoscopic cryoablation versus partial nephrectomy for the treatment of small renal masses: systematic review and cumulative analysis of observational studies. *Eur Urol.* 2011;60(3):435-43. PMID: 21616582
24. El Dib R, Touma NJ,Kapoor A. Cryoablation vs radiofrequency ablation for the treatment of renal cell carcinoma: a meta-analysis of case series studies. *BJU international.* 2012;110(4):510-6. PMID: 22304329
25. Matin SF,Ahrar K. Nephron-sparing probe ablative therapy: long-term outcomes. *Current opinion in urology.* 2008;18(2):150-6. PMID: 18303535
26. Rodriguez R, Cizman Z, Hong K, et al. Prospective analysis of the safety and efficacy of percutaneous cryoablation for pT1NxMx biopsy-proven renal cell carcinoma. *Cardiovascular and interventional radiology.* 2011;34(3):573-8. PMID: 20628879
27. Shelley M, Wilt TJ, Coles B, et al. Cryotherapy for localised prostate cancer. *Cochrane Database Syst Rev.* 2007(3):CD005010. PMID: 17636783
28. Chin JL, Ng CK, Touma NJ, et al. Randomized trial comparing cryoablation and external beam radiotherapy for T2C-T3B prostate cancer. *Prostate cancer and prostatic diseases.* 2008;11(1):40-5. PMID: 17579613
29. Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. *Cancer.* 2010;116(2):323-30. PMID: 19937954
30. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. *Cancer.* 2009;115(20):4695-704. PMID: 19691092
31. Huang YZ, Zhou SC, Zhou H, et al. Radiofrequency Ablation versus Cryosurgery Ablation for Hepatocellular Carcinoma: A Meta-Analysis. *Hepato-gastroenterology.* 2013;60(127). PMID: 23321123
32. Yang Y, Wang C, Lu Y, et al. Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma. *Journal of hepato-biliary-pancreatic sciences.* 2012;19(6):674-84. PMID: 22187145
33. Saxena A, Chua TC, Chu F, et al. Optimizing the surgical effort in patients with advanced neuroendocrine neoplasm hepatic metastases: a critical analysis of 40 patients treated by hepatic resection and cryoablation. *American journal of clinical oncology.* 2012;35(5):439-45. PMID: 21654315
34. Wenske S, Quarrier S,Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. *Eur Urol.* 2013;64(1):1-7. PMID: 22840351

35. Valerio M, Ahmed HU, Emberton M, et al. The Role of Focal Therapy in the Management of Localised Prostate Cancer: A Systematic Review. *Eur Urol.* 2013. PMID: 23769825
36. Martin J,Athreya S. Meta-analysis of cryoablation versus microwave ablation for small renal masses: is there a difference in outcome? *Diagn Interv Radiol.* 2013;19(6):501-7. PMID: 24084196
37. Cordeiro ER, Barwari K, Anastasiadis A, et al. Laparoscopic cryotherapy for small renal masses: Current State. *Archivos espanoles de urologia.* 2013;66(1):41-53. PMID: 23406799
38. Kapoor A, Touma NJ,Dib RE. Review of the efficacy and safety of cryoablation for the treatment of small renal masses. *Can Urol Assoc J.* 2013;7:E38-44. PMID: 23401737
39. Durand M, Barret E, Galiano M, et al. Focal Cryoablation: A Treatment Option For Unilateral Low-Risk Prostate Cancer. *BJU international.* 2013. PMID: 24053685
40. Punnen S, Cooperberg MR, D'Amico AV, et al. Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. *Eur Urol.* 2013;64(6):905-15. PMID: 23721958
41. Tang K, Yao W, Li H, et al. Laparoscopic renal cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal masses: a systematic review and meta-analysis of comparative studies. *Journal of laparoendoscopic & advanced surgical techniques Part A.* 2014;24(6):403-10. PMID: 24914926
42. Klatte T, Shariat SF,Remzi M. Systematic review and meta-analysis of perioperative and oncologic outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors. *J Urol.* 2014;191(5):1209-17. PMID: 24231845
43. Korpan NN. Hepatic cryosurgery for liver metastases. Long-term follow-up. *Annals of surgery.* 1997;225(2):193-201. PMID: 9065296
44. Wang C, Wang H, Yang W, et al. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology.* 2015;61(5):1579-90. PMID: 25284802
45. Xiong T, Turner RM, Wei Y, et al. Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. *BMJ Open.* 2014;4:e004285. PMID: 24833678
46. Zargar H, Atwell TD, Cadeddu JA, et al. Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. *Eur Urol.* 2015. PMID: 25819723
47. Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. *Eur J Cancer.* 2015;51(16):2345-67. PMID: 26254809
48. Caputo PA, Ramirez D, Zargar H, et al. Laparoscopic Cryoablation for Renal Cell Carcinoma: 100-Month Oncologic Outcomes. *J Urol.* 2015;194(4):892-6. PMID: 25912493
49. Ratko TA, Vats V, Brock J, et al. Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non-Small-Cell Lung Cancer. *AHRQ Comparative Effectiveness Reviews.* 2013. PMID: 23865091
50. Pessoa RR, Autorino R, Laguna MP, et al. Laparoscopic Versus Percutaneous Cryoablation of Small Renal Mass: Systematic Review and Cumulative Analysis of Comparative Studies. *Clinical genitourinary cancer.* 2017;15(5):513-19 e5. PMID: 28442227

51. Moore W, Talati R, Bhattacharji P, et al. Five-year survival after cryoablation of stage I non-small cell lung cancer in medically inoperable patients. *J Vasc Interv Radiol.* 2015;26(3):312-9. PMID: 25735518
52. Zhao Z,Wu F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. *Eur J Surg Oncol.* 2010;36(12):1149-55. PMID: 20889281
53. Pfleiderer SO, Freesmeyer MG, Marx C, et al. Cryotherapy of breast cancer under ultrasound guidance: initial results and limitations. *Eur Radiol.* 2002;12(12):3009-14. PMID: 12439583
54. Suzuki Y. Cryosurgical treatment of advanced breast cancer and cryoimmunological responses. *Skin Cancer.* 1995;10:19-26. PMID: No PMID Entry
55. Morin J, Traore A, Dionne G, et al. Magnetic resonance-guided percutaneous cryosurgery of breast carcinoma: technique and early clinical results. *Can J Surg.* 2004;47(5):347-51. PMID: 15540687
56. Littrup PJ, Jallad B, Chandiwala-Mody P, et al. Cryotherapy for breast cancer: a feasibility study without excision. *J Vasc Interv Radiol.* 2009;20(10):1329-41. PMID: 19800542
57. Sabel MS, Kaufman CS, Whitworth P, et al. Cryoablation of early-stage breast cancer: work-in-progress report of a multi-institutional trial. *Ann Surg Oncol.* 2004;11(5):542-9. PMID: 15123465
58. Kaufman CS, Bachman B, Littrup PJ, et al. Office-based ultrasound-guided cryoablation of breast fibroadenomas. *Am J Surg.* 2002;184(5):394-400. PMID: 12433600
59. Kaufman CS, Littrup PJ, Freman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas: 12-month followup. *J Am Coll Surg.* 2004;198(6):914-23. PMID: 15194073
60. Kaufman CS, Bachman B, Littrup PJ, et al. Cryoablation treatment of benign breast lesions with 12-month follow-up. *Am J Surg.* 2004;188(4):340-8. PMID: 15474424
61. Littrup PJ, Freeman-Gibb L, Andea A, et al. Cryotherapy for breast fibroadenomas. *Radiology.* 2005;234(1):63-72. PMID: 15550369
62. Kaufman CS, Littrup PJ, Freeman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas with long-term follow-up. *Breast J.* 2005;11(5):344-50. PMID: 16174156
63. Nurko J, Mabry CD, Whitworth P, et al. Interim results from the FibroAdenoma Cryoablation Treatment Registry. *Am J Surg.* 2005;190(4):647-51; discussion 51-2. PMID: 16164941
64. Manenti G, Perretta T, Gaspari E, et al. Percutaneous local ablation of unifocal subclinical breast cancer: clinical experience and preliminary results of cryotherapy. *Eur Radiol.* 2011;21(11):2344-53. PMID: 21681574
65. Pusztaszeri M, Vlastos G, Kinkel K, et al. Histopathological study of breast cancer and normal breast tissue after magnetic resonance-guided cryotherapy ablation. *Cryobiology.* 2007;55(1):44-51. PMID: 17604016
66. Simmons RM, Ballman KV, Cox C, et al. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. *Ann Surg Oncol.* 2016;23(8):2438-45. PMID: 27221361
67. Lee SH, Choi WJ, Sung SW, et al. Endoscopic cryotherapy of lung and bronchial tumors: a systematic review. *Korean J Intern Med.* 2011;26(2):137-44. PMID: 21716589
68. Gu XY, Jiang Z,Fang W. Cryoablation Combined with Molecular Target Therapy Improves the Curative Effect in Patients with Advanced Non-small Cell Lung Cancer. *J Int Med Res.* 2011;39(5):1736-43. PMID: 22117974
69. Callstrom MR, Woodrum DA, Nichols FC, et al. Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE). *Journal of*

thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2020;15(7):1200-09. PMID: 32151777
70. de Baere T, Tselikas L, Woodrum D, et al. Evaluating Cryoablation of Metastatic Lung Tumors in Patients--Safety and Efficacy: The ECLIPSE Trial--Interim Analysis at 1 Year. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2015;10(10):1468-74. PMID: 26230972
71. Khanmohammadi S, Noroozi A, Yekaninejad MS, et al. Cryoablation for the Palliation of Painful Bone Metastasis: A Systematic Review. *Cardiovascular and interventional radiology.* 2023;46(11):1469-82. PMID: 36631660
72. Sagoo NS, Haider AS, Ozair A, et al. Percutaneous image-guided cryoablation of spinal metastases: A systematic review. *J Clin Neurosci.* 2022;96:120-26. PMID: 34840092
73. Lindquester WS, Crowley J,Hawkins CM. Percutaneous thermal ablation for treatment of osteoid osteoma: a systematic review and analysis. *Skeletal Radiol.* 2020;49(9):1403-11. PMID:
74. Cazzato RL, Jennings JW, Autrusseau PA, et al. Percutaneous image-guided cryoablation of spinal metastases: over 10-year experience in two academic centers. *Eur Radiol.* 2022;32(6):4137-46. PMID: 35028752
75. Jennings JW, Prologo JD, Garnon J, et al. Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study. *Radiol Imaging Cancer.* 2021;3(2):e200101. PMID: 33817650
76. Meller I, Weinbroum A, Bickels J, et al. Fifteen years of bone tumor cryosurgery: a single-center experience of 440 procedures and long-term follow-up. *Eur J Surg Oncol.* 2008;34(8):921-7. PMID: 18158228
77. Keane MG, Bramis K, Pereira SP, et al. Systematic review of novel ablative methods in locally advanced pancreatic cancer. *World J Gastroenterol.* 2014;20(9):2267-78. PMID: 24605026
78. Tao Z, Tang Y, Li B, et al. Safety and effectiveness of cryosurgery on advanced pancreatic cancer: a systematic review. *Pancreas.* 2012;41(5):809-11. PMID: 22695092
79. Kovach SJ, Hendrickson RJ, Cappadona CR, et al. Cryoablation of unresectable pancreatic cancer. *Surgery.* 2002;131(4):463-4. PMID: 11935137
80. Xu KC, Niu LZ, Hu YZ, et al. A pilot study on combination of cryosurgery and (125)iodine seed implantation for treatment of locally advanced pancreatic cancer. *World J Gastroenterol.* 2008;14(10):1603-11. PMID: 18330956
81. Li J, Chen X, Yang H, et al. Tumour cryoablation combined with palliative bypass surgery in the treatment of unresectable pancreatic cancer: a retrospective study of 142 patients. *Postgrad Med J.* 2011;87(1024):89-95. PMID: 21131612
82. Thacker PG, Callstrom MR, Curry TB, et al. Palliation of painful metastatic disease involving bone with imaging-guided treatment: comparison of patients' immediate response to radiofrequency ablation and cryoablation. *AJR Am J Roentgenol.* 2011;197(2):510-5. PMID: 21785102
83. Masala S, Guglielmi G, Petrella MC, et al. Percutaneous ablative treatment of metastatic bone tumours: visual analogue scale scores in a short-term series. *Singapore Med J.* 2011;52(3):182-9. PMID: 21451927
84. Welch BT, Atwell TD, Nichols DA, et al. Percutaneous image-guided adrenal cryoablation: procedural considerations and technical success. *Radiology.* 2011;258(1):301-7. PMID: 20971772
85. Yamauchi Y, Izumi Y, Kawamura M, et al. Percutaneous cryoablation of pulmonary metastases from colorectal cancer. *PLoS One.* 2011;6(11):e27086. PMID: 22096520

86. Callstrom MR, Dupuy DE, Solomon SB, et al. Percutaneous image-guided cryoablation of painful metastases involving bone: multicenter trial. *Cancer.* 2013;119(5):1033-41. PMID: 23065947
87. Poplack SP, Levine GM, Henry L, et al. A Pilot Study of Ultrasound-Guided Cryoablation of Invasive Ductal Carcinomas up to 15 mm With MRI Follow-Up and Subsequent Surgical Resection. *AJR Am J Roentgenol.* 2015;204(5):1100-8. PMID: 25905948
88. Saltiel S, Bize PE, Goetti P, et al. Cryoablation of Extra-Abdominal Desmoid Tumors: A Single-Center Experience with Literature Review. *Diagnostics (Basel, Switzerland).* 2020;10(8). PMID: 32759783
89. Zheng Z, Zhao Y, An Y, et al. Efficacy of argon-helium cryoablation andits effects on immune function of patients with neck malignant tumors. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2020. PMID: 32920994
90. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Prostate Cancer. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Prostate Cancer [cited 12/6/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
91. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Kidney Cancer. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Kidney Cancer [cited 12/6/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
92. Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. *J Urol.* 2008;180:1993-2004. PMID: 18817934
93. Sun F, Oyesanmi O, Fontanarosa J, et al. 2014. PMID: 25610935
94. Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol.* 2009;182(4):1271-9. PMID: 19683266
95. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-small cell lung cancer. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-small cell lung cancer [cited 12/6/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
96. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Uveal Melanoma. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Uveal Melanoma [cited 12/6/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/uveal_blocks.pdf.
97. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Bone Cancer. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Bone Cancer [cited 12/6/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.
98. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma [cited 12/6/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

CODES

Codes	Number	Description
CPT	0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral
	17260-17286	Destruction, malignant lesion (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement)
	19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma
	20983	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation
	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	32994	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation
	50250	Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed
	50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
	50593	Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy
	55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance and monitoring)
	57511	Cautery of cervix; cryocautery, initial or repeat
HCPCS	None	

Date of Origin: *March 2004*

Regence

Medical Policy Manual Surgery, Policy No. 134

Sacral Nerve Neuromodulation (Stimulation) for Pelvic Floor Dysfunction

Effective: March 1, 2024

Next Review: December 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Sacral nerve neuromodulation involves the implantation of a permanent electrical stimulation device that modulates the neural pathways controlling bladder or rectal function.

MEDICAL POLICY CRITERIA

Note: Sacral nerve neuromodulation should be initiated with a *trial period* of sacral nerve neuromodulation (peripheral nerve stimulation test) with a *temporarily implanted* lead and may be followed by *permanent implantation*. This policy addresses these services as one combined episode beginning with the temporary placement.

I. Sacral nerve neuromodulation (including a *trial period* of sacral nerve neuromodulation [peripheral nerve stimulation test] with a *temporarily implanted* lead and, when used, the *permanent implantation*) may be considered **medically necessary** when one or more of the following criteria are met:

   A. For the treatment of urinary incontinence and non-obstructive retention in patients who meet **all** of the following criteria (1. – 3.):

1. There is a diagnosis of at least one of the following:
    a. Urge incontinence
    b. Urgency-frequency syndrome
    c. Non-obstructive urinary retention
    d. Overactive bladder
2. There is documented failure or intolerance to at least 2 conventional conservative therapies (e.g., behavioral training such as bladder training, prompted voiding, or pelvic muscle exercise training, pharmacologic treatment for at least a sufficient duration to fully assess its efficacy, and/or surgical corrective therapy); and
3. Incontinence is not related to a neurologic condition.

B. For the treatment of fecal incontinence in patients who meet **all** of the following criteria (1. - 5.):

1. There is a diagnosis of chronic fecal incontinence of greater than 2 incontinent episodes on average per week with duration greater than 6 months or for more than 12 months after vaginal childbirth;
2. There is documented failure or intolerance to conventional conservative therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment for at least a sufficient duration to fully assess its efficacy);
3. The condition is not related to an anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60 degrees; visible sequelae of pelvic radiation; active anal abscesses and fistulae) or chronic inflammatory bowel disease;
4. Incontinence is not related to another neurologic condition; and
5. The patient has not had rectal surgery in the previous 12 months, or in the case of rectal cancer, the patient has not had rectal surgery in the past 24 months.

II. Revision(s) or removal of an existing sacral nerve neuromodulation device may be considered **medically necessary** after the device has been placed.

III. Replacement of all or part of an existing sacral nerve neuromodulation device and/or generator is considered **medically necessary** when the existing device and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

IV. Replacement of all or part of an existing sacral nerve neuromodulation device and/or generator is considered **not medically necessary** when Criterion III. is not met.

V. Sacral nerve neuromodulation for the treatment of urinary incontinence, non-obstructive retention, and fecal incontinence is considered **not medically necessary** when Criterion I. is not met, including but not limited to stress incontinence and urge incontinence due to a neurologic condition (e.g., detrusor hyperreflexia, multiple sclerosis, spinal cord injury, or diabetes with peripheral nerve involvement).

VI. Sacral nerve neuromodulation for the treatment of all other indications is considered **investigational**, including but not limited to chronic pelvic pain and constipation.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Documented applicable Diagnosis/Diagnoses and any neurological diagnoses present
- Documented failure or intolerance to conventional conservative therapies attempted as detailed in criteria I.A.2. and I.B.2.
- Documentation of surgical history within the last 24 months as applicable to fecal incontinence

CROSS REFERENCES

1. Pelvic Floor Stimulation as a Treatment of Urinary Incontinence, Allied Health, Policy No. 4
2. Periurethral Transperineal Adjustable Balloon Continence Device, Medicine, Policy No. 176
3. Subcutaneous Tibial Nerve Stimulation, Surgery, Policy No. 154

BACKGROUND

Sacral nerve neuromodulation (SNM), previously known as sacral nerve stimulation is defined as the implantation of a permanent device that modulates the neural pathways controlling bladder or rectal function. The SNM device consists of an implantable pulse generator (neurostimulator) that delivers controlled electrical impulses. The neurostimulator is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root. A remote control is provided to the patient to adjust the stimulation level.

Treatment using SNM is one of several alternative modalities for patients with fecal or urinary incontinence who have failed behavioral (e.g., prompted voiding) and/or pharmacologic therapies.

Prior to implantation of the permanent device, patients undergo a peripheral nerve stimulation test to estimate potential response to SNM. This procedure is done under local anesthesia, using a test needle to identify the appropriate sacral nerve(s). Once identified, a temporary wire lead is inserted through the test needle and left in place for several days. This lead is connected to an external stimulator which is carried by patients in their pocket or on their belt. Patients then keep track of symptoms while the temporary device is functioning. The results of this test phase are used to determine whether patients are appropriate candidates for the permanent device. If patients show a 50% or greater reduction in incontinence frequency, they are deemed eligible for the permanent device. The permanent device is implanted with the patient under general anesthesia. An incision is made over the lower back and the electrical leads are placed in contact with the sacral nerve root(s). A second incision is made in the upper buttock where the neurostimulator is inserted and connected to the wire leads. The stimulator is turned on after the procedure is completed and the patient is provided a remote control to adjust the stimulation level. Manufacturers recommend the patients receive stimulation 24 hours per day, 7 days a week.

Newer generation stimulators have long life batteries (15-20 years) either requiring recharging weekly or are recharge free with an estimated recharge free life of 15 + years depending on level of stimulation.

REGULATORY STATUS

Axonics Sacral Neuromodulation System

In 2019, The Axonics Sacral Neuromodulation System received U.S. Food and Drug Administration (FDA) approval (PMA#: P190006) for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments. Product code: QON

In 2019, The Axonics Sacral Neuromodulation System received FDA approval (PMA#: P P180046) for the treatment of urinary retention and the symptoms of overactive bladder, including urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments. Product code: EZW

Axonic currently has two devices:

- The Axonics R15™ System which has a rechargeable with a battery designed to last 15 years or more.
- The Axonics F15™ System which has a long life battery that does not require recharging (15 -20 year battery life). FDA Approved 3/7/22 for above indications.

Axonics SNM Therapy is contraindicated for patients who have not demonstrated an appropriate response to test stimulation; or patients who are unable to operate the Axonics SNM Systems.

Medtronic Interstim® Sacral Nerve Stimulation™ system

In 1997, the Medtronic Interstim® Sacral Nerve Stimulation™ system received FDAapproval (PMA# P970004) for marketing for the indication of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments. In 1999 the device received FDA approval for the additional indications of urgency-frequency and urinary retention in patients without mechanical obstruction. Product Code: EZW

In 2006, the Medtronic Interstim® II System received FDA approval for treatment of intractable cases of overactive bladder and urinary retention. The new device is smaller and lighter than the original system and is reported to be suited for those with lower energy requirements or small stature. The device also includes updated software and programming options.

In 2011, the Medtronic InterStim System received FDA approval (PMA#: P080025) for the indication of chronic fecal incontinence in patients who have failed or could not tolerate more conservative treatments. Product Code: QON

In 2020, the Medtronic InterStim™ Micro system received FDA approval for above indications. This small device has a rechargeable battery designed to last 15 years. Recharging can be done 1x per week.

In 2022, the Medtronic InterStimX™ system received FDA approval for the above indications. This device does not require recharging and has a 15 year battery life when using low energy settings.

Virtis™ Sacral Neuromodulation System (Nuvectra)

In 2023, the Virtis™ Sacral Neuromodulation System (Nuvectra) was approved by the FDA for treatment of urinary retention and symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency in patients who have failed more conservative treatments.

Note: Sacral Neuromodulation devices are not currently approved by the FDA for treatment of chronic pelvic pain or constipation.

Note: Sacral nerve neuromodulation should be distinguished from pelvic floor stimulation. Pelvic floor stimulation refers to electrical stimulation of the pudendal nerve. This therapy is addressed in a separate medical policy (see Cross References).

EVIDENCE SUMMARY

Assessment of the safety and efficacy of sacral nerve modulation (SNM) as a treatment for urinary or fecal incontinence requires large, blinded, long-term randomized controlled trials to determine whether 1) the benefits of SNM outweigh any risks, and 2) whether SNM offers advantages over conventional conservative treatments. The appropriate control group(s) against which SNM should be compared is sham stimulation, on- versus off-phases in which patients act as their own controls, or conventional conservative therapies.

URINARY DYSFUNCTION

Urge Incontinence

Systematic Reviews

Initially, the policy for SNM as a treatment of urge incontinence was based on a 1998 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment.[1] Based on a multicenter RCT[2] conducted as part of the FDA approval process, the TEC Assessment concluded that SNM reduced urge incontinence compared with control patients.

Brazzelli performed a review of articles published between 1966 and 2003 which included four randomized controlled trials (RCT) and 30 case series.[3] The authors reported that about 80% of patients in the randomized trials achieved greater than 50% improvement in their main incontinence symptoms after SNM compared with about 3% of controls receiving conservative treatments. The case series, which were larger but methodically less reliable, showed similar results. Benefits were reported to persist three to five years after implantation. The authors noted that technical changes over time were associated with decreased complication rates.

Randomized Controlled Trials

No new RCTs for urge incontinence were identified since the above systematic reviews were published.

Nonrandomized Studies

Groen (2011) reported five year follow-up results for patients (n=60) after SNM treatment for refractory idiopathic urge urinary incontinence.[4] Success was defined as at least a 50% decrease in the number of incontinent episodes or pads used per day. The success rate was 52 of 60 (87%) at one month and gradually decreased to 37 (62%) at five years. The number of women who were completely continent was 15 (25%) at one month and 9 (15%) at five years. At the five-year follow-up, SNM was still used by 48/60 (80%) women. A total of 57 adverse events were reported in 32 of 60 (53%) patients. The most frequent adverse events were hardware-related or pain or discomfort. There were a total of 23 reoperations in 15 patients. In most cases, pain problems were managed conservatively.

Urinary Urgency/Incontinence/Frequency/Overactive Bladder

Systematic Reviews

No recent systematic reviews were identified.

Randomized Controlled Trials

In the multicenter randomized clinical study of 581 patients with a variety of urinary dysfunctions submitted to the FDA as part of the device approval process, 220 had significant urgency-frequency symptoms.[5] After six months of SNM therapy, 83% of patients with urgency-frequency symptoms reported increased voiding volumes with the same or reduced degree of frequency. At 12 months, 81% of patients had reached normal voiding frequency. Compared to a control group, patients with implants reported significant improvements in quality of life, as evaluated by the SF-36 health survey. The trial was well-designed, using standardized clinical and functional status outcomes measurements, and enrolled patients with severe urge incontinence who had failed extensive prior treatments. The magnitude of effect (approximately one-half of patients became dry, three-quarters experienced at least 50% reduction in incontinence) was fairly large, probably at least as great as with surgical procedures, and larger than expected from a placebo effect or conservative measures such as behavioral therapy or drugs. The therapy evaluation test, in which the device was turned off (ie, sham treatment was provided) and patients thus served as their controls, provided further evidence that the effect on incontinence was due to electrical stimulation and demonstrated that the effect of sacral nerve neuromodulation is reversible. The cohort analysis of the clinical trial provided some evidence that the effect of sacral nerve neuromodulation could be maintained for up to two years. There was a high rate of adverse events reported in this trial. Most were minor and reversible; however, approximately one-third of patients required surgical revision for pain at the operative sites or migration of the leads.

In 2016, Amundsen reported on a RCT comparing intradetrusor injection of onabotulinumtoxinA (n=192) with SNM (n=189) in women with refractory urgency urinary incontinence, defined as at least one supervised behavioral or physical therapy intervention and the use of a minimum of two anticholinergics (or inability to tolerate or contraindications to the medication).[6] In intention-to-treat analysis, onabotulinumtoxinA-treated patients had greater reductions in urge incontinence per day than SNM-treated patients: 3.9 vs 3.3 per day (mean difference: 0.63; 95% confidence interval [CI] 0.13 to 1.14, p=0.01). OnabotulinumtoxinA-treated patients had greater reductions in some overactive bladder-related quality of life questionnaire-related measures, although the clinical meaningfulness of the changes was uncertain. Patients in the onabotulinumtoxinA-treated group were more likely to have urinary tract infections (UTIs, 35% vs 11%; risk difference -23%, 95% CI -33% to -13%, p<0.001).

In 2014 Siegel published an industry-sponsored FDA-mandated postapproval randomized study and is known as the Insite trial.[7] This study compared SNM using a two-stage surgical procedure with standard medical therapy. Study inclusion criteria included a diagnosis of overactive bladder (OAB) (at least eight voids per day and/or at least two involuntary leaking episodes in 72 hours) and a failed trial of at least one anticholinergic or antimuscarinic medication. In addition, there needed to be at least one such medication that had not yet been attempted. Patients with neurologic diseases and with primary stress incontinence were excluded. A total of 70 patients were allocated to SNM and 77 to standard medical therapy. Of the 70 patients in the SNM group, 11 elected not to receive test stimulation with the tined lead and eight received the lead but did not receive a full system implant due to lack of response to a 14-day test stimulation period (response was defined as at least a 50% reduction in average leaks and/or voids). Patients in the medical treatment group tried the next recommended medication or restarted a discontinued medication. Therapeutic success was defined as at least a 50% improvement in average leaks/day or at least a 50% improvement in the number of voids per day or a return to fewer than eight voids per day. In an intention-to-treat analysis, the therapeutic success rate at six months was 61% in the SNM group and 42% in the standard medical treatment group; the difference between groups was statistically significant ($p=0.02$). Quality of Life (QOL) at six months was a secondary outcome. Several validated QOL scales were used, and all favored the SNM group compared with the standard medical treatment group ($p<0.002$ for all comparisons).

In 2014, Noblett published twelve-month follow-up results of the Insite trial. The analysis included patients included in the SNM group of initial RCT plus additional patients enrolled and implanted in the interim.[8] A total of 340 patients underwent test stimulation, 272 underwent implantation, and 255 completed 12 months of follow-up. In a modified completers' analysis, the therapeutic success rate was 82%. This modified completers' analysis included patients who were implanted and had either a baseline or 12-month evaluation, or withdrew from the trial due to a device-related adverse event or lack of efficacy. In an analysis limited to study completers, the therapeutic response rate was 85%. The Noblett analysis did not include data from the control group of patients receiving only standard medical therapy.

In 2014 Tang published the results of an RCT in which 240 women with OAB were randomized to receive tolterodine with (n=120) or without (n=120) sacral neuromodulation.[9] Participants were also divided into subgroups based on the presence or absence of urinary incontinence. The treatment period was three months; results were measured by voiding diaries and urodynamic parameters, in addition to psychological depression and anxiety scores. The group receiving SNM reported significantly greater improvements in the conditions of first desire to void, maximum cystometric capacity, daily average volumes, and daily single maximum voided volumes compared to the group receiving medication alone ($p=.001$). The SNM group also reported greater decreases in self-rated depression and anxiety scales ($p<0.001$). The authors concluded that combined treatment with SNM and tolterodine could improve the quality of life in women with OAB by decreasing voiding dysfunction symptoms and related depression and anxiety.

Nonrandomized Studies

Chartier-Kastler (2022) published 3-year results from a prospective, observational, multicenter study from France (SOUNDS).[10] Patients with overactive bladder (N=229) underwent InterStim implantation (either a first device or a replacement) and were followed for a mean of 33.7 ± 3.7 months. During the 3-year follow-up, average daily voids and leaks were

significantly reduced (all $p < 0.05$) and response (defined as ≥ 50% reduction in voids per day or return to normal voiding frequency) ranged from 72% to 86%. Quality of life scores were improved at all study visits. About half of the patients experienced adverse events, which were mostly minor, but surgical revision was required in 33% of patients. Lack of a control arm may limit the clinical applicability of these results.

Several groups have published results of the Axonics® Sacral Neuromodulation System for Urinary Urgency Incontinence Treatment (ARTISAN-SNM) study-a single arm, prospective, multicenter trial of the Axonics r-SNM System™.[11-13] All participants (n=129) were implanted with a tined lead and the rechargeable sacral neuromodulation system in a nonstaged procedure. Efficacy data were collected using a 3-day bladder diary, the validated International Consultation on Incontinence Questionnaire Overactive Bladder quality of life (ICIQ-OABqol) questionnaire and a participant satisfaction questionnaire. Pezzell (2021) published a two year follow-up analysis and reported that 93% of the participants (n = 121 Completers at two years) were therapy responders, of which 82% achieved ≥ 75% reduction in UUI episodes and 37% were dry (100% reduction).[13] Daily UUI episodes reduced from 5.6 ± 0.3 at baseline to 1.0 ± 0.2 at two years. Statistically significant improvements in ICIQ-OABqol were reported. Geynisman-Tan (2021) published a secondary analysis in Participants (n=124) at one year.[11] Participants were classified as responders (n=110) and non-responders (14) based on a ≥50% reduction in UUI episodes in a three-day period at one-month post-implant. Most participants reported being satisfied with the SNM treatment (68.5% were "very satisfied," 25.8% were "moderately satisfied," and 2.4% were "slightly satisfied). Twelve of the 14 "non-responders" continued to see improvements in symptom reduction from one month to one year; 9/14 (64%) were "responders" at one year with six reporting being "very satisfied" and one reporting being "moderately satisfied." McCrery (2020) reported at six-months that 90% of participants were therapy responders (≥50% reduction in UUI episodes compared to baseline).[12] With a mean (+ SE) reduction of 5.6 ± 0.3 at baseline to 1.3 ± 0.2. Participants experienced a clinically meaningful 34-point improvement on the ICIQ-OABqol questionnaire. There were no serious device related adverse events reported. The authors conclude that The Axonics r-SNM System™ demonstrates sustained safe and effective treatment for patients experiencing urinary urgency incontinence symptoms. They also report no unanticipated or serious device-related adverse events at two years.

Blok (2020) published the two year safety and efficacy outcomes using SNM for the treatment of Overactive Bladder (OAB) using the Axonics system.[14] Subjects (n=51) with confirmed OAB were implanted with the Axonics system using a nonstaged procedure. At two years 90% of test responders (defined as subjects who were responders at one month) to respond based on voiding diary criteria. Satisfaction with therapy was reported by 93% of subjects and 86% found their charging experience acceptable. Of the urinary incontinence Test Responders, 88% continued to be responders at two years, and 28% were completely dry. There were no unanticipated (AEs) or serious device-related AEs. The authors conclude that the Axonics System® provides sustained clinically meaningful improvements in OAB subjects at two years.

There has also been interest in the use of SNM as a treatment of interstitial cystitis, a condition characterized by painful urinary urgency and frequency.[15-17] These studies reported a decrease in both urgency/frequency and pain. These patients would be considered candidates for SNM therapy based on the presence of urgency and frequency alone.

Urinary Retention

Systematic Review

A 2009 Cochrane review[18] described eight randomized studies on implanted devices for urinary storage and voiding dysfunction in adults. In spite of methodologic problems (e.g., generally poor-quality studies), the evidence “seems clear that continuous stimulation offers benefits for carefully selected people with overactive bladder syndrome and for those with urinary retention but no structural obstruction.” The authors concluded that while some people benefit, more research is needed to improve patient selection, to carry out the implant, and to find why so many fail.

In 2014, the Agency for Healthcare Research and Quality published a comparative effectiveness review focused on chronic urinary retention treatments.[19] The authors identified the previously described Cochran review as providing “low-strength evidence that neuromodulation improves the rate at which patients with Fowler’s syndrome can be catheter free after treatment,” but noted that there were few studies overall, and most were small and had other methodologic limitations.

Randomized Controlled Trial

No new RCTs for urinary retention were identified since the above systematic review was published.

Complications of SNM for Urinary Dysfunctions

A large prospective series by White focused on complications associated with SNM in 202 patients with urge incontinence, urinary urgency, or urinary retention.[20] At a mean follow-up of 37 months (range, 7 to 84), 67 patients (30%) had experienced adverse events that required either lead or implantable pulse generator revisions. Complications included pain (3%), device malfunction secondary to trauma (9%), infection (4%), postoperative hematoma (2%), and lead migration (6%).In addition, 5% of patients underwent elective removal, 4% had device removal due to lack of efficacy, and 2% required removal due to battery expiration. At the last follow-up, 172 patients (85%) had functional implanted units.

Section Summary

Data from RCTs and case series with long-term follow-up provides sufficient evidence to conclude that SNM is effective and safe in selected patients with urge incontinence, overactive bladder, urgency-frequency syndrome, and non-obstructive urinary retention.

DEFECATION DYSFUNCTION

Fecal Incontinence

Systematic Reviews

In 2019, Simillis published a systematic review and meta-analysis of treatments for fecal incontinence (FI).[21] A total of 47 RCTs were included and 37 treatments were addressed. Overall, no treatment was ranked best or worst for any outcome. With respect to SNM, significant improvements compared to placebo were reported for incontinence scores.

A 2018 SR by Dulskas evaluated the literature on treatments for lower anterior resection syndrome.[22] The authors identified a total of 21 studies that met inclusion criteria, of which eight evaluated the use of SNM. Only one of the identified studies was determined not to be of

poor quality. Therefore, the authors concluded that high quality RCTs are needed to determine the efficacy of SNM.

A 2015 Cochrane review evaluated SNM for FI and constipation in adults.[23] This review included six trials assessing the effects of SNM for FI. Two parallel group trials found that SNM reduced the number of incontinence episodes when compared with optimal medical therapy or percutaneous tibial nerve stimulation. Three of the four included crossover trials found reductions in incontinence episodes during the SNM "on" period relative to the "off" period; in the other crossover trial, participants did not experience any episodes of FI during either period. The primary methodological quality issue noted was related to lack of clarity around randomization techniques and allocation concealment. The review authors concluded that there was limited evidence that SNM could improve continence in some patients with FI.

In 2016, the Agency for Healthcare Research and Quality published a comparative effectiveness review on treatments for FI.[24] There were 63 studies that met inclusion criteria for the review, and 53 surgical case series were reviewed for adverse events. There were 38 RCTs that assessed nonsurgical treatments and 12 that reviewed surgical interventions, including five studies of SNM. Regarding SNM, the authors concluded that the evidence was "insufficient because all five studies had moderate or high risk of bias, and none assessed the same treatment-outcome combination."

In 2013, Thin published a SR of randomized trials and observational studies on SNM for treating FI.[25] A total of 61 studies met eligibility criteria; including at least 10 patients, having a clear follow-up interval and reporting the success rate of therapy based on a 50% or greater improvement in fecal incontinence episodes. Only two of the studies were RCTs.[26, 27] and 50 were prospective case series. Data from two studies with long-term follow-up could be pooled to calculate median success rates using an intention-to-treat analysis. These median success rates were 63% in the short term (no more than 12 months' follow-up), 58% in the medium term (12 to 36 months), and 54% in the long term (>36 months). The per-protocol short-, medium-, and long-term success rates were 79%, 80%, and 84%, respectively.

In 2011, Maeda published a SR of studies on complications following permanent implantation of a SNM device for FI and constipation.[28] The authors identified 94 articles. The vast majority of studies addressed FI. A combined analysis of data from 31 studies on SNM for fecal incontinence reported a 12% suboptimal response to therapy (149 of 1,232 patients). A review of complications reported in the studies found that the most commonly reported complication was pain around the site of implantation, with a pooled rate of 13% (81/621 patients). The most common response to this complication was repositioning the stimulator, followed by explantation of the device and reprogramming. The second most common adverse event was infection, with a pooled rate of 4% (40/1025 patients). Twenty-five of the 40 infections (63%) led to explantation of the device.

In 2011, Tan published a meta-analysis of randomized trials and observational studies published between 2000 and 2008 on SNM for treating FI.[29] They identified a total of 34 studies that reported on at least one of their outcomes of interest and clearly documented how many patients underwent temporary and permanent SNM. Only one of these studies was an RCT; this was the study by Tjandra discussed earlier.[26] In the 34 studies, a total of 944 patients underwent temporary SNM and 665 subsequently underwent permanent SNM implantation. There were 279 patients who did not receive permanent implantation, and 154 of these were lost to follow-up. Follow-up in the studies ranged from 2 weeks to 35 weeks. In a

pooled analysis of findings of 28 studies, there was a statistically significant decrease in incontinence episodes per week with SNM compared to maximal conservative therapy (weighted mean difference: -6.83; 95% CI -8.05 to -5.60, p<0.001). Fourteen studies reported incontinence scores, and when these results were pooled, there was also a significantly greater improvement in scores with SNM compared to conservative therapy (weighted mean difference: -10.57, 95% CI -11.89 to -9.24, p<0.001).

A 2016 systematic review by Bielefeldt focused on the adverse events associated with SNM treatment of FI.[30] A literature search of PubMed and Embase was performed for studies that included at least five patients with fecal incontinence treated with SNM. The researchers additionally searched the FDA's Manufacturer and User Device Experience (MAUDE) database for reports from 2005 to October 2015. There were 45 articles included in the review that described distinct patient cohorts and provided information about adverse events. These included a total of 1,953 patients and a median follow-up time of 27 months. There were two studies with a total of 201 that provided the most detailed information.[31, 32] In these two studies, approximately 20% of the patients had their devices explanted by the end of follow-up and a substantial number required additional surgeries. There were five more studies that reported adverse events with less detail, and these reported a significantly lower incidence of such events. Information on infectious complications was reported in 44 studies with 1,953 patients, and the pooled rate of these was 5.1%. There were 39 studies with 1,810 patients that reported explant rates, with an average rate of 10.0%. Increases in explant rates were seen with increased follow-up duration. An overall re-operation rate of 18.6% was seen, based on data from 1,784 patients. According to the MAUDE database, there was an average of ten incidents per month related to the Interstim device in 2005. This rose to approximately 100 incidents per month within the next three years and stabilized until the year prior to FDA approval of the device as a treatment for fecal incontinence, and have since tripled. From August 1 - October 31, there were 1,684 problem reports received by the FDA, with 652 reports mentioning gastrointestinal issues as indications for SNM treatment and 278 reports specifically referring to fecal incontinence or bowel dysfunction. Most adverse events were reported within two years after device implantation.

In 2015, a systematic review was published that evaluated the impact of SNM on clinical symptoms and gastrointestinal physiology in patients with FI.[33] There were 81 studies included in the review, and the clinical outcomes assessed included frequency of fecal incontinence episodes, fecal incontinence severity score, and treatment success rates. A meta-analysis of the data from these studies was not possible, as most lacked a comparison group. Following SNM device implantation, 'perfect' continence was reported in 13% to 88% of patients. The majority of studies found a reduction in incontinence episodes per week (mean, -7.0; range, -24.8 to -2.7) and Wexner scores. The studies did not demonstrate any consistent, statistically significant effects of SNM on physiological parameters or identify any clinicophysiological factors that predicted success.

Randomized Controlled Trials

No new RCTs for FI were identified since the above systematic review was published.

Nonrandomized studies

Picciariello (2022) published a retrospective study to assess the long-term effectiveness of SNM treatment in patients with FI.[34] Of the patients (n=58) who met the inclusion criteria, 36 (58%) participated in the study the remainder (n=22; 38%) were lost to follow-up. The authors

report that 17 (27%) of patients included still experience efficacy with SNM, after a median follow-up of 13 years. The authors suggest that very long-term outcome further deteriorates with time compared with the 60–70% success rate reported at five years.

Jottard (2021) published the 6-month follow-up data for efficacy, clinical outcomes and ease of use of the Axonics rechargeable SNM (ArSNM) system in patients (n=15) with FI.[35] Patients were implanted with the SNM device using a single-stage procedure. At four weeks, 13 participants (87%) were test responders based on ≥50% reduction in FI episodes as documented on their bowel diary. Weekly FI episodes decreased from a median of 8 (5.8-20.3) at baseline to a median of 1.5 (0.4-4.5) at four weeks (p = 0.001), and 1.5 (0-2.6) at six months (p = 0.001), corresponding to 75% and 79% reduction in weekly FI episodes. Of the 13 subjects having ≥50% reduction in FI episodes at four weeks, 12 (PP = 92%) were therapy responders at six months. There were no unanticipated device or procedure-related adverse events. The authors conclude that the The ArSNM system provides safe and effective therapy in patients with FI at six months.

Desprez (2020) published results of a study that retrospectively analyzed prospectively collected data and found that long-term efficacy with SNM was maintained for at least 10 years post-implantation in approximately half of the patients treated for FI.[36] A similarly designed study by De Meyere (2020) in a single-center in Belgium demonstrated that the efficacy of sacral nerve stimulation in patients with fecal incontinence or low anterior resection syndrome was maintained for at least five years.[37]

Leo (2020) reported medium- and long-term outcomes following sacral nerve stimulation for FI.[38] This prospective observational study included 256 patients with medium-term results and, of those, 185 were followed up for long term outcomes. At the six-month follow-up, 65.2% (167/256) of patients showed a reduction of more than 50% in their St Marks fecal incontinence score and at the medium-term and long-term follow-ups it was 60.4% (142/235) and 62.1% (115/185), respectively. There was a reduction in median St Mark's score from baseline at six months ($p<0.00001$), which was maintained at the medium-term (110 months) and long-term (132 months) follow-ups. Twelve patients had lack of efficacy at the first postoperative follow-up, which was resolved with surgical correction in three patients and resulted in removal in the remainder. Of the 256 initial patients, 61 reported complications. This resulted in device removal for complications in 11 patients (4.2%), revisional surgery in 14 (5.4%), successful conservative treatment in 36 (14%), and a change of their SNS stimulation parameters in 51 (19.9%). Fourteen patients experienced wound infection/implant rejection.

In 2017, Koh reported on outcomes following SNM at a single Scottish center.[39] Of a total of 83 patients undergoing temporary SNM testing, 52 patients were permanently implanted. There were four failures, one removal due to cancer, seven infections, one lead migration, and three reports of post-operative pain or numbness.

Irwin (2017) assessed morbidity following SNM implantation for FI. Seventy-five patients were evaluated, 61 received insertion of a temporary SNM, and 40 received a permanent SNM.[40] Significant reduction in the Cleveland Clinic Incontinence Scores (14 pre-SNM to 9 post-SNM) and improvements in Role Physical, General Health, Vitality, Social Functioning, Role Emotional, Mental Health, and Mental Health Summary measures were reported.

Rice (2016) compared the commonly used staging procedure for evaluating candidacy for implantation of SNM to an office-based evaluation.[41] In this retrospective study, a total of 86 patients were evaluated, with 45 in the office-based evaluation group and 41 in the staged

group. The primary outcome was >50% improvement in Wexner score, resulting in patients progressing to permanent implantation. There was no significant difference in the primary outcome between groups or in the mean three-month Wexner score. Infection was significantly more likely in the staged group.

Patton (2016) evaluated medium-term outcomes from SNM patients at a single institution.[42] Of the 166 patients that underwent preliminary nerve stimulation testing, 112 had a permanent device implanted, and an additional 15 patients received a device without an initial testing phase for a total of 127 patients with SNM devices. The mean follow-up was 2.7 years (range, two months to 8.5 years), and 14 patients had the device removed and four had died, leaving 109 patients. Of these, 91 (83%) responded to the follow-up survey. There were significant improvements from baseline in St Mark's continence score (from 10.3 to 14.4, $p<0.01$), bowel control score, and fecal incontinence quality of life measures. Complications from the device included 12 infections, five of which required surgery, 17 lead dislodgements, and five rotated SNM devices that required repositioning.

Duelund (2016) published the results of a two-center prospective registry study that included 164 FI patients treated with SNM between 2009 and 2013.[43] The median follow-up in the study was 22 months (range, 1 to 50 months). There were improvements in Wexner incontinence scores and VAS impact on daily life. During follow-up, additional surgeries were required in 19.5% of patients. The most common complication was repositioning of the device due to pain or migration in 12.1% of patients, and infections leading to explantation were reported for 3% of patients. The same group also evaluated the effects of bilateral versus unilateral SNM for fecal incontinence treatment, and found no significant differences between groups.[44]

Altomare (2014) reported long-term outcomes (minimum of 60-month follow-up, median of 84-month follow-up) in patients implanted with a sacral nerve stimulator for FI.[45] Patients were identified in a European registry and surveyed. Long-term success was defined as maintaining the temporary stimulation success criteria, i.e., at least 50% improvement in the number of fecal incontinence episodes (or fecal incontinence symptom score) at last follow-up, compared with baseline. A total of 272 patients underwent permanent implantation of an SNM device and 228 were available for follow-up. A total of 194 of the 272 (71.3%) implanted patients maintained improvement in the long term.

Hull (2013) reported outcomes in 72 patients (60% of the 120 implanted patients) who had completed a five-year follow-up visit.[31] Sixty-four (89%) of the patients who contributed bowel diary data at five years had at least a 50% improvement from baseline in weekly incontinent episodes and 26 of the 72 patients (36%) had achieved total continence. It is uncertain whether outcomes differed in the 40% of patients who were missing from the five-year analysis.

Other case series have reported the experiences of patients with FI who were treated with sacral neuromodulation. These series are not summarized in depth here because methodological limitations do not permit conclusions on the safety and effectiveness of SNM for fecal incontinence. These limitations included patients with a variety of etiologies of fecal incontinence, including obstetric injury, spinal cord injury, prior surgery, sacral malformation, or idiopathic incontinence, lack of a comparator, and a wide range of follow-up periods (e.g., two months to 9.5 years). Thus, it is difficult to determine the complication rates or the durability of any benefits initially reported.

Section Summary

With longer term results from two randomized controlled trials, prospective case series, and a pooled analysis of data from the RCTs and observational studies, evidence is considered sufficient to conclude that sacral nerve neuromodulation/stimulation improves outcomes when used for the treatment for chronic fecal incontinence in well-selected patients who have failed conservative therapy.

Constipation

Systematic Review

Pauwels (2021) published a SR evaluating the different modalities of neurostimulation and their effect on chronic functional constipation in adults.[46] Seventeen studies were included on SNM. Although multiple uncontrolled retrospective and prospective studies demonstrated positive effects of SNM in constipation, the 3 RCTs included in the analysis demonstrated no significant improvements in outcomes.

Pilkington (2017) published a SR on behalf of the NIHR CapaCiTY working group, Pelvic floor Society that assessed outcomes of sacral nerve stimulation in adults with chronic constipation.[47] Seventy articles were included, with a total of 375 patients. Morbidity rates were heterogeneous and varied from 13 to 34%. Device removal rates were also heterogenous and ranged from 8 to 23%. Harms were inconsistently reported. Treatment success was reported between 57 and 87%. Reviewers concluded that the quality of studies was poor and therefore although the results were positive in favor of sacral nerve stimulation for chronic constipation, they urged caution.

The 2015 Cochrane review of SNM for fecal incontinence and constipation, described earlier, included two studies assessing SNM as a constipation treatment.[23] One trial, which included only two participants, found that the participants experienced a greater number of bowel movements per week when the device was on. The other trial, a larger randomized trial by Dinning, found that SNM did not affect the frequency of bowel movements.[48] The study included patients aged 18 to 75 years with slow transit constipation. Potentially eligible patients completed a three-week stool diary and, in order to continue participating, they needed to indicate in the diary that they had complete bowel movements less than three days per week for at least two of the three weeks. Patients with metabolic, neurogenic or endocrine disorders known to cause constipation were excluded. There were 57 patients that met eligibility criteria and had temporary percutaneous nerve evaluation (PNE), and 55 underwent permanent implantation. In random order, patients received active stimulation or sham stimulation. The primary outcome measure, determined by stool diaries, was a bowel movement with feelings of complete evacuation more than two days per week for at least two of three weeks; it was only assessed in phase 2. Compared with sham stimulation, 16 of 54 patients (29.6%) met the primary outcome during stimulation and 11 of 53 patients (20.8%) met it during sham stimulation; the difference was not statistically significant (p=0.23). Other outcomes did not differ significantly by group. The review authors concluded that SMN did not improve constipation symptoms and there were some adverse events associated with its use.

In 2013, Thomas published a systematic review of controlled and uncontrolled studies evaluating sacral nerve stimulation for treatment of chronic constipation.[49] The authors identified 11 case series and two blinded cross-over studies. Sample sizes in the case series ranged from 4 to 68 patients implanted with a permanent SNM device; in 7 of the 11 studies,

fewer than 25 patients underwent SNM implantation. Among the two cross-over studies, one included two patients implanted with an SNM device. The other, a 2012 study by Knowles and colleagues, temporary stimulation was evaluated in 14 patients.[50] Patients were included if they were diagnosed with evacuatory dysfunction and rectal hyposensitivity and had failed maximal conservative treatment. Patients were randomized to two weeks of stimulation with the SNM device turned on and two weeks with the SNM device turned off, in random order. There was no wash-out period between treatments. The primary efficacy outcome was change in rectal sensitivity and was assessed using three measures of rectal sensory thresholds. The study found a statistically significantly greater increase in rectal sensitivity with the device turned on in two of the three measures. Among the secondary outcome measures, there was a significantly greater benefit of active treatment on the percentage of successful bowel movements per week and the percentage of episodes with a sense of complete evacuation. In addition to its small sample size, the study was limited by the lack of a wash-out period between treatments i.e., there could have been a carry-over effect when the device was used first in the “on” position. Moreover, the authors noted that the patients were highly selected; only 14 of the approximately 1800 patients approached met the eligibility criteria and agreed to participate in the study.

Randomized Controlled Trials

One RCT has been published since the 2015 Cochrane review. This double-blind crossover trial, by Zerbib, included 36 patients (34 women) with refractory constipation, defined as at least two of the following criteria: fewer than three bowel movements per week, sensation of incomplete evacuation on more than a quarter of attempts, or straining to evacuate on more than a quarter of attempts.[51] This study defined a positive response to therapy as a more than 50% improvement in symptoms and/or at least three bowel movements per week. Of the 36 patients, 20 responded to the initial peripheral nerve evaluation and had a permanent stimulator implanted. Positive responses were seen in 12 of the patients during the active stimulation period and 11 of the patients during the sham stimulation period. Adverse events noted by the researchers included device-related pain in five patients and wound infection or hematoma in three patients, leading to device removal in two patients. SNM did not have a significant effect on colonic transit time. The authors concluded that the results of the study did not support the placement of SNM devices in patients with refractory constipation. The improvements seen with sham stimulation highlight the importance of control groups for comparison in studies of this technology.

Additionally, longer-term follow-up results to the study by Dinning[48] were published in 2016.[52] There were 53 patients that entered long-term follow-up, with one patient death. Adverse events or patient dissatisfaction lead to 44 patients withdrawing from the study by the end of the second year. Because of this, only ten patients met the primary outcome measure after one year, and only three patients met this measure after two years. There was no difference in colonic isotope retention at 72 hours at one-year follow-up.

Nonrandomized Studies

A 2019 report by Widmann analyzed a prospective database of fecal incontinence and constipation patients treated with SNM therapy. A total of 101 patients underwent test stimulation, 79 received permanent implantation, and 57 were still receiving SNM at the end of follow-up. The five-year success rate was 88.2% (95% CI 80.1 to 97.0%) for fecal incontinence and 31.2% (95% CI 10.2 to 95.5%) in patients with isolated constipation. Complications

necessitation reinterventions were reported in 24 patients. Battery replacement was reported in 23 patients, and the median battery life was 6.2 years.

In 2017, Maeda published a prospective multicenter study.[53] Of the 62 patients who underwent test stimulation, 45 proceeded to permanent implantation and 18 were followed up through 60 months. Fourteen patients reported improved Cleveland Clinic constipation score, which was sustained at 60 months. Ten patients submitted a bowel diary. Analysis of these showed significantly increased defecations per week and reduced sensation of incomplete emptying. Device-related adverse events were reported in 61% of patients.

In 2010, Maeda published a retrospective review of 38 patients with constipation who received permanent SNM after a successful trial period.[54] The study focused on reportable events, defined as suboptimal outcomes (lack of or loss of efficacy) or adverse events. The authors did not report detailed criteria for temporary or permanent placement of an SNM device. At the time of chart review, a mean of 25.7 months had elapsed since implantation. A total of 58 reportable events were identified in 22 of the 38 (58%) patients. A median of two (range 1-9) events per patient were reported; 26 of 58 events (45%) were reported in the first six months after device implantation. The most common reportable events were lack or loss of efficacy (26 of 58 events, 45%), and pain (16 events, 28%). Twenty-eight (48%) of the events were resolved by reprogramming. Surgical interventions were required for 19 (33%) of the events, most commonly permanent electrode replacement (14 events). Three of 38 (8%) patients discontinued use of the device due to reportable events.

A prospective registry study published in 2016 evaluated the effects of SNM on antigrade continence enema use in pediatric patients with severe constipation.[55] There were 22 patients below age 21 included; 55% were male and the median age was 12 years. The median frequency of antigrade continence enema use dropped from seven per week to one per week at 12 months. The Fecal Incontinence Severity index improved after six months, while other outcomes, including laxative use, Gastrointestinal Symptom Scale, and Fecal Incontinence Quality of Life Scale did not change. Ten children received cecostomy/appendicostomy closure within two years.

Several small case series were identified that focused on patients with slow transit constipation.[56-59] While promising results were reported, these case series are inadequate to permit scientific conclusions due to methodological limitations such as lack of lack of randomization and blinding, and lack of an adequate comparison group.

Section Summary

Only three controlled cross-over studies are available; one study was very small and had only two patients, the second study had methodological limitations, and the third and largest study showed no statistical difference between sham and stimulation. In addition, there are several, mainly small, case series. There is insufficient evidence to permit scientific conclusions about the efficacy and safety of sacral nerve neuromodulation/stimulation for patients with constipation.

Chronic Pelvic Pain

Systematic Review

Tirlapur assessed the effectiveness of tibial and sacral nerve stimulation in the treatment of bladder pain syndrome (BPS) and chronic pelvic pain (CPP).[60] Authors included randomized

and prospective quasi-randomized controlled studies vs. sham nerve stimulation treatment or usual care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Three studies with 169 patients treated with tibial nerve stimulation were included: two for CPP and one for BPS. There were improvements in pain, urinary and quality of life scores. There were no reported data for sacral nerve stimulation. Authors concluded that due to the quality of the literature, a large multi-centered clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP is recommended.

Nonrandomized studies

Several case series have evaluated SNM for treating chronic pelvic pain. For example, in 2012 Martelluci reported on 27 patients with chronic pelvic pain (at least six months) who underwent testing for SNM implantation[61]. After a four-week temporary stimulation phase, 16 of 27 patients (59%) underwent implantation of an Interstim device. In the 16 implanted patients, mean pain on a visual analogue scale (VAS) was 8.1 prior to implantation and 2.1 at the six- and 12-month follow-ups. An earlier study by Siegel reported on 10 patients and stated that 9 of the 10 experienced a decrease in pain with SNM.[62]

Section Summary

Data from several small case series with heterogenous patients represents insufficient evidence that sacral nerve neuromodulation/stimulation is safe and effective for treating chronic pelvic pain. RCTs are needed, with sham control groups, to assess the efficacy of neuromodulation/stimulation as a treatment of chronic pelvic pain.

PRACTICE GUIDELINE SUMMARY

AMERICAN UROLOGICAL ASSOCIATION AND THE SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE & UROGENITAL RECONSTRUCTION

The joint American Urological Association (AUA) and The Society of Urodynamics (SUFU) guidelines for non-neurogenic OAB in adults (updated in 2019) considers SNM an option for third-line treatment in carefully selected patients who failed conservative therapies and are characterized by severe OAB symptoms or those not considered candidates for pharmacologic therapy.[63] The strength of evidence was given a Grade C defined as low quality/low certainty based on observational studies that are inconsistent, small, or have other limitations that potentially confound interpretation of the data.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

A 2015 practice bulletin on urinary incontinence (replaced practice bulletin number 63, 2005; reaffirmed in 2018) from the American College of Obstetricians and Gynecologists (ACOG) stated, “sacral neuromodulation may be considered for patients with recalcitrant urinary urge incontinence who have failed other conservative measures, including bladder training, pelvic floor physical therapy with biofeedback, and pharmacologic treatment.”[64]

A 2019 ACOG practice bulletin (No. 210) on fecal incontinence included the following Level B (based on limited or inconsistent scientific evidence) recommendation: “sacral nerve stimulation can be considered as a surgical treatment option for women with fecal incontinence with or without anal sphincter disruption who have failed conservative treatments.”[65]

AMERICAN COLLEGE OF GASTROENTEROLOGY

The 2014 clinical guideline on the management of benign anorectal disorders, including fecal incontinence, from the American College of Gastroenterology (ACG) found that "sacral nerve stimulation should be considered in [fecal incontinence] who do not respond to conservative therapy (strong recommendation, moderate quality of evidence)."[66] The 2021 updated ACG guidelines continue the recommendation for sacral nerve stimulation in patients with fecal incontinence refractory to medical therapy.[67] Additionally, due to a lack of evidence supporting efficacy and the risk of adverse events and complications, the 2021 ACG Panel states that sacral nerve stimulation "cannot be recommended in patients with constipation of any type".

AMERICAN SOCIETY OF COLON AND RECTAL SURGEONS

In 2015, the American Society of Colon and Rectal Surgeons released a clinical practice guideline for the treatment of fecal incontinence.[68] They stated that "sacral neuromodulation may be considered as a first-line surgical option for incontinent patients with and without sphincter defects (Grade of Recommendation: Strong, based on moderate-quality evidence, 1B)."

In 2016, the Society released a clinical practice guideline for the management of constipation.[69] They stated "sacral neuromodulation may be an effective treatment for patients with chronic constipation and successful peripheral nerve evaluation test when conservative measures have failed; however, it is not currently approved by the US Food and Drug Administration for this condition in the United States (Grade of Recommendation: Weak, based on moderate quality evidence, 2B)."

SUMMARY

There is enough research to show that sacral nerve neuromodulation/stimulation (SNM) can improve health outcomes and quality of life in some patients with urinary incontinence, non-obstructive urinary retention, overactive bladder or fecal incontinence. Therefore, SNM, including temporary and the potential permanent implantation, may be considered medically necessary for these conditions when the policy criteria are met.

A SNM device may require revision or removal after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing sacral nerve neuromodulation device or removal of the device may be considered medically necessary after the device has been placed.

In certain situations, a SNM device may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of SNM device and/or generator may be considered medically necessary when device replacement Criteria are met.

When a SNM device is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a sacral nerve neuromodulation device and/or

generator is considered not medically necessary when device replacement Criteria are not met.

Sacral nerve neuromodulation/stimulation is considered not medically necessary for the treatment of urinary incontinence, non-obstructive urinary retention, and fecal incontinence in patients who do not meet criteria, including for individuals with urinary stress incontinence, or urge incontinence due to neurologic conditions such as multiple sclerosis, spinal cord injury, diabetes-related peripheral nerve conditions, and detrusor hyperreflexia because the procedure is not considered clinically effective or appropriate for these individuals.

There is not enough research to show that sacral nerve neuromodulation/stimulation (SNM) improves health outcomes for people with conditions other than urge incontinence, non-obstructive urinary retention, overactive bladder and fecal incontinence. Therefore, SNM is considered investigational for other conditions, including but not limited to chronic constipation and chronic pelvic pain.

REFERENCES

1. TEC Assessment 1998. "Sacral Nerve Simulation for the Treatment of Urge Incontinence." BlueCross BlueShield Association Technology Evaluation Center, Tab 18.
2. Brubaker L, Benson JT, Bent A, et al. Transvaginal electrical stimulation for female urinary incontinence. *Am J Obstet Gynecol.* 1997;177:536-40. PMID: 9322620
3. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. *J Urol.* 2006;175(3 Pt 1):835-41. PMID: 16469561
4. Groen J, Blok BF, Bosch JL. Sacral neuromodulation as treatment for refractory idiopathic urge urinary incontinence: 5-year results of a longitudinal study in 60 women. *J Urol.* 2011;186(3):954-9. PMID: 21791355
5. Food and Drug Administration (FDA). Summary of Safety and Effectiveness: Medtronic Interstim System for Urinary Control. [cited 12/28/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf/P970004S004b.pdf.
6. Amundsen CL, Richter HE, Menefee SA, et al. OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A Randomized Clinical Trial. *Jama.* 2016;316(13):1366-74. PMID: 27701661
7. Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. *Neurourol Urodyn.* 2014. PMID: 24415559
8. Noblett K, Siegel S, Mangel J, et al. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. *Neurourol Urodyn.* 2014. PMID: 25546568
9. Tang H, Chen J, Wang Y, et al. Combination of sacral neuromodulation and tolterodine for treatment of idiopathic overactive bladder in women: a clinical trial. *Urol J.* 2014;11:1800-5. PMID: 25194079
10. Chartier-Kastler E, Normand LL, Ruffion A, et al. Sacral Neuromodulation with the InterStim System for Overactive Bladder: 3-Year Results from the French Prospective,

Multicenter, Observational SOUNDS Study. *Eur Urol Focus.* 2022;8(5):1399-407. PMID: 34334342
11. Geynisman-Tan J, Mueller MG, Kenton KS. Satisfaction with a rechargeable sacral neuromodulation system-A secondary analysis of the ARTISAN-SNM study. *Neurourol Urodyn.* 2021;40(1):549-54. PMID: 33326643
12. McCrery R, Lane F, Benson K, et al. Treatment of Urinary Urgency Incontinence Using a Rechargeable SNM System: 6-Month Results of the ARTISAN-SNM Study. *J Urol.* 2020;203(1):185-92. PMID: 31347955
13. Pezzella A, McCrery R, Lane F, et al. Two-year outcomes of the ARTISAN-SNM study for the treatment of urinary urgency incontinence using the Axonics rechargeable sacral neuromodulation system. *Neurourol Urodyn.* 2021;40(2):714-21. PMID: 33508155
14. Blok B, Van Kerrebroeck P, de Wachter S, et al. Two-year safety and efficacy outcomes for the treatment of overactive bladder using a long-lived rechargeable sacral neuromodulation system. *Neurourol Urodyn.* 2020;39(4):1108-14. PMID: 32243625
15. Maher CF, Carey MP, Dwyer PL, et al. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. *J Urol.* 2001;165(3):884-6. PMID: 11176493
16. Whitmore KE, Payne CK, Diokno AC, et al. Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. *Int Urogynecol J Pelvic Floor Dysfunct.* 2003;14(5):305-8; discussion 08-9. PMID: 14618305
17. Comiter CV. Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. *J Urol.* 2003;169(4):1369-73. PMID: 12629364
18. Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. *Cochrane Database Syst Rev.* 2009(2):CD004202. PMID: 19370596
19. Brasure M, Fink H, Risk M, et al. Chronic Urinary Retention: Comparative Effectiveness and Harms of Treatments. [cited 1/3]. 'Available from:'
20. White WM, Mobley JD, 3rd, Doggweiler R, et al. Incidence and predictors of complications with sacral neuromodulation. *Urology.* 2009;73:731-5. PMID: 19193415
21. Simillis C, Lal N, Pellino G, et al. A systematic review and network meta-analysis comparing treatments for faecal incontinence. *Int J Surg.* 2019;66:37-47. PMID: 31022519
22. Dulskas A, Smolskas E, Kildusiene I, et al. Treatment possibilities for low anterior resection syndrome: a review of the literature. *Int J Colorectal Dis.* 2018;33(3):251-60. PMID: 29313107
23. Thaha MA, Abukar AA, Thin NN, et al. Sacral nerve stimulation for faecal incontinence and constipation in adults. *Cochrane Database of Systematic Reviews.* 2015(8). PMID: CD004464
24. Forte M, Andrade K, Butler M, et al. Forte ML, Andrade KE, Butler M, et al. Treatments for Fecal Incontinence [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Mar. (Comparative Effectiveness Review, No. 165.). [cited 12/28/2023]. 'Available from:' https://www.ncbi.nlm.nih.gov/books/NBK356097/.
25. Thin NN, Horrocks EJ, Hotouras A, et al. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. *Br J Surg.* 2013;100(11):1430-47. PMID: 24037562
26. Tjandra JJ, Chan MK, Yeh CH, et al. Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: a randomized, controlled study. *Dis Colon Rectum.* 2008;51(5):494-502. PMID: 18278532

27. Leroi AM, Parc Y, Lehur PA, et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. *Ann Surg.* 2005;242(5):662-9. PMID: 16244539
28. Maeda Y, Matzel K, Lundby L, et al. Postoperative issues of sacral nerve stimulation for fecal incontinence and constipation: a systematic literature review and treatment guideline. *Dis Colon Rectum.* 2011;54(11):1443-60. PMID: 21979192
29. Tan E, Ngo NT, Darzi A, et al. Meta-analysis: sacral nerve stimulation versus conservative therapy in the treatment of faecal incontinence. *Int J Colorectal Dis.* 2011;26(3):275-94. PMID: 21279370
30. Bielefeldt K. Adverse events of sacral neuromodulation for fecal incontinence reported to the federal drug administration. *World journal of gastrointestinal pharmacology and therapeutics.* 2016;7(2):294-305. PMID: 27158546
31. Hull T, Giese C, Wexner SD, et al. Long-term durability of sacral nerve stimulation therapy for chronic fecal incontinence. *Dis Colon Rectum.* 2013;56:234-45. PMID: 23303153
32. Maeda Y, Lundby L, Buntzen S, et al. Outcome of sacral nerve stimulation for fecal incontinence at 5 years. *Ann Surg.* 2014;259(6):1126-31. PMID: 23817505
33. Mirbagheri N, Sivakumaran Y, Nassar N, et al. Systematic review of the impact of sacral neuromodulation on clinical symptoms and gastrointestinal physiology. *ANZ journal of surgery.* 2016;86(4):232-6. PMID: 26245170
34. Picciariello A, Rinaldi M, Dibra R, et al. Ageing with sacral nerve modulation for fecal incontinence: how many patients get benefit after more than 10 years? *Updates Surg.* 2022;74(1):185-91. PMID: 34982410
35. Jottard K, Van den Broeck S, Komen N, et al. Treatment of Fecal Incontinence With a Rechargeable Sacral Neuromodulation System: Efficacy, Clinical Outcome, and Ease of Use-Six-Month Follow-Up. *Neuromodulation.* 2021;24(7):1284-88. PMID: 33107663
36. Desprez C, Damon H, Meurette G, et al. Ten-year Evaluation of a Large Retrospective Cohort Treated by Sacral Nerve Modulation for Fecal Incontinence: Results of a French Multicenter Study. *Ann Surg.* 2020. PMID: 32740249
37. De Meyere C, Nuytens F, Parmentier I, et al. Five-year single center experience of sacral neuromodulation for isolated fecal incontinence or fecal incontinence combined with low anterior resection syndrome. *Techniques in coloproctology.* 2020;24(9):947-58. PMID: 32556866
38. Leo CA, Thomas GP, Bradshaw E, et al. Long-term outcome of sacral nerve stimulation for faecal incontinence. *Colorectal Dis.* 2020. PMID: 32954658
39. Koh H, McSorley S, Hunt S, et al. Sacral neuromodulation for faecal incontinence - 10 years' experience at a Scottish tertiary centre. *The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland.* 2017. PMID: 29102296
40. Irwin GW, Dasari BV, Irwin R, et al. Outcomes of Sacral Nerve Stimulation For Faecal Incontinence in Northern Ireland. *The Ulster medical journal.* 2017;86(1):20-24. PMID: 28298708
41. Rice TC, Quezada Y, Rafferty JF, et al. Dynamic Article: Percutaneous Nerve Evaluation Versus Staged Sacral Nerve Stimulation for Fecal Incontinence. *Dis Colon Rectum.* 2016;59(10):962-7. PMID: 27602927
42. Patton V, Abraham E, Lubowski DZ. Sacral nerve stimulation for faecal incontinence: medium-term follow-up from a single institution. *ANZ journal of surgery.* 2016. PMID: 27193192

43. Duelund-Jakobsen J, Lehur PA, Lundby L, et al. Sacral nerve stimulation for faecal incontinence - efficacy confirmed from a two-centre prospectively maintained database. *Int J Colorectal Dis.* 2016;31(2):421-8. PMID: 26490052
44. Duelund-Jakobsen J, Buntzen S, Lundby L, et al. Bilateral compared with unilateral sacral nerve stimulation for faecal incontinence: results of a randomized, single-blinded crossover study. *Colorectal Dis.* 2015;17(12):1085-93. PMID: 26354517
45. Altomare DF, Giuratrabocchetta S, Knowles CH, et al. Long-term outcomes of sacral nerve stimulation for faecal incontinence. *Br J Surg.* 2015;102(4):407-15. PMID: 25644687
46. Pauwels N, Willemse C, Hellemans S, et al. The role of neuromodulation in chronic functional constipation: a systematic review. *Acta Gastroenterol Belg.* 2021;84(3):467-76. PMID: 34599572
47. Pilkington SA, Emmett C, Knowles CH, et al. Surgery for constipation: systematic review and practice recommendations: Results V: Sacral Nerve Stimulation. *Colorectal Dis.* 2017;19 Suppl 3:92-100. PMID: 28960926
48. Dinning PG, Hunt L, Patton V, et al. Treatment efficacy of sacral nerve stimulation in slow transit constipation: a two-phase, double-blind randomized controlled crossover study. *Am J Gastroenterol.* 2015;110(5):733-40. PMID: 25895520
49. Thomas GP, Dudding TC, Rahbour G, et al. Sacral nerve stimulation for constipation. *Br J Surg.* 2013;100(2):174-81. PMID: 23124687
50. Knowles CH, Thin N, Gill K, et al. Prospective randomized double-blind study of temporary sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. *Ann Surg.* 2012;255:643-9. PMID: 22418005
51. Zerbib F, Siproudhis L, Lehur PA, et al. Randomized clinical trial of sacral nerve stimulation for refractory constipation. *Br J Surg.* 2017;104(3):205-13. PMID: 27779312
52. Patton V, Stewart P, Lubowski DZ, et al. Sacral Nerve Stimulation Fails to Offer Long-term Benefit in Patients With Slow-Transit Constipation. *Dis Colon Rectum.* 2016;59(9):878-85. PMID: 27505117
53. Maeda Y, Kamm MA, Vaizey CJ, et al. Long-term outcome of sacral neuromodulation for chronic refractory constipation. *Techniques in coloproctology.* 2017;21(4):277-86. PMID: 28429130
54. Maeda Y, Lundby L, Buntzen S, et al. Sacral nerve stimulation for constipation: suboptimal outcome and adverse events. *Dis Colon Rectum.* 2010;53(7):995-9. PMID: 20551750
55. Lu PL, Asti L, Lodwick DL, et al. Sacral nerve stimulation allows for decreased antegrade continence enema use in children with severe constipation. *Journal of pediatric surgery.* 2016. PMID: 27887683
56. Kenefick NJ, Nicholls RJ, Cohen RG, et al. Permanent sacral nerve stimulation for treatment of idiopathic constipation. *Br J Surg.* 2002;89(7):882-8. PMID: 12081738
57. Malouf AJ, Wiesel PH, Nicholls T, et al. Short-term effects of sacral nerve stimulation for idiopathic slow transit constipation. *World J Surg.* 2002;26(2):166-70. PMID: 11865344
58. Holzer B, Rosen HR, Novi G, et al. Sacral nerve stimulation in patients with severe constipation. *Dis Colon Rectum.* 2008;51(5):524-29; discussion 29-30. PMID: 18322757
59. Schiano di Visconte M, Pasquali A, Cipolat Mis T, et al. Sacral nerve stimulation in slow-transit constipation: effectiveness at 5-year follow-up. *Int J Colorectal Dis.* 2019;34(9):1529-40. PMID: 31309325
60. Tirlapur SA, Vlismas A, Ball E, et al. Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review. *Acta obstetricia et gynecologica Scandinavica.* 2013;92(8):881-7. PMID: 23710833

61. Martellucci J, Naldini G, Carriero A. Sacral nerve modulation in the treatment of chronic pelvic pain. *Int J Colorectal Dis.* 2012;27(7):921-6. PMID: 22203519
62. Siegel S, Paszkiewicz E, Kirkpatrick C, et al. Sacral nerve stimulation in patients with chronic intractable pelvic pain. *J Urol.* 2001;166(5):1742-5. PMID: 11586214
63. Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. *J Urol.* 2019;202(3):558-63. PMID: 31039103
64. ACOG Practice Bulletin No. 155: Urinary Incontinence in Women. *Obstet Gynecol.* 2015;126(5):e66-e81. PMID: 26488524
65. ACOG Practice Bulletin No. 210: Fecal Incontinence. *Obstetrics & Gynecology.* 2019;133(4):e260-e73. PMID: 00006250-201904000-00057
66. Wald A, Bharucha AE, Cosman BC, et al. ACG clinical guideline: management of benign anorectal disorders. *The American journal of gastroenterology.* 2014;109(8):1141-058. PMID: 25022811
67. Wald A, Bharucha AE, Limketkai B, et al. ACG Clinical Guidelines: Management of Benign Anorectal Disorders. *Am J Gastroenterol.* 2021;116(10):1987-2008. PMID: 34618700
68. Paquette IM, Varma MG, Kaiser AM, et al. The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Treatment of Fecal Incontinence. *Dis Colon Rectum.* 2015;58(7):623-36. PMID: 26200676
69. Paquette IM, Varma M, Ternent C, et al. The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Evaluation and Management of Constipation. *Dis Colon Rectum.* 2016;59(6):479-92. PMID: 27145304

CODES

NOTE: HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
CPT	0786T	Insertion or replacement of percutaneous electrode array, sacral, with integrated neurostimulator, including imaging guidance, when performed
	0787T	Revision or removal of neurostimulator electrode array, sacral, with integrated neurostimulator
	0788T	Electronic analysis with simple programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, spinal cord or sacral nerve, 1-3 parameters
	0789T	Electronic analysis with complex programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, spinal cord or sacral nerve, 4 or more parameters
	64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
	64581	Open implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)

Codes	Number	Description
	64585	Revision or removal of peripheral neurostimulator electrode array
	64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver
	64595	Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array
	64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array
	64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)
	64598	Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non- rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Date of Origin: *February 1999*

Regence

Medical Policy Manual Surgery, Policy No. 137

Orthognathic Surgery

Effective: May 1, 2024

Next Review: December 2024
Last Review: April 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Orthognathic surgery involves the surgical manipulation of the facial skeleton, particularly the maxilla and mandible, to restore the proper anatomic and functional relationship in patients with dentofacial skeletal anomalies.[1]

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address the surgical management of sleep apnea, which is addressed in a separate medical policy (see Cross References). Also, this policy does not address temporomandibular joint (TMJ) surgical interventions, which may require pre-authorization.
- Member contracts for covered services vary. Member contracts may have specific language defining congenital and developmental anomalies. Member contract language takes precedence over medical policy. A congenital anomaly is defined as an anomaly that is present at birth (e.g., cleft palate). Developmental anomalies are conditions that develop some time after birth.

I. Orthognathic surgery for the treatment of obstructive sleep apnea may be considered **medically necessary** when the criteria in Surgery, Policy No. 166 are met.

II. Orthognathic surgery to treat conditions other than obstructive sleep apnea may be considered **medically necessary** to correct jaw and craniofacial deformities when all of the following Criteria (A-D) are met:

A. Significant functional impairment that is documented to be directly attributable to jaw and craniofacial deformities and to include one or more of the following:

1. Chewing-induced trauma secondary to malocclusion; or
2. Significantly impaired swallowing and/or choking due to inadequate mastication secondary to malocclusion; or
3. Significant speech abnormalities (e.g., sibilant distortions or velopharyngeal distortion) which have not responded to speech therapy and are secondary to malocclusion; or
4. Loss of masticatory or incisive function due to malocclusion or skeletal abnormality; or
5. Airway restriction; and

B. Significant over- or underjet as documented by one of the following:

1. In mandibular excess or maxillary deficiency, a reverse overjet of 3mm or greater; or
2. In mandibular deficiency, an overjet of 5mm or greater; or
3. Open bite of 4mm or greater; or
4. Deep bite of 7mm or greater and/or palatal impingement of the mandibular teeth on the palatal tissue; or
5. Less than six posterior teeth in functional opposition to other teeth secondary to a developmental or congenital growth abnormality (as opposed to a consequence of the loss of teeth); and

C. The functional impairment and over- or underjet are not correctable with non-surgical treatment modalities (e.g. orthodontics) and;

D. The following documentation is required to determine medical necessity for orthognathic surgery:

1. Clinical record of history and physical performed demonstrating medical necessity of orthognathic surgery and when appropriate, any other pertinent diagnostic findings; and
2. Intra-oral and extra-oral photographs; and
3. Cephalometric and panoramic radiographs with either a written report or a summary of radiographic findings in the clinical record (e.g. cephalometric tracings).

III. Reduction of the masseter muscle and bone may be considered **medically necessary** as a component of orthognathic surgery only when there is clinical documentation of the presence of masseteric hypertrophy.

IV. Orthognathic surgery is considered **cosmetic** when Criteria are not met, including but not limited to when used for improvement of appearance.

V. Genioplasty is considered **cosmetic** when performed in conjunction with orthognathic surgery for the sole purpose of improving appearance and/or profile.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Administrative Guidelines to Determine Dental vs Medical Services, Allied Health, Policy No. 35
2. Prefabricated Oral Appliances for Obstructive Sleep Apnea, Allied Health, Policy No. 36
3. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
4. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166
5. Hypoglossal Nerve Stimulation, Surgery, Policy No. 215

SUMMARY

Orthognathic surgery improves health outcomes including functional impairments for some people with dentofacial skeletal anomalies that are not correctable with non-surgical treatment modalities. Therefore, orthognathic surgery may be considered medically necessary when policy Criteria are met.

The reduction of the masseter muscle and bone improves health outcomes for some people with masseteric hypertrophy when performed as a component of orthognathic surgery. Therefore, reduction of the masseter muscle and bone may be considered medically necessary when policy Criteria are met.

In all other situations, it is unclear how orthognathic surgery improves health outcomes or corrects functional impairments. Therefore, orthognathic surgery is considered cosmetic when policy Criteria are not met including but not limited to for the sole purpose of improving appearance.

REFERENCES

1. Patel PK. Craniofacial, Orthognathic Surgery. [cited 1/17/2024]. 'Available from:' http://emedicine.medscape.com/article/1279747-overview.
2. American Association of Oral and Maxillofacial Surgeons. Reconstructive Oral and Maxillofacial Surgery. [cited 1/17/2024]. 'Available from:' https://www.aaoms.org/docs/practice_resources/clinical_resources/ortho_criteria.pdf.
3. Ahn SJ, Kim JT, Nahm DS. Cephalometric markers to consider in the treatment of Class II Division 1 malocclusion with the bionator. *Am J Orthod Dentofacial Orthop.* 2001;119(6):578-86. PMID: 11395700
4. Cain KK, Rugh JD, Hatch JP, et al. Readiness for orthognathic surgery: a survey of practitioner opinion. *Int J Adult Orthodon Orthognath Surg.* 2002;17(1):7-11. PMID: 11934058
5. Kim JC, Mascarenhas AK, Joo BH, et al. Cephalometric variables as predictors of Class II treatment outcome. *Am J Orthod Dentofacial Orthop.* 2000;118(6):636-40. PMID: 11113798

6. Mogavero FJ, Buschang PH, Wolford LM. Orthognathic surgery effects on maxillary growth in patients with vertical maxillary excess. *Am J Orthod Dentofacial Orthop.* 1997;111(3):288-96. PMID: 9082851
7. Park JU, Baik SH. Classification of Angle Class III malocclusion and its treatment modalities. *Int J Adult Orthodon Orthognath Surg.* 2001;16(1):19-29. PMID: 11563392
8. Proffit WR, White RP, Jr. Who needs surgical-orthodontic treatment? *Int J Adult Orthodon Orthognath Surg.* 1990;5(2):81-9. PMID: 2074379
9. Proffit WR, Phillips C, Tulloch JF, et al. Surgical versus orthodontic correction of skeletal Class II malocclusion in adolescents: effects and indications. *Int J Adult Orthodon Orthognath Surg.* 1992;7(4):209-20. PMID: 1298780
10. Throckmorton GS, Buschang PH, Ellis E, 3rd. Morphologic and biomechanical determinants in the selection of orthognathic surgery procedures. *J Oral Maxillofac Surg.* 1999;57(9):1044-56; discussion 56-7. PMID: 10484105
11. Thomas PM. Orthodontic camouflage versus orthognathic surgery in the treatment of mandibular deficiency. *J Oral Maxillofac Surg.* 1995;53(5):579-87. PMID: 7722728
12. Throckmorton GS, Ellis E, 3rd, Sinn DP. Functional characteristics of retrognathic patients before and after mandibular advancement surgery. *J Oral Maxillofac Surg.* 1995;53(8):898-908; discussion 08-9. PMID: 7629618
13. Tucker MR. Orthognathic surgery versus orthodontic camouflage in the treatment of mandibular deficiency. *J Oral Maxillofac Surg.* 1995;53(5):572-8. PMID: 7722727
14. Vallino LD. Speech, velopharyngeal function, and hearing before and after orthognathic surgery. *J Oral Maxillofac Surg.* 1990;48(12):1274-81; discussion 81-2. PMID: 2231145
15. Wilmot JJ, Barber HD, Chou DG, et al. Associations between severity of dentofacial deformity and motivation for orthodontic-orthognathic surgery treatment. *Angle Orthod.* 1993;63(4):283-8. PMID: 8297053
16. Wolford LM, Karras SC, Mehra P. Considerations for orthognathic surgery during growth, part 1: mandibular deformities. *Am J Orthod Dentofacial Orthop.* 2001;119(2):95-101. PMID: 11174553
17. Wolford LM, Karras SC, Mehra P. Considerations for orthognathic surgery during growth, part 2: maxillary deformities. *Am J Orthod Dentofacial Orthop.* 2001;119(2):102-5. PMID: 11174554
18. Wolford LM, Mehra P, Reiche-Fischel O, et al. Efficacy of high condylectomy for management of condylar hyperplasia. *Am J Orthod Dentofacial Orthop.* 2002;121(2):136-50; discussion 50-1. PMID: 11840126
19. Zarrinkelk HM, Throckmorton GS, Ellis E, 3rd, et al. Functional and morphologic changes after combined maxillary intrusion and mandibular advancement surgery. *J Oral Maxillofac Surg.* 1996;54(7):828-37. PMID: 8676227

CODES

Codes	Number	Description
CPT	21085	Impression and custom preparation; oral surgical splint
	21110	Application of interdental fixation device for conditions other than fracture or dislocation, includes removal
	21120	Genioplasty; augmentation (autograft, allograft, prosthetic material)
	21121	Genioplasty; sliding osteotomy, single piece
	21122	Genioplasty; sliding osteotomies, two or more osteotomies (e.g., wedge excision or bone wedge reversal for asymmetrical chin)
	21123	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)

Codes	Number	Description
	21125	Augmentation, mandibular body or angle; prosthetic material
	21127	Augmentation, mandibular body or angle; with bone graft, onlay or interpositional (includes obtaining autograft)
	21141	Reconstruction midface, LeFort I; single piece, segment movement in any direction (e.g., for Long Face Syndrome), without bone graft
	21142	Reconstruction midface, LeFort I; two pieces, segment movement in any direction, without bone graft
	21143	Reconstruction midface, LeFort I; three or more pieces, segment movement in any direction, without bone graft
	21145	Reconstruction midface, LeFort I; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts)
	21146	Reconstruction midface, LeFort I; two pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (e.g., ungrafted unilateral alveolar cleft)
	21147	Reconstruction midface, LeFort I; three or more pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (e.g., ungrafted bilateral alveolar cleft or multiple osteotomies)
	21150	Reconstruction midface, LeFort II; anterior intrusion (e.g., Treacher-Collins Syndrome)
	21151	Reconstruction midface, LeFort II; any direction, requiring bone grafts (includes obtaining autografts)
	21154	Reconstruction midface, LeFort III (extracranial), any type, requiring bone grafts (includes obtaining autografts); without LeFort I
	21155	Reconstruction midface, LeFort III (extracranial), any type, requiring bone grafts (includes obtaining autografts); with LeFort I
	21159	Reconstruction midface, LeFort III (extra and intracranial) with forehead advancement (e.g., mono bloc), requiring bone grafts (includes obtaining autografts); without LeFort I
	21160	Reconstruction midface, LeFort III (extra and intracranial) with forehead advancement (e.g., mono bloc), requiring bone grafts (includes obtaining autografts); with LeFort I
	21188	Reconstruction midface, osteotomies (other than LeFort type) and bone grafts (includes obtaining autografts)
	21193	Reconstruction of mandibular rami, horizontal, vertical C, or L osteotomy; without bone graft
	21194	Reconstruction of mandibular rami, horizontal, vertical C, or L osteotomy; with bone graft
	21195	Reconstruction of mandibular rami and/or body, sagittal split; without internal rigid fixation
	21196	Reconstruction of mandibular rami and/or body, sagittal split; with internal rigid fixation
	21198	Osteotomy, mandible, segmental;
	21206	Osteotomy, maxilla, segmental (e.g., Wassmund or Schuchard)
	21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
	21209	Osteoplasty, facial bones; reduction
	21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)
	21215	Graft, bone; mandible (includes obtaining graft)
	21230	Graft; rib cartilage, autogenous, to face, chin, nose or ear (includes obtaining graft)
	21295	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); extraoral approach

Codes	Number	Description
	21296	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); intraoral approach
CDT	D7940	Osteoplasty – for orthognathic deformities
	D7941	Osteotomy; mandibular rami
	D7943	Osteotomy; mandibular rami with bone graft; includes obtaining the graft
	D7944	Osteotomy; segmented of subapical – per sextant or quadrant
	D7945	Osteotomy; body of mandible
	D7946	LeFort I (maxilla – total)
	D7947	LeFort I (maxilla – segmented)
	D7948	LeFort II or LeFort III (osteoplasty of facial bones for midface hypoplasia or retrusion); without bone graft
	D7949	LeFort II or LeFort III; with bone graft
	D7950	Osseous, osteoperiosteal, or cartilage graft of the mandible or facial bones – autogenous or nonautogenous, by report
	D7995	Synthetic graft – mandible or facial bones, by report
	D7996	Implant – mandible for augmentation purposes (excluding alveolar ridge), by report

Date of Origin: *October 2004*

Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation

Effective: November 1, 2022

Next Review: August 2023
Last Review: September 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) concentrate high-energy ultrasound waves via probe on a single location to cause coagulative necrosis.

MEDICAL POLICY CRITERIA

I. High-intensity focused ultrasound (HIFU) may be considered **medically necessary** as a local treatment for prostate cancer when all of the following (A.-D.) criteria are met:
   A. For the treatment of radiation recurrence (see Policy Guidelines); and
   B. The patient is a candidate for local therapy (see Policy Guidelines); and
   C. Transrectal ultrasound guided (TRUS) biopsy positive; and
   D. In the absence of metastatic disease.

II. High-intensity focused ultrasound (HIFU) is considered **investigational** for all other indications not meeting Criterion I.

III. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) may be considered **medically necessary** for either of the following indications:

A. Medicine-refractory essential tremors; or

B. Pain palliation in an adult (greater than or equal to 18 years) with metastatic bone cancer for whom radiotherapy has failed or who are not candidates for radiotherapy.

IV. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is considered **investigational** for all other indications not meeting Criterion III., including but not limited to treatment of the following:

A. Uterine fibroids; and

B. All tumors, including but not limited to brain, breast, prostate and renal; and

C. Tremor-dominant Parkinson's disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

CANDIDATE FOR LOCAL THERAPY

According to National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 1.2023), in the presence of radiation therapy recurrence (see below), a candidate for local therapy includes:[1]

- Biopsy positive
- Studies negative for distant metastatic disease
- Life expectancy > 5y

RADIATION RECURRENCE

NCCN guidelines for prostate cancer (version 1.2023) cite radiation therapy recurrence as either 1) a positive digital rectal exam (DRE), or 2) Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) Phoenix Consensus biochemical failure.

RTOG-ASTRO Phoenix Consensus PSA recurrence is further defined as:

1.) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without hormonal therapy; and
2.) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy.

Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical
- Treatment plan including treatment area
- For essential tremors, clinical documentation must demonstrate medicine-refractory symptoms
- For prostate cancer treatment, clinical documentation must also demonstrate results from transrectal ultrasound guided (TRUS) biopsy
- For pain palliation bone metastases, clinical documentation that radiotherapy has failed for the patient or the patient is not a candidate for radiotherapy

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE), Medicine, Policy No. 140
2. Radiofrequency Ablation (RFA) of Tumors Other than Liver, Surgery, Policy No. 92
3. Cryosurgical Ablation of Miscellaneous Solid Tumors, Surgery, Policy No. 132
4. Microwave Tumor Ablation, Surgery, Policy No. 189
5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204
6. Focal Laser Ablation of Prostate Cancer, Surgery, Policy No. 222

BACKGROUND

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) are proposed as less invasive approaches than surgery for treatment of localized prostate cancer, uterine fibroids, and pain palliation of bone metastases. Broadly, these devices use an integrated imaging system to take measurements, confirm the treatment area, and monitor thermal destruction in real time.

MRgFUS is a noninvasive treatment that combines focused ultrasound and magnetic resonance imaging (MRI). The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. Ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. Ultrasound waves from each sonication are focused at a focal point that has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (to approximately 65°C-85°C), which is sufficient to achieve tissue ablation at the focal point. In addition to providing guidance, the associated MRI can provide online thermometric imaging that provides a temperature “map” to confirm the therapeutic effect of the ablation treatment and allow for real-time adjustment of the treatment parameters.

HIFU focuses high-energy ultrasound waves on a single location, which increase the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3×3×10 mm. In the treatment of prostate cancer, HIFU is a minimally invasive localized option. The surgeon uses a transrectal probe to plan, carry out, and monitor ablative treatment in a real-time sequence with a combination of ultrasound and MRI imaging.

REGULATORY STATUS

Devices have received U.S. Food and Drug Administration (FDA) approval via the *De Novo* and Premarket Application (PMA) processes:

High-Intensity Focused Ultrasound

The Sonablate® 450 (SonaCare Medical) is the first high-intensity ultrasound system for prostate tissue ablation to receive FDA approval, and therefore underwent the *De Novo* application process, obtaining clearance in 2015. Shortly thereafter, Ablatherm Integrated Imaging® (EDAP TMS) received PMA approval. In June 2018, EDAP received 510(k) clearance for its Focal-One® HIFU device designed for prostate tissue ablation procedures. This device fuses magnetic resonance and 3D biopsy data with real-time ultrasound imaging, allowing urologists to view detailed images of the prostate on a large monitor and direct high-intensity ultrasound waves to ablate the targeted area.

Magnetic Resonance-Guided Focused Ultrasound

The ExAblate® 2000 System (InSightec, Inc.) received premarket approval (PMA) from the FDA for the indications: “ablation of uterine fibroid tissue in pre- or peri- menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure,” and for palliation of pain associated with tumors metastatic to bone.[2]

For uterine fibroids, the FDA approval letter states that patients must have a uterine gestational size of less than 24 weeks and those patients must have completed childbearing.

In the initial safety and efficacy studies, the FDA limited MRI-guided focused ultrasound to 33% of fibroid volume with a maximum treatment time of 120 minutes. Guidelines were later modified to allow up to 50% treatment volume, 180-minute maximum treatment time, and a second treatment if within a 14-day period.

The ExAblate 2000 treatment is contraindicated for use in women who have MRI-related issues, such as metallic implants, or sensitivity to MRI contrast agents; obstructions in the treatment beam path, such as a scar, skin fold, or irregularity, bowel, pubic bone, intrauterine device, surgical slips, or any hard implants; and fibroids that are close to sensitive organs such as the bowel or bladder or are outside the image area.

The ExAblate® 2100 System also received approval through the PMA process.[3] It includes several modifications to the previous system including enhanced sonication and a detachable cradle, and only certain cradle types can be used for palliation of pain associated with metastatic bone cancer. Approval remains limited to treatment of patients with metastatic bone cancer who failed or are not candidates for radiation therapy; or, in patient with symptomatic uterine fibroids with a uterine size of less than 24 weeks and those who have completed childbearing.

In October 2012, the FDA granted PMA approval for ExAblate® System, for pain palliation due to metastatic bone cancer.[4] For pain palliation, the intended use of the device is in adult patients with metastatic bone cancer who failed or are not candidates for radiation therapy. The device was evaluated through an expedited review process. The FDA required a post-approval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

In July 2016, the FDA granted premarket approval (PMA) of the ExAblate® Neuro System for the treatment of essential tremor in patients who have not responded to medication (beta-

blockers or anticonvulsant drugs).[5] This PMA outlined required pending studies for the device, including investigational treatment with the ExAblate Neuro in 75 patients to be evaluated at two-, three-, four- and five-years post-operative.

In December 2018, the FDA granted premarket approval (PMA) of the ExAblate Model 4000 (Neuro) for the treatment of tremor-dominant PD with medication-refractory tremor.[6] This PMA outlined required post-approval study, including a prospective, multi-center, new enrollment, long-term safety and effectiveness study in 50 patients. The study is designed to evaluate the long-term safety of the device when used to treat patients who have failed medication.

FDA product codes: NRZ, POH.

MRgFUS is also being investigated for the treatment of other tumors, including breast, prostate, brain, and desmoid tumors as well as nonspinal osteoid osteoma.

EVIDENCE SUMMARY

HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. Locally directed therapies, also termed *focal treatment* includes several ablative methods, one of which is high-intensity focused ultrasound (HIFU). The overall goal of any focal treatment is to minimize the risk of tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.

Maestroni (2021) published a systematic review (SR) of studies evaluating the safety and cancer control rates of HIFU following failure of External Beam Radiation Therapy (EBRT).[7] Data from 1241 patients across 13 publications were included in the analysis. The mean age of the patients was 68.6 years (range 53 to 83 years, SD ±6.11). Of those included in the analysis, 38.3% of the patients were on androgen-deprivation therapy at the time of salvage HIFU, and 24.71% continued the therapy after the treatment. PSA nadir was 1.1 ng/mL (SD ±3.39). The time to which PSA nadir was reached was not reported in all series. Limited to these series, PSA nadir was achieved in a mean time of 11.7 weeks (SD ±9.1). Mean follow-up was 24.3 months after salvage HIFU treatment, ranging from 3 to 168 months. Overall survival (OS) was 85.2% at five years. One study reported OS of 72% at seven years.

Valle (2021) published a SR comparing the efficacy and toxicity of salvage radical prostatectomy (RP), HIFU, cryotherapy, stereotactic body radiotherapy (SBRT), low-dose-rate (LDR) brachytherapy, and high-dose-rate (HDR) brachytherapy in the management of locally recurrent prostate cancer.[8] Two- and five-year recurrence-free survival (RFS) rates and crude incidences of severe genitourinary (GU) and gastrointestinal (GI) toxicity were endpoints of interest. A total of 150 studies were included for analysis. Significant heterogeneity between studies was found within each modality, and covariates differed between modalities, necessitating adjustment. Adjusted five-year RFS ranged from 50% after cryotherapy to 60%

after HDR brachytherapy and SBRT, with no significant differences between any modality and RP.

A SR of functional and oncological outcomes of focal therapy in patients with localized prostate cancer was published by Hopstaken (2021).[9] Seventy-two studies on eight different modalities to deliver focal therapy in 5827 patients were assessed including 27 studies reporting on high-intensity focused ultrasound (HIFU). One of these studies was considered IDEAL stage 1 study; the majority (n=23) were considered stage 2 studies. One large retrospective study (n=1032) stated as IDEAL stage 4. There were no RCTs assessing the effectiveness of HIFU. Studies of HIFU reported a median of 95% pad-free patients and a median of 85% patients with no clinically significant cancer (CSC) in the treated area and the treatment was well-tolerated.

Ingrosso (2020) published a SR with meta-analysis on nonsurgical therapeutic strategies in patients with radiorecurrent prostate cancer.[10] The review addressed the clinical outcomes and toxicity profiles of treatments including HIFUS, brachytherapy, external beam radiotherapy, and cryotherapy. Thirteen of the 64 case-series studies were publications reporting HIFUS as the salvage treatment. Among the treatments studied, biochemical control rates were lowest for patients treated with HIFU (58%, 95% confidence interval [CI] 47–68%). The prevalence of incontinence was highest among patients treated with HIFU (28%, 95% CI 19–38%; I2 = 89.7%). The authors concluded that good efficacy and tolerability was found after local treatment of radiorecurrent prostate cancer, but that high-quality data from prospective trials are needed to validate the long-term outcomes of these strategies for the treatment of intraprostatic recurrence after previous radiotherapy.

A 2020 SR by Khoo also evaluated 15 studies (14 case series and one comparative study) reporting outcomes after focal salvage brachytherapy (five studies), cryotherapy (seven studies) and HIFU (three studies) in the treatment of localized non-metastatic radiorecurrent prostate cancer.[11] Rates of biochemical disease-free survival (BDFS), metastasis, conversion to second-line therapies, and adverse events were assessed and median follow-up ranged from 10 to 56 months. At three years, BDFS ranged from 61% to 71.4% after brachytherapy, 48.1–72.4% after cryotherapy and 48% after HIFU. The authors note high heterogeneity in patient selection, individual treatment protocols and outcome reporting. Additional studies comparing the treatment modalities is recommended.

As a salvage treatment, that is, for recurrent disease following initial therapy, Crouzet (2017) reported that HIFU is associated with cancer-specific (CSS) and metastasis-free survival (MFS) of at least 80% at seven years in a study of over 400 men.[12] Morbidity rate for grade III/IVa complications was 3.6%. Smaller studies with shorter-duration of follow-up are in general agreement[1, 13-16], however, patient selection criteria is an important predictor of treatment outcomes[17-20]. While this is still an area of investigation, there may be limited treatment for this population of men with recurrent disease. Current practice guidelines based on research recommend HIFU in the presence of radiation recurrence for carefully selected patients (e.g., no metastases, and good candidate for local therapy).[1]

Primary Treatment of Prostate Cancer

As a primary treatment, evidence for HIFU is still accumulating. Data in the published literature are available for shorter follow-up times than in salvage treatment studies (e.g., two years).[13, 16, 21]

Bakavicius (2022) published a SR of data from studies with at least 50 patients published 2010 to 2020 that evaluated focal HIFU therapy as a primary treatment for localized prostate cancer.[22] Data from 20 publications were included in the final analysis consisting of one randomized feasibility study (Hamdy 2018),[23] ten prospective development studies, and nine retrospective case series (total N=4209). Across all studies, clinically significant in-field recurrence and out-of-field progression were detected in 22% and 29% patients, respectively. The authors conclude intermediate- and long-term outcomes are needed from high-quality comparative trials evaluating the HIFU in comparison to standard of care.

Bates (2021) published a SR that evaluated studies published from January 2000 to June 2020 on focal therapy as a treatment for histologically proven, clinically localized prostate cancer compared to standard management.[24] Focal therapy interventions included HIFU, vascular targeted photodynamic therapy, laser ablation, thermal ablation, focal brachytherapy, radiofrequency waves, microwave ablation, focal external-beam radiotherapy, and irreversible electroporation. The comparator intervention included any standard management option such as radical prostatectomy, external beam radiotherapy, whole gland brachytherapy, and active surveillance/monitoring. Overall, five articles reporting on four primary comparative studies (one RCT and three retrospective nonrandomized comparative studies; N=3961) and 10 eligible systematic reviews were identified. One retrospective study comparing focal HIFU with robotic radical prostatectomy found no significant difference in treatment failure at three years, with better continence and erectile function recovery with HIFU. Regarding the included systematic reviews, virtually all concluded that there was insufficient high certainty evidence to make definitive conclusions regarding the clinical effectiveness of focal therapy. The authors conclude that the "certainty of the evidence regarding the comparative effectiveness of focal therapy as a primary treatment for localized prostate cancer was low, with significant uncertainties" and that "until higher certainty evidence emerges...focal therapy should ideally be performed within clinical trials or well-designed prospective cohort studies."

Uterine Fibroids

Tsai (2021) published a SR with meta-analysis of studies comparing the outcome of HIFU and conventional surgery (myomectomy and hysterectomy) for the treatment of uterine myomas.[25] The review included 10 studies inclusive of one RCT, six prospective studies and three retrospective studies with sample sizes ranging from 39 to 1353 (total N = 4217). HIFU improved uterine myoma symptoms compared with conventional surgery at six months (MD −1.61; 95% confidence interval [CI], −2.88 to −0.33) and 12 months (MD −2.44; 95% CI, −3.68 to −1.20) after treatment as well as quality-of-life score at six (MD 2.14; 95% CI, 0.86–3.42) and 12 (MD 2.34; 95% CI, 0.82–3.86) months after treatment compared to the surgery group. Overall, nine studies, including RCTs and non-RCTs had moderate risk of bias and one study had serious risk of bias. Three studies reported the incidence of skin burns in the HIFU group. Considerable heterogeneity was observed across the studies with respect to treatment techniques, outcomes, and timepoints of assessment of outcomes. Patients with more than three uterine myomas or larger myomas were not included in any of the studies and four studies recruited patients with only certain types of uterine myoma, which limits the generalizability of observations.

Barnard (2017) published preliminary results from Fibroid Interventions: Reducing Symptoms Today and Tomorrow trial, a parallel RCT and cohort study comparing MRgFUS with fibroid embolization to treat uterine fibroids.[26] For the RCT, patients were randomized to uterine artery embolization (UAE; n=22) or to MRgFUS (n=27). Patients and investigators were not

blinded. Women who did not want to be randomized were enrolled in the cohort study; 16 underwent UAE and 16 underwent MRgFUS. After six weeks of follow-up, there were no differences between groups in fatigue, hot flashes, discomfort urinating, vaginal discharge, or constipation. Recovery was significantly faster in the MRgFUS group, as measured by the first day back to work and the first day back to normal. Medication use (ie, opioids, nonsteroidal anti-inflammatory drugs, acetaminophen or aspirin, nausea medication, bowel medication) was also significantly lower in the MRgFUS group. Analyses combining the RCT and cohort patients showed similar results. The MRgFUS procedure took significantly longer than the UAE procedure. A trial limitation was the inability to recruit more patients. Long-term follow-up results were reported by Laughlin-Tommaso (2019).[27] Patients in both the RCT and cohort studies had follow-up for up to three years. The primary outcome assessed was reintervention for uterine fibroids within three years; secondary outcomes included change in anti-Mullerian hormone levels and standardized measures of quality of life, pain, sexual function, and fibroid symptoms. Among the women in the MRgFUS arm (n=43), 13 (30%) had a second fibroid procedure compared to 5 (13%) women in the UAE arm (hazard ratio [HR], 2.81; 95% confidence interval [CI], 1.01 to 7.79). Both quality of life and pain scores improved in both arms, however there was a larger improvement in the UAE arm. There was a significantly greater absolute decrease in anti-Mullerian hormone levels at 24 months in the UAE arm compared to the MRgFUS arm.

A 2017 SR published by the Agency for Healthcare Research and Quality (AHRQ) on the management of uterine fibroids included evaluation studies of HIFUS.[28] Outcomes following HIFUS were symptoms (two studies, N=53), sexual function (one study, n=50), and fibroid characteristics (five studies, N=216). The duration of follow-up studied ranged from less than one to 24 months. The conclusion of the review was that HIFU reduced fibroid size, but strength of evidence is low because of short followup and poor quality of overall study design. Evidence related to patient reported outcomes is insufficient.

Other Indications

HIFU has been investigated as a treatment for other indications, such as adenomyosis[29] and thyroid disorders,[30, 31] but these are generally small, noncomparative studies. Systematic reviews of HIFU in the treatment of malignant lesions of the hepatobiliary system,[32] pancreas,[33] and benign thyroid nodules[34, 35] have concluded that although volumetric reduction or complete ablation was achieved with HIFU, additional studies are needed to determine the added benefit and long-term outcomes of the technology either alone or as a combination therapy on net health outcomes in these patient populations.

MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)

Essential Tremors

Systematic Reviews

Miller (2021) published a meta-analysis that evaluated the efficacy of MRgFUS for treating medication-refractory essential tremor (ET) with a focus on long-term trends and the durability of the response.[36] Data from patients with comorbid conditions such as Parkinson’s disease, were not included. Twenty-one studies (N=395) were included; 17 were prospective studies, three were retrospective, and one was the RCT published by Elias (2016) discussed below. Hand tremor scores decreased from a weighted mean pre-operative value of 19.2±5.0 to 7.4±5.0 after three months. Over time, the hand tremor score values gradually increased:

8.3±5.3 after 12 months and 9.1±5.4 after 36 months. The pooled standardized mean difference of hand tremor scores compared to pre-treatment values was 2.68 (95% CI, 1.94 to 3.41) at three months (five studies), 2.44 (95% CI, 1.97 to 2.91) at the 12-month time point (seven studies), and 2.18 (95% CI, 1.50 to 2.86) at the 24-month time point (three studies). Clinical Rating Scale for Tremor scores were reported through 12 months. The pooled standardized mean difference in Clinical Rating Scale for Tremor (CRST) scores compared to pre-treatment values was 1.86 (95% CI, 1.51 to 1.21) at the three-month time point (eight studies) and 2.24 (95% CI, 1.55 to 2.94) at the 12-month time point (six studies). Six studies reported Quality of Life in Essential Tremor Questionnaire (QUEST) scores as a quality-of-life measure. The pooled pre-treatment QUEST score was 48.2±22.4, which improved to 24.9±18.2 at three months. Additionally, a single study detailed a mean 23.8±19.6 QUEST score at 36 months follow-up, an increase of 2.2 over 30 months.

A SR of 29 studies (N = 617) on MRgFUS in the treatment of ET was published by Agrawal (2021).[37] Studies that reported outcomes in patients with tremors secondary to any other causes, such as drug-induced tremor, trauma, psychogenic tremor, or co-morbid Parkinson disease and dystonia were excluded. The ventral intermediate nucleus of the thalamus is the common target region. Of the 29 studies, only one (Elias 2016, below) was a RCT, the remaining were observational studies. Pre- and post- procedure changes in the CRST score, hand score, disability and quality of life scores were evaluated. A significant difference was observed in the pooled standard mean difference between pre- and post-operative total CRST score ($p < 0.001$), hand score ($p < 0.05$), and disability at 12 months ($p < 0.01$), although the number of included studies ranged from five to nine for the assessed outcomes. Disability, assessed by the CRST Part C at three months after MRgFUS, was reported by five studies in which the pooled standard mean difference was −2.66 with 95% CI: −3.53 to −1.79 ($p = 0.08$). Disability at 12 months after MRgFUS was reported by eight cohorts and the pooled standard mean difference was −4.54 (95% CI: −8.95 to −0.12, $p < 0.01$). More than one third of patients developed sonication related complications, amongst which head pain and dizziness were the most common. The pooled proportion of ataxia, which included gait disturbance and hand ataxia, was 50% at the short-term was found to be as high as 31% at three years post-treatment. No hemorrhage, seizure or trajectory related complications were reported.

Giordano (2020) conducted a systematic review with meta-analysis to compare unilateral MRgFUS to unilateral and bilateral DBS for medication-refractory ET.[38] Forty-five studies published between 1996 and 2019 were identified. Thirty-seven studies (n=1202) evaluated DBS and eight studies (n=477) evaluated MRgFUS. Fifteen studies had a retrospective study design, while 30 were prospectively designed. Means and standard deviations were calculated for each intervention and differences between groups were compared where appropriate. The average percentage improvement in tremor severity was significantly improved in the pooled DBS group (60.1%±9.7%) compared to the MRgFUS group (55.6%±8.2%, $p<0.001$). Subgroup analyses demonstrated that the improvement in tremor severity was significantly greater with the bilateral DBS (61.2%±5.2%) compared to both unilateral DBS (56.4%±9.7%) and MRgFUS; there was no significant difference between unilateral DBS and MRgFUS. MRgFUS was associated with significantly improved quality of life compared to DBS (61.9%±7.9% vs 52.5%±16.2%, $p<0.001$). There were 517 complications reported in the DBS group and 484 complications reported in the MRgFUS group. The most common adverse events reported with DBS were lead-related complications (11.4%) and speech disturbances (11.1%). For MRgFUS, adverse events of sensory nature (36.7%) and gait disturbances/muscle problems (34.4%) were most common. Limitations of the review included the different scales used in

studies to measure tremor severity and quality of life. There was only one retrospective study that directly compared DBS and MRgFUS.

A technology assessment was published by Health Quality Ontario (2018).[39] The literature search, conducted through April 2017, identified nine studies for inclusion: four single cohort studies, two retrospective chart reviews, two uncontrolled prospective studies, and an RCT. The RCT compared MRgFUS with sham treatment, the chart reviews compared MRgFUS with deep brain stimulation and radiofrequency thalamotomy. Study quality was evaluated using the GRADE system. The RCT was rated high quality, the uncontrolled comparative studies were rated very low quality, and the remaining studies were rated low quality. All studies reported tremor severity as an outcome. Pooling of results was not conducted due to heterogeneity in study designs, analyses, and outcomes across the studies. Reviewers determined that, overall, MRgFUS decreased tremor severity and improved QOL. The high-quality RCT by Elias (2016) is discussed below.

Mohammed (2018) conducted a meta-analysis evaluating the use of MRgFUS to treat medicine-refractory essential tremors.[40] The literature search, conducted through August 2017 identified 9 studies (total n=160 patients) for inclusion, eight of which were also evaluated in the Ontario technology assessment. Pooled analyses found significant improvements in the mean percentage change in Clinical Rating Scale for Tremor scores (62.2%) and Quality of Life in Essential Tremor scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up.

Randomized Controlled Trials

A high-quality double-blind, sham-controlled randomized trial by Elias (2016)[41] was identified by the systematic reviews above. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand (≥2 on the Clinical Rating Scale for Tremor) and refractory to at least two medical therapies. Patients were excluded if they had a neurodegenerative condition, unstable cardiac disease, coagulopathy, risk factors for deep-vein thrombosis, severe depression or cognitive impairment or if they had undergone a previous brain procedure (transcranial magnetic stimulation, deep-brain stimulation, stereotactic lesioning, or electroconvulsive therapy). Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at three months postprocedure. Patients in the treatment group were followed for an additional 12 months. Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with the sham group (0.1%) at three months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at three months. Change in Quality of Life in Essential Tremor Questionnaire scores also differed significantly in the treatment group compared with the sham group, with the largest improvements experienced in the psychosocial domain. The improvements in hand tremor score, functional improvement, and QOL were maintained at 12 months in the MRgFUS group.

Chang (2018) published results from 67 patients who participated in the open-label extension of the RCT.[42] Because nine patients from the original trial received additional treatment during the two-year follow-up, they were excluded from the analysis. Improvements in tremor and disability scores were maintained at the two-year follow-up (tremor, 19.8±4.9 [baseline] to 8.8±5.0 [at two years]; disability, 16.4±4.5 [baseline] to 6.5±5.0 [at two years]).

Nonrandomized Studies

Several nonrandomized studies (n=11 to 15) reported results from trials implementing MRgFUS as a treatment for essential tremor and many were included in the systematic reviews discussed above.[43-46]

Parkinson's Disease

Ge (2021) published a SR of data from RCTs comparing MRgFUS to sham procedure in the treatment of Parkinson's Disease (PD).[47] The available data from RCTs consisted of the trials by Bond (2017) and Martinez-Fernandez (2020) below, in which the blinded phase lasted for four months three months, respectively. The MRgFUS group showed significant improvement in limb tremor on the treated side (SMD: - 1.20; 95% CI: - 2.06, - 0.34) and the ability to perform daily activities (SMD: - 0.86; 95% CI: - 1.41, - 0.32) compared to the sham group, however, no other treatment effects were found. Dizziness was more common in the treatment group (OR: 4.68; 95% CI: 1.20, 18.23) and symptoms such as hemiparesis, ataxia, dysmetria, speech impairment, and anxiety were found only in the treatment group in both studies. Heterogeneity in patient selection (asymmetric motor symptoms vs. tremor-dominant PD) surgical target site (dorsolateral subthalamic nucleus or ventral intermediate thalamus), and assessed outcomes, as well as small sample sizes, and limited follow-up times are limitations to the available data. Larger, longer-term trials are needed to determine the role of MRgFUS in the treatment of Parkinson's disease.

Martinez-Fernandez (2020) published the results of a RCT of 40 patients with asymmetric PD with predominant motor features randomly assigned to focused ultrasound subthalamotomy (n=27, active treatment) or sham procedure (n=13, control).[48] The lesion site was targeted to the dorsolateral subthalamic nucleus and immediately dorsally to impinge on the pallidothalamic tract and adjusted according to clinical effects. The primary efficacy outcome was between-group difference in the change from baseline in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score and the primary safety outcome was procedure-related complications, both assessed at four months post-procedure. MDS-UPDRS III score for the more affected side decreased from 19.9 at baseline to 9.9 in the active-treatment group (least-squares mean difference, 9.8 points; 95% confidence interval [CI], 8.6 to 11.1) and from 18.7 to 17.1 in the control group (least-squares mean difference, 1.7 points; 95% CI, 0.0 to 3.5); between group difference = 8.1 (95% CI, 6.0 to 10.3; $p < 0.001$). Adverse events in the active-treatment group were dyskinesia in the off-medication state in six patients and in the on-medication state in six, which persisted in three and one, respectively, at four months; weakness on the treated side in five patients, which persisted in two patients at four months; speech disturbance in 15 patients, which persisted in three at four months; facial weakness in three patients, which persisted in one at four months; and gait disturbance in 13 patients, which persisted in two at four months. In six patients in the active-treatment group, some of these deficits were present at 12 months.

A double-blind, sham-controlled, randomized pilot trial by Bond (2017) assessed the safety and efficacy of unilateral MRgFUS thalamotomy in patients with tremor-dominant PD.[49] Adult patients over 30 years with idiopathic PD were included if their subtype was tremor-dominant that was deemed medication-refractory, severe, and disabling. A total of 27 patients were randomized (2:1) to MRgFUS thalamotomy (n=20) or a sham procedure (n=7) at two centers. The lesion target described in the study was the ventral intermediate thalamus. The primary efficacy outcome was change from baseline (on-medication state) to three months after post-procedure in the hand tremor subscore in the Clinical Rating Scale for Tremor (CRST). On-medication median tremor scores improved 62% (IQR, 22%-79%) from a baseline of 17 points

(IQR, 10.5-27.5) following MRgFUS thalamotomy and 22% (IQR, -11% to 29%) from a baseline of 23 points (IQR, 14.0-27.0) after sham procedures (Wilcoxon p= 0.04). The most common thalamotomy-related adverse events reported for all 26 patients treated were finger paresthesia (39%), ataxia (35%), and orofacial paresthesia (27%). Paresthesia and ataxia persisted to one year in 19% and 4% of patients, respectively. Eight severe adverse events were reported in four patients, and three were thalamotomy-related (two patients with persistent mild hemiparesis and one patient had an associated persistent mild ataxia). After unblinding at three months, six of the seven patients who received sham procedures crossed over to undergo open-label treatment with MRgFUS. Limitations to the study include small sample size, comparison to a sham treatment instead of an alternative surgical procedure and lack of long-term follow-up.

Uterine Fibroids

There are several approaches that are currently available to treat symptomatic uterine fibroids: hysterectomy; abdominal myomectomy; laparoscopic and hysteroscopic myomectomy; hormone therapy; uterine artery embolization; and watchful waiting. Hysterectomy and various myomectomy procedures are considered the gold standard treatment. Comparisons to these procedures in well-designed prospective randomized clinical trials are needed to determine whether MRI-guided high-intensity focused ultrasound ablation (MRgFUS) results in the same or better health outcomes with respect to long-term treatment effects, recurrence rates and impact on future fertility and pregnancy. The focus of this review is therefore on randomized controlled trials.

Systematic Reviews

A SR with meta-analysis published by Xu (2021) assessed re-intervention rates of myomectomy, uterine artery embolization (UAE), and MRgFUS for the treatment of uterine fibroids across 31 studies (N = 42,103).[50] Shorter-term (12-month) pooled re-intervention rate estimations of MRgFUS, UAE, and myomectomy were 0.12 (95%CI, 0.04–0.20; I2=89.1%; p = 0.000), 0.07 (95%CI, 0.06–0.09; I2=14.2%; p = 0.324), and 0.06 (95%CI, 0.01–0.11; I2=95.1%; p = 0.000), respectively. Twenty-four-month: 0.14 (95%CI, 0.07–0.21), 0.08 (95%CI, 0.01–0.17; I2=75.7%; p = 0.016), and 0.10 (95%CI, 0.04–0.16; I2=76.0%; p = 0.002), and 36-month: 0.22 (95%CI, 0.11–0.32; I2=86.3%; p = 0.002), 0.14 (95%CI, 0.05–0.23; I2=94.7%; p = 0.000), and 0.09 (95%CI, 0.05–0.13; I2=0.0%; p = 0.508), respectively. Longest-term (60-month) estimations of the pooled re-intervention rates for MRgFUS, UAE, and myomectomy were 0.49 (95%CI, 0.21–0.77; I2=96.5%; p = 0.000), 0.21 (95%CI, 0.17–0.25; I2=84.1%; p = 0.000), and 0.19 (95%CI, 0.15–0.24; I2=53.7%; p = 0.071), respectively. No evidence of publication bias was found. In sum, estimations of the pooled 12-month, 24-month, 36-month and 60-month re-intervention rates of MRgFUS were 12%, 14%, 22% and 49%, which were the highest rates across all interventions assessed. Myomectomy had the lowest re-intervention rate.

In the 2017 AHRQ review of management of uterine fibroids summarized above, of the six studies assessing HIFU for fibroid ablation, only one fair quality pilot study (n=20) used magnetic resonance imaging (MRI) guidance.

A SR published by Gizzo (2013) identified 38 uncontrolled studies with a total of 2,500 patients (mean age 43.67 years) who underwent MRgFUS for treatment of uterine fibroids.[51] All of the published studies included women older than age 18 years with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. The authors of the systematic

review did not pool study findings, noting there was no uniform consensus regarding the parameters for evaluating treatment results and considerable variety in the inclusion criteria and follow-up periods. The review confirms the continued absence of published randomized controlled trials on MRgFUS for uterine fibroids.

Clark (2014) published a review of the evidence regarding the role of MRgFUS in the treatment of fibroids and its impact upon future fertility and reproductive outcomes.[52] The authors identified 35 reports of pregnancy after MRgFUS in the available literature; however, additional studies are needed to evaluate the impact of MRgFUS upon future fertility and reproductive outcomes.

Randomized Controlled Trials

A pilot sham-controlled RCT with 20 patients was published by Jacoby (2015). The study was designed to determine the feasibility of a full scale randomized study evaluating MRgFUS for treatment of uterine fibroids.[53] The study included premenopausal women with symptomatic uterine fibroids. Women who were pregnant or had a desire for future fertility were excluded. Patients were randomized to MRgFUS with the ExAblate 2000 system (n=13) or a sham treatment in which no thermal energy was delivered (n=7). The investigators did not specify primary outcomes. The sample size of 20 was selected, not to have sufficient statistical power, but to assess the feasibility of a larger trial. All patients assigned to the MRgFUS group and six of seven in the placebo group received their allocated treatment and all treated patients completed three months of follow-up. Patients were unblinded at three months and given the sham group was given the option of active treatment.

Quality of life outcomes included the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL), which has subscales including the Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) score. Other measure was the Medical Outcomes Study (MOS), which has a Mental Component Summary (MCS) and Physical Component Summary (PCS). At both the 4- and 12-week follow-ups, there were no statistically significant differences (at the $p<0.05$ level) between the MRgFUS and sham groups in the SSS, HRQL, PCS, or MCS. Change in uterine and fibroid volume, however, differed significantly between groups at 12 weeks. Uterine volume decreased by 17% in the MRgFUS group and by 3% in the sham group ($p=0.04$). Total fibroid volume decreased 18% in the MRgFUS group and did not change in the sham group ($p=0.03$). The authors concluded that women are willing to participate in a sham-controlled RCT of MRgFUS and that larger trials are feasible.

Nonrandomized Studies

The “pivotal” study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.[54, 55] Additional study outcomes have been subsequently reported from this same study, although interpretation of any such results is limited by the weak strength of the evidence from the original trial. For example, Taran (2009) failed to report on the original primary outcome measure and instead reported findings on a different quality of life measure.[56] The different measures were subject to a multiple comparison bias; a large number of statistical comparisons were done for secondary outcomes, and p-values were not adjusted for increased risk of chance statistical findings.

Another nonrandomized study compared two variations on the MRgFUS procedure.[57] Patients were either treated with the original protocol (33% of fibroid volume with a maximum treatment

time of 120 minutes, n=96) or modified protocol (50% treatment volume, 180 minutes maximum treatment time, and a second treatment if within a 14-day period, n=64). Interpretation of these results was limited by 49% loss to follow-up; 55 patients (57%) from the original treatment protocol completed follow-up. Only 21 patients (33%) from the modified protocol group were evaluable at 12-month follow-up.

A prospective registry of pregnancies after MRgFUS was maintained by the manufacturer of the ExAblate device. A 2008 article reported that there were 54 known pregnancies a mean of eight months after treatment.[58] They included 8 pregnancies from clinical trials designed for women who did not desire pregnancy, 26 pregnancies after commercial treatment, and 20 pregnancies in 17 patients from an ongoing study of MRgFUS in women trying to conceive. Twenty-two of the 54 pregnancies (42%) resulted in deliveries, 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 miscarriages (26%) and seven elective terminations (13%). Among the 22 live births, the mean birth weight of live births was 3.3 kg, and the vaginal delivery rate was 64%. The article provides initial information on the impact of MRgFUS for uterine fibroids on pregnancy; findings suggest that fertility may be maintained but that the number of cases is too small to draw definitive conclusions. Moreover, the study does not address the possible impact of MRgFUS treatment on the ability to become pregnant.

Other non-comparative, prospective and retrospective case series have been published; however, conclusions concerning health outcomes cannot be reached from these studies due to small study populations, high rate of loss to follow-up, and failure to control for bias which could impact treatment results.[59-66]

Although results from these trials contribute to the body of evidence on MRgFUS, interpretation of such results is limited by the lack of a comparative treatment group, the absence of which does not allow for the comparison of the relative treatment effect of MRgFUS with standard medical alternatives. In addition, there is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy.

Section Summary

There is insufficient evidence regarding the use of MRgFUS as a treatment of uterine fibroids compared to other established procedures. Evidence from randomized controlled trials is lacking and conclusions concerning the safety and efficacy of MRgFUS cannot be drawn from nonrandomized studies due to methodological limitations such as an inability to isolate treatment effects. Systematic review of long-term follow-up results indicate that there is a lower reintervention rate and greater improvement in symptoms after uterine artery embolization compared to MRgFUS. Questions remain regarding the durability of MRgFUS treatment or the impact of this treatment upon future fertility.

Palliative Treatment of Bone Metastases

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, RCTs are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

Therefore, the assessment of the safety and efficacy of MRgFUS treatment for bone metastases requires large, long-term, randomized controlled trials comparing this technique with the current standard of care for the condition being treated.

Systematic Reviews

Baal (2021) conducted a systematic review (SR) of studies published between 2007 and 2019 evaluating MRgFUS treatment for painful bone metastases.[67] A total of 33 studies were reviewed, inclusive of three noted as randomized control trials, six retrospective studies, and 24 prospective studies (N=1082). The 2014 RCT by Hurwitz discussed below appears to be the only RCT reporting clinical outcomes in a full publication; one randomized trial evaluated molecular outcomes and one RCT was published only as a conference abstract. Overall, thirteen studies were available in abstract form only. The median study sample size was 21 patients (range 5 to 140) with a median follow-up period of three months (range, 1 to 12 months). The median age of patients was 60 years (22 studies including one study on a pediatric study population, range 4.3–69). Efficacy was assessed by treatment response (complete response or partial response [≥ 2-point improvement in pain score]) and the mean difference in pain scores (10-point VAS [visual analog scale] or NRS [numeric rating scale]) from baseline to month one/month three. The pooled proportion of patients with a treatment response to MRgFUS was 79% (95% confidence interval [CI], 73% to 83%; based on 20 studies [N=636]). The pooled one-month and three-month mean difference from baseline in pain scores were -3.8 (95% CI, -4.3 to -3.3) and -4.4 (95% CI, -5.0 to - 3.7), respectively (based on 20 studies [N=543]). Across 26 studies (N=799), seven high-grade adverse events were observed (one deep vein thrombosis, two cases of grade 3 skin burn, and four fractures). Approximately 11.8% of patients experienced sonication-related pain during MRgFUS treatment. The analysis was limited by a lack of a pooled comparator and heterogeneity of data with respect to populations (eg, type of primary cancer), reported data, and treatment details. Most studies had follow-up periods that were limited to three months.

A SR with meta-analysis by Han (2021) included 15 studies (N = 362) inclusive of the 2014 RCT by Hurwitz and a matched-pair study by Lee (2017) described below and.[68] The studies were conducted in China (n = 112), the United States (n = 112), Israel (n = 38), Italy (n = 23), France (n = 17), Netherlands (n = 15), Canada (n = 21), Japan (n = 10), South Korea (n = 5), and the United Kingdom (n = 9). Most of the included studies were single-arm clinical studies. The quality of studies was assessed by the MINORS score, a validated instrument for assessment of quality in non-randomized surgical studies ranging from 0-24. The mean MINORS score was 14.6 (range: 9–24). Lack of blinding and control groups were found in most of the studies, which contributed to risk of bias in study quality evaluations, however no evidence of publication bias was found. All but one paper included in the study used 10-point scales to assess pain and the data of the one paper using a 100-point scale was transformed into a 10-point scale for comparison purposes. Compared with baseline, pain was significantly improved at 0 to 1 week (mean reduced pain scores = 2.54 [95% CI: 1.92–3.16, $p < 0.01$] and at 1 to 5 weeks (3.56 [95% CI: 3.11–4.02, $p < 0.01$]), and at 5 to 14 weeks (4.22 [95% CI: 3.68–4.76, $p < 0.01$]). Pain outcomes were not assessed at all timepoints across trials and heterogeneity was high in all timeframes; nine studies (N = 268) assessed pain at 0 to 1 week (I^2 = 98.7%), 10 trials (N = 291) assessed at 1 to 5 weeks (I^2 = 98.2%), and nine trials (N = 289) assessed pain at 5 to14 weeks (I^2 = 99.7%). The overall complete response rate, defined as a pain score of 0 with no medication increase was 0.36 (95% CI: 0.24–0.48) and the partial response rate, defined as a drop of 2 on a 10-point scale without an increase in pain medications or a drop of 25% in pain medication without increase in the reported pain score,

was 0.47 (95% CI: 0.36–0.58), and no response (no drop of score and no changes in medication use) rate was 0.23 (95% CI: 0.13–0.34). Among the 14 studies (N = 352) reporting complications, 93 (26.4%) patients had minor complications and five (1.42%) had major complications.

A SR by Gennaro (2019) evaluated multiple thermal ablation techniques for relief of bone pain due to metastatic disease, including MRgFUS, radiofrequency ablation, microwave ablation and cryoablation.[69] The review included 11 papers and reported a mean reduction in pain scores of 26% to 91% at four weeks and 16% to 95% at 12 weeks. The authors noted that MRgFUS was associated with a higher rate of adverse events than the other modalities. All techniques achieved pain relief at one and three months in up to 91% and 95% of patients respectively. Across all modalities, the number of minor complications ranged from 0 to 59 (complication ratio 0–1.17), and the number of significant adverse effects ranged from 0 to 4 (complication ratio 0–0.04). Specific to MRgFUS, only the RCT by Hurwitz (2014, below) reported complications, which are summarized below.

Randomized Controlled Trials

Hurwitz (2014) published results from a randomized trial that evaluated the safety and efficacy of MRgFUS on palliation of pain due to bone metastases.[70] The study was included in the SRs discussed above and included patients age 18 years and older with at least three months of life expectancy who had bone metastases that were painful, despite radiotherapy treatment, or who were unsuitable for or declined radiotherapy. Patient-rated tumor pain on a numeric rating scale (NRS) at four or higher on a 10-point scale and up to five painful lesions were inclusion criteria, however, only one lesion was treated and it had to cause at least two points greater pain on the NRS than any other lesion. In addition, targeted tumors needed to be device accessible.

Study participants were randomized in a 3:1 ratio to active (n=122) or sham (n=39) MRgFUS treatment. Ten patients in the treatment group and four in the sham group did not receive the allocated treatment. An additional 26 patients in the treatment group and 23 in the sham group did not complete the three-month follow-up. A much larger proportion of the placebo group dropped out; 17 (49%) of 35 who were treated decided to have rescue MRgFUS treatment after lack of response to placebo. A modified intention-to-treat analysis was used that included patients who had at least one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method.

The primary efficacy end point, assessed at three months, was a composite outcome comprised of change in baseline in worst NRS score and morphine equivalent daily dose (MEDD) intake. Patients were considered responders if their worst NRS score decreased by at least two points and if their MEDD intake did not increase more than 25% from baseline to three months. NRS score and MEDD intake separately were reported as secondary outcomes.

Seventy-two (64%) of 112 patients in the MRgFUS group and seven (20%) of 35 patients in the control group were considered responders, as previously defined. The difference between groups was statistically significant (p=0.01), favoring active treatment. When the two measures comprising the primary end point were analyzed separately, there was a statistically significant difference between groups in change in worst NRS score and a nonsignificant difference in change from baseline in pain medication. The NRS score decreased by a mean (SD) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group (p<0.01). Change in MEDD was only reported in a figure. Fifty-one (46%) patients in the MRgFUS group

and one (3%) in the placebo group experienced at least one adverse event (AE). Most AEs were transient, and the most common was sonication pain, experienced by 36 (32%) patients in the MRgFUS group. In 17 (15%) patients, sonication pain was severe; three patients did not complete treatment due to pain. The most clinically significant AEs that lasted more than a week were third-degree skin burns in one patient (associated with noncompliance with the treatment protocol) and fracture in two patients (one of which was outside the treatment location). Potential limitations of the trial included a nonconventional primary outcome measure and the small initial size of the sham group. Moreover, a large number of sham patients (66%) did not complete the three-month follow-up; the authors did state that this low completion rate was due to lack of response to placebo treatment. Additional randomized studies are required to isolate the treatment effect of MRgFUS upon pain and better characterize the benefit and length of symptom relief with MRgFUS in patients with bone metastases.

Nonrandomized Studies

Lee (2017) published the results of a matched-pair study of MRgFUS or conventional radiation therapy (RT) as a treatment for patients with painful bone metastasis.[71] A total of 63 patients (21 MRgFUS and 42 RT-treated) were matched 1:2 by age, sex, primary cancer, pretreatment pain score, and treated site. All patients were followed for at least three months post-treatment. Mean numerical rating scale (NRS) for the MRgFUS-treated group was significantly lower at one week post-treatment (2.5 versus 4.8, $p < 0.0001$), two weeks (2.1 versus 3.6, $p < 0.05$) and three months (1.0 versus 2.3, $p < 0.05$) post-treatment compared to the RT-treated group, however, no significant difference was found at one or two month timepoints. Mean morphine-equivalent daily dose change from baseline did not differ between groups. At one week post-treatment, 71% of the MRgFUS and 26% of the RT- treated patients had experienced a treatment response (successful pain palliation), a statistically significant difference ($p<0.001$). No statistically significant group difference in response rate were found at subsequent timepoints. No adverse events above grade 2 were observed for either group. This study was limited by small sample size and short-term follow-up.

Examples of nonrandomized trials include four small (n=11 to 31), nonrandomized prospective studies evaluating MRgFUS for the treatment of bone metastases, the majority of which are industry-sponsored.[72-75] Although none reported any treatment-related adverse effects, and all reported improvements in pain and two reported decreases in analgesic use, independent verification of treatment effects with larger groups of patients is needed. At present, results from these trials are not sufficient to reach conclusions regarding the impact of MRgFUS in palliation of pain related to bone metastases due to methodological limitations such as lack of an appropriate control group for comparison.

In addition, there have been several small case series published on the use of MRgFUS for treatment of bone metastases. However, these series did not compare the safety and efficacy of this treatment to other treatment options.

Other Tumors

MRgFUS is also being studied for several other clinical applications, including the treatment of benign and malignant tumors. As with MRgFUS treatment for uterine fibroids and bone metastases, randomized controlled trials comparing this technique with the current standard of care for the condition being treated are required in order to assess the efficacy of this treatment approach.

Breast Tumors

Nonrandomized Studies

No controlled studies evaluating MRgFUS for treating breast cancer have been identified in the published literature. Evidence is limited to small case series, examples of which include six feasibility studies that describe preliminary results only[76-81] Fibroadenoma, ductal carcinomas, adenocarcinomas, and lobular carcinomas were treated. The adverse effects profile includes a few second-degree skin burns, and protocols maintain a roughly 1cm distance between the tumor margin and the skin or rib cage. Residual tumor in the treated area appears to be a problem, with authors recommending treatment of the entire tumor plus 1 cm of surrounding tissue, as is done in lumpectomy. No long-term outcome studies are available. As with uterine fibroids, interpretation of these results is limited by the lack of a comparative treatment group. A 2016 case series by Merckel[82] included ten patients with early-stage invasive breast cancer who underwent MRgFUS prior to surgical resection. Ablation was confirmed histopathologically in six of these patients. The investigators concluded that MRgFUS is safe and feasible. A noted limitation is the long procedure time (average, 145 minutes), due to waiting time after contrast injection and time to find a proper magnetic resonance navigator signal.

Brain Cancer

Nonrandomized Studies

Evidence on MRgFUS in brain cancer is similarly restricted to case series, which include a report of initial findings in three patients.[83] The authors reported that it was possible to focus an ultrasound beam into the brain transcranially, and they believe that thermal ablation without overheating the brain is possible; however, substantial technical barriers to using MRgFUS for treating brain tumors remain. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating this indication.

Prostate Cancer

Nonrandomized Studies

Ghai (2021) conducted a phase II trial to evaluate the safety and efficacy of transrectal MRgFUS treatment for intermediate-risk prostate cancer in 44 men, 36 with grade group (GG) 2 and eight with GG 3 disease.[84] The primary efficacy endpoint was the presence of residual disease at the treatment site at five months post- procedure. The International Prostate Symptom Score (IPSS) and International Index of Erectile Function-15 (IIEF-15) score were assessed at six weeks and five months, and multiparametric MRI and targeted biopsy of the treated area was obtained at five months post-procedure. Ninety-three percent of patients (95% CI: 82, 98) were free of clinically significant prostate cancer, defined as (≥6 mm GG 1 disease or any volume ≥GG 2 disease) at the five-month biopsy. Median IIEF-15 and IPSS scores were not significantly different at baseline compared to five months (IIEF-15 score at baseline, 61 [IQR, 34–67] and at five months, 53 [IQR, 24–65.5], p = 0.18; IPSS score at baseline, 3.5 [IQR, 1.8–7] and at five months, 6 [IQR, 2–7.3], p = 0.43). Seven percent (95% CI, 2.4 to 18.2) had residual disease at five months after ablation. No major treatment-related adverse events were reported, however, 16 patients reported dysuria; five patients required antispasmodics for bladder spasm in the first week; two patients had urinary retention; and one patient had severe pelvic pain. Study limitations include the short follow-up time to assess

efficacy; however, a biopsy at a 24-month follow-up is planned, which will address persistence and recurrent prostate cancer.

Small (n=1 to 5) feasibility studies regarding the use of MRgFUS in patients with biopsy-proven prostate cancer have demonstrated that the procedure may be performed in this patient population.[85-87] At least one study was conducted using the ExAblate® 2100 System, which is not FDA approved for this indication. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating prostate cancer.

Other tumors

Several studies have investigated the use of MRgFUS for nonspinal osteoid osteoma.[88-90] Arrigoni (2021) conducted a propensity score-matched retrospective study to compare treatment with radiofrequency ablation and MRgFUS.[89] A total of 116 patients were treated (61 with radiofrequency ablation and 55 with MRgFUS). After propensity score matching, both radiofrequency ablation and MRgFUS treatment resulted in a significant reduction in pain from baseline as measured by VAS (8.9 to 0.02 and 8.8 to 0.54, respectively). There was no statistically significant difference between the mean values of both groups after the treatment. Four cases of relapse (one with radiofrequency ablation and three with MRgFUS) were observed. Arrigoni (2019) prospectively enrolled children into a study to evaluate MRgFUS treatment for osteoid osteoma.[88] The primary clinical endpoint was defined as the absence of pain (evaluated on the Faces Pain Scale-Revised) at the first follow-up study one week after the procedure. A total of 33 children were included in the study and treated with MRgFUS. The mean pain score at baseline was 7.6; the score at week one after the procedure significantly improved in all children (mean score, 0.21). Complete absence of pain was reported in 32 of 33 (97%; 95% CI, 84 to 100) of patients at week one. At the 24-month follow-up visit, imaging results confirmed the complete disappearance of bone edema around all lesions. Geiger (2014) prospectively enrolled patients into a study to evaluate MRgFUS treatment for osteoid osteoma.[90] Clinical success was evaluated based on pain reduction (evaluated on a VAS) through 12 months. At the 12-month follow-up, complete clinical success was achieved in 90% of the 29 patients enrolled (mean VAS, 0±0 points); partial success was achieved in the remaining patients (mean VAS, 5±0 points).

PRACTICE GUIDELINE SUMMARY

AMERICAN CONGRESS OF OBSTETRICS AND GYNECOLOGISTS

A practice bulletin from American Congress of Obstetrics and Gynecologists (ACOG) considered MRgFUS as an alternative to hysterectomy as a treatment of uterine fibroids, but did not specifically recommend its use, stating:[91]

> Whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound surgery will lead to durable results beyond 24 months. Protocols for treating larger leiomyoma volumes are being studied.

AMERICAN COLLEGE OF RADIOLOGY

The 2017 American College of Radiology (ACR) Appropriateness Criteria guidelines regarding the treatment of uterine fibroids mention the use of MRgFUS indicating that, “(t)o date, there is

little long-term information on the efficacy of [MRgFUS] technology."[92] However, the MRgFUS approach is not recommended as treatment for fibroids.

AMERICAN UROLOGICAL ASSOCIATION

In 2017, the American Urological Association (AUA) published a joint guideline (with the American Society for Radiation Oncology [ASTRO], and the Society of Urologic Oncology [SUO] regarding clinically localized prostate cancer.[93] Nearly all recommendations regarding HIFU as a treatment for prostate cancer were Expert Opinion, that is, the committee did not have sufficient evidence to grade the strength of the evidence. Additionally, the following recommendation was made:

> *Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)*
>
> Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guideline for prostate cancer (version 1.2023) include high-intensity focused ultrasound ablation as a recommended treatment option in the presence of radiation recurrence in a manner that is consistent with the policy criteria. (Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate).[1]

The NCCN Guideline on adult cancer pain (version 2.2022) does not include ultrasound ablation specifically in pain management algorithms, however, the guideline states:[94]

> Image-guided ablation of bone lesions has proven successful in pain management, especially for those failing to achieve adequate analgesia without intolerable effects. Several small studies also have demonstrated the palliative effects of HIFU treatment of bone lesions.

SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

In 2015, the Society of Obstetricians and Gynaecologists of Canada published a clinical practice guideline entitled "Management of Uterine Fibroids in Women with Otherwise Unexplained Fertility."[95] The guideline states that there are no studies comparing MRgFUS with myomectomy or in women with fibroids who have infertility as their primary complaint, and thus additional data are needed before the treatment is offered to this patient population.

SUMMARY

HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION

It appears that high-intensity focused ultrasound (HIFU) ablation may improve overall health outcomes for select men with localized recurrent prostate cancer. Clinical guidelines based

on research recommend HIFU for specific patient populations. Therefore, high-intensity focused ultrasound may be considered medically necessary to treat localized prostate cancer when policy criteria are met. Due to a lack of research and clinical practice guidelines, HIFU is considered investigational for all other indications that do not meet the policy criteria.

MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)

Movement Disorders

Medicine-Refractory Essential Tremor

It appears that Magnetic Resonance-guided focused ultrasound (MRgFUS) may help those with medicine-refractory essential tremor. At least one high quality randomized study and several large systematic reviews of MRgFUS use specifically in the treatment of essential tremor have demonstrated improvement in symptoms with MRgFUS treatment and improved overall quality of life. Therefore, MRgFUS may be considered medically necessary for medicine-refractory essential tremors when policy criteria are met.

Parkinson's Disease

There is not enough research to know if or how well Magnetic Resonance-guided focused ultrasound (MRgFUS) works to treat people with Parkinson's Disease. There is evidence that the use of MRgFUS in the treatment of Parkinson's Disease is associated with high rates of adverse events. No evidence-based clinical practice guidelines recommend MRgFUS for the treatment of Parkinson's Disease. Therefore, treatment of Parkinson's Disease with MRgFUS is considered investigational.

Palliative Treatment of Bone Metastases

It appears that Magnetic Resonance-guided focused ultrasound (MRgFUS) may provide effective palliation of pain due to bone metastases in adults. Evidence-based clinical practice guidelines note the success of image-guided ablation in pain management, especially for those failing to achieve adequate analgesia without intolerable effects Therefore, pain palliation of bone metastases with MRgFUS may be considered medically necessary when policy criteria are met.

Uterine Fibroids

The evidence for MRgFUS in individuals who have uterine fibroids includes a pilot RCT, nonrandomized comparative studies, and case series. The pilot RCT (N=20 patients) reported some health outcomes, but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in quality of life outcomes between active and sham treatment groups, but did find lower fibroid volumes after active treatment. The pivotal Food and Drug Administration trial was not randomized, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond one year. The limited nature of this evidence-base raises concerns about the reliability and validity of reported findings. In particular, the durability of any early treatment effect with MRgFUS given the potential for regrowth of treated fibroids, is not clearly understood. Therefore, treatment of uterine fibroids with MRgFUS is considered investigational.

Other Tumors and Other Indications

(MRI)-guided focused ultrasound (MRgFUS) is being investigated for use in several applications that are not currently approved by the FDA. There are some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Due to the lack of evidence from well-designed randomized controlled trials, the use of MRgFUS for the treatment of any condition is considered investigational when policy criteria are not met.

REFERENCES

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer. Version 1.2023. [cited 9/20/2022]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
2. US Food and Drug Administration (2004). ExAblate® 2000 System - P040003 - Premarket Approval. [cited 9/14/2022]. 'Available from:' http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P040003.
3. US Food and Drug Administration (2009). ExAblate® 2100 System - P040003 - Premarket Approval. [cited 9/14/2022]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110039b.pdf.
4. US Food and Drug Administration (FDA) ExAblate for pain palliation of metastatic bone cancer PMA P110039. [cited 9/14/2022]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P110039.
5. US Food and Drug Administration (FDA) ExAblate Model 4000 Type 1.0 System (ExAblate Neuro) for Essential Tremor PMA P150038. [cited 9/14/2022]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150038A.pdf.
6. US Food and Drug Administration (FDA) ExAblate Model 4000 (ExAblate Neuro) for tremor-dominant Parkinson's Disease. [cited 9/14/2022]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150038S006A.pdf.
7. Maestroni U, Tafuri A, Dinale F, et al. Oncologic outcome of salvage high-intensity focused ultrasound (HIFU) in radiorecurrent prostate cancer. A systematic review. *Acta Biomed.* 2021;92(4):e2021191. PMID: 34487074
8. Valle LF, Lehrer EJ, Markovic D, et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *European urology.* 2021;80(3):280-92. PMID: 33309278
9. Hopstaken JS, Bomers JGR, Sedelaar MJP, et al. An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? *European urology.* 2021. PMID: 34489140
10. Ingrosso G, Becherini C, Lancia A, et al. Nonsurgical Salvage Local Therapies for Radiorecurrent Prostate Cancer: A Systematic Review and Meta-analysis. *European urology oncology.* 2020;3(2):183-97. PMID: 31411996
11. Khoo CC, Miah S, Connor MJ, et al. A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer. *Transl Androl Urol.* 2020;9:1535-45. PMID: 32676441
12. Crouzet S, Blana A, Murat FJ, et al. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients. *BJU international.* 2017;119(6):896-904. PMID: 28063191

13. Rischmann P, Gelet A, Riche B, et al. Focal High Intensity Focused Ultrasound of Unilateral Localized Prostate Cancer: A Prospective Multicentric Hemiablation Study of 111 Patients. *European urology.* 2017;71(2):267-73. PMID: 27720531
14. Crouzet S, Murat FJ, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;105(2):198-202. PMID: 23068708
15. Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. *Cancer.* 2012;118(17):4148-55. PMID: 22907704
16. Nahar B, Bhat A, Reis IM, et al. Prospective Evaluation of Focal High Intensity Focused Ultrasound for Localized Prostate Cancer. *The Journal of urology.* 2020;204(3):483-89. PMID: 32167866
17. Shah TT, Peters M, Kanthabalan A, et al. PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure. *Prostate cancer and prostatic diseases.* 2016;19(3):311-6. PMID: 27431499
18. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. *European urology.* 2013;63(4):618-22. PMID: 23265382
19. Uddin Ahmed H, Cathcart P, Chalasani V, et al. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. *Cancer.* 2012;118(12):3071-8. PMID: 22071795
20. Devos B, Al Hajj Obeid W, Andrianne C, et al. Salvage high-intensity focused ultrasound versus salvage radical prostatectomy for radiation-recurrent prostate cancer: a comparative study of oncological, functional, and toxicity outcomes. *World journal of urology.* 2019;37(8):1507-15. PMID: 30666400
21. Albisinni S, Aoun F, Bellucci S, et al. Comparing High-Intensity Focal Ultrasound Hemiablation to Robotic Radical Prostatectomy in the Management of Unilateral Prostate Cancer: A Matched-Pair Analysis. *Journal of endourology / Endourological Society.* 2017;31(1):14-19. PMID: 27799004
22. Bakavicius A, Marra G, Macek P, et al. Available evidence on HIFU for focal treatment of prostate cancer: a systematic review. *Int Braz J Urol.* 2022;48(2):263-74. PMID: 34003610
23. Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. *Health Technol Assess.* 2018;22(52):1-96. PMID: 30264692
24. Bates AS, Ayers J, Kostakopoulos N, et al. A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. *European urology oncology.* 2021;4(3):405-23. PMID: 33423943
25. Tsai MC, Chang LT, Tam KW. Comparison of High-Intensity Focused Ultrasound and Conventional Surgery for Patients with Uterine Myomas: A Systematic Review and Meta-Analysis. *Journal of minimally invasive gynecology.* 2021. PMID: 34126271
26. Barnard EP, AbdElmagied AM, Vaughan LE, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. *Am J Obstet Gynecol.* 2017;216(5):500 e1-00 e11. PMID: 28063909

27. Laughlin-Tommaso S, Barnard EP, AbdElmagied AM, et al. FIRSTT study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery. *Am J Obstet Gynecol.* 2019;220(2):174 e1-74 e13. PMID: 30696556
28. Hartmann KE, Fonnesbeck C, Surawicz T, et al. Management of Uterine Fibroids. *AHRQ Comparative Effectiveness Reviews.* 2017. PMID: 30789683
29. Marques ALS, Andres MP, Kho RM, et al. Is High-intensity Focused Ultrasound Effective for the Treatment of Adenomyosis? A Systematic Review and Meta-analysis. *Journal of minimally invasive gynecology.* 2019. PMID: 31377454
30. Lang BHH, Woo YC, Chiu KW. Two sequential applications of high-intensity focused ultrasound (HIFU) ablation for large benign thyroid nodules. *European radiology.* 2019;29(7):3626-34. PMID: 30778718
31. Lang BH, Woo YC, Chiu KW. Two-year outcomes of single-session high-intensity focused ultrasound (HIFU) treatment in persistent or relapsed Graves' disease. *European radiology.* 2019. PMID: 31209622
32. Sehmbi AS, Froghi S, Oliveira de Andrade M, et al. Systematic review of the role of high intensity focused ultrasound (HIFU) in treating malignant lesions of the hepatobiliary system. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2020. PMID: 32830069
33. Stanislavova N, Karamanliev M, Ivanov T, et al. Is high-intensity focused ultrasound (HIFU) an option for neoadjuvant therapy for borderline resectable pancreatic cancer patients? - a systematic review. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2021;38(2):75-80. PMID: 34420446
34. Spartalis E, Karagiannis SP, Plakopitis N, et al. Single-session high-intensity focused ultrasound (HIFU) ablation for benign thyroid nodules: a systematic review. *Expert review of medical devices.* 2020:1-13. PMID: 32749167
35. Chung SR, Baek JH, Suh CH, et al. Efficacy and safety of high-intensity focused ultrasound (HIFU) for treating benign thyroid nodules: a systematic review and meta-analysis. *Acta Radiol.* 2020:284185120909339. PMID: 32202137
36. Miller WK, Becker KN, Caras AJ, et al. Magnetic resonance-guided focused ultrasound treatment for essential tremor shows sustained efficacy: a meta-analysis. *Neurosurg Rev.* 2021. PMID: 33978922
37. Agrawal M, Garg K, Samala R, et al. Outcome and Complications of MR Guided Focused Ultrasound for Essential Tremor: A Systematic Review and Meta-Analysis. *Front Neurol.* 2021;12:654711. PMID: 34025558
38. Giordano M, Caccavella VM, Zaed I, et al. Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. *J Neurol Neurosurg Psychiatry.* 2020;91(12):1270-78. PMID: 33055140
39. Health Quality Ontario (HQO). Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2018;18(4):1-141. PMID: 29805721
40. Mohammed N, Patra D, Nanda A. A meta-analysis of outcomes and complications of magnetic resonance-guided focused ultrasound in the treatment of essential tremor. *Neurosurgical focus.* 2018;44(2):E4. PMID: 29385917
41. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *The New England journal of medicine.* 2016;375(8):730-9. PMID: 27557301

42. Chang JW, Park CK, Lipsman N, et al. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: Results at the 2-year follow-up. *Annals of neurology.* 2018;83(1):107-14. PMID: 29265546
43. Chang WS, Jung HH, Kweon EJ, et al. Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J Neurol Neurosurg Psychiatry.* 2015;86:257-64. PMID: 24876191
44. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *The New England journal of medicine.* 2013;369(7):640-8. PMID: 23944301
45. Jung HH, Chang WS, Rachmilevitch I, et al. Different magnetic resonance imaging patterns after transcranial magnetic resonance-guided focused ultrasound of the ventral intermediate nucleus of the thalamus and anterior limb of the internal capsule in patients with essential tremor or obsessive-compulsive disorder. *Journal of neurosurgery.* 2015;122(1):162-8. PMID: 25343176
46. Park YS, Jung NY, Na YC, et al. Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Movement disorders : official journal of the Movement Disorder Society.* 2019;34(5):727-34. PMID: 30759322
47. Ge Y, Wang Z, Gu F, et al. Clinical application of magnetic resonance-guided focused ultrasound in Parkinson's disease: a meta-analysis of randomized clinical trials. *Neurol Sci.* 2021;42(9):3595-604. PMID: 34216307
48. Martinez-Fernandez R, Manez-Miro JU, Rodriguez-Rojas R, et al. Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease. *The New England journal of medicine.* 2020;383(26):2501-13. PMID: 33369354
49. Bond AE, Shah BB, Huss DS, et al. Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol.* 2017;74(12):1412-18. PMID: 29084313
50. Xu F, Deng L, Zhang L, et al. The comparison of myomectomy, UAE and MRgFUS in the treatment of uterine fibroids: a meta analysis. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2021;38(2):24-29. PMID: 34420449
51. Gizzo S, Saccardi C, Patrelli TS, et al. Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review. *Reprod Sci.* 2014;21:465-76. PMID: 23868442
52. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. *Current opinion in obstetrics & gynecology.* 2014;26(3):151-61. PMID: 24751998
53. Jacoby VL, Kohi MP, Poder L, et al. PROMISe trial: a pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids. *Fertil Steril.* 2016;105(3):773-80. PMID: 26658133
54. Hindley J, Gedroyc WM, Regan L, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. *AJR Am J Roentgenol.* 2004;183(6):1713-9. PMID: 15547216
55. Stewart EA, Rabinovici J, Tempany CM, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril.* 2006;85(1):22-9. PMID: 16412721
56. Taran FA, Tempany CM, Regan L, et al. Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. *Ultrasound Obstet Gynecol.* 2009;34(5):572-8. PMID: 19852046

57. Fennessy FM, Tempany CM, McDannold NJ, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols. *Radiology.* 2007;243(3):885-93. PMID: 17446521
58. Rabinovici J, David M, Fukunishi H, et al. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. *Fertil Steril.* 2008,:[Epub ahead of print]. PMID: No PMID Entry for Epub
59. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. *Ultrasound Obstet Gynecol.* 2009;34(5):584-9. PMID: 19852041
60. Morita Y, Ito N, Hikida H, et al. Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids - early experience. *Eur J Obstet Gynecol Reprod Biol.* 2008;139(2):199-203. PMID: 18160200
61. Okada A, Morita Y, Fukunishi H, et al. Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome. *Ultrasound Obstet Gynecol.* 2009;34(5):579-83. PMID: 19852042
62. Gorny KR, Woodrum DA, Brown DL, et al. Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. *Journal of vascular and interventional radiology : JVIR.* 2011;22(6):857-64. PMID: 21482137
63. Kim HS, Baik JH, Pham LD, et al. MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. *Academic radiology.* 2011;18(8):970-6. PMID: 21718955
64. Kamp JE, David M, Scheurig-Muenkler C, et al. [Clinical outcome of magnetic-resonance-guided focused ultrasound surgery (MRgFUS) in the treatment of symptomatic uterine fibroids]. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin.* 2013;185(2):136-43. PMID: 23196835
65. Froeling V, Meckelburg K, Schreiter NF, et al. Outcome of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for uterine fibroids: long-term results. *European journal of radiology.* 2013;82(12):2265-9. PMID: 24075785
66. Cheung VYT, Lam TPW, Jenkins CR, et al. Efficacy and safety of ultrasound-guided high-intensity focused ultrasound for uterine fibroids: a preliminary experience. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2019;39(6):833-39. PMID: 31006301
67. Baal JD, Chen WC, Baal U, et al. Efficacy and safety of magnetic resonance-guided focused ultrasound for the treatment of painful bone metastases: a systematic review and meta-analysis. *Skeletal radiology.* 2021. PMID: 34018007
68. Han X, Huang R, Meng T, et al. The Roles of Magnetic Resonance-Guided Focused Ultrasound in Pain Relief in Patients With Bone Metastases: A Systemic Review and Meta-Analysis. *Front Oncol.* 2021;11:617295. PMID: 34458131
69. Gennaro N, Sconfienza LM, Ambrogi F, et al. Thermal ablation to relieve pain from metastatic bone disease: a systematic review. *Skeletal radiology.* 2019;48(8):1161-69. PMID: 30627778
70. Hurwitz MD, Ghanouni P, Kanaev SV, et al. Magnetic resonance-guided focused ultrasound for patients with painful bone metastases: phase III trial results. *Journal of the National Cancer Institute.* 2014;106(5). PMID: 24760791
71. Lee HL, Kuo CC, Tsai JT, et al. Magnetic Resonance-Guided Focused Ultrasound Versus Conventional Radiation Therapy for Painful Bone Metastasis: A Matched-Pair Study. *J Bone Joint Surg Am.* 2017;99(18):1572-78. PMID: 28926387

72. Gianfelice D, Gupta C, Kucharczyk W, et al. Palliative treatment of painful bone metastases with MR imaging--guided focused ultrasound. *Radiology.* 2008;249(1):355-63. PMID: 18695209
73. Liberman B, Gianfelice D, Inbar Y, et al. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. *Ann Surg Oncol.* 2009;16(1):140-6. PMID: 19002530
74. Napoli A, Anzidei M, Marincola BC, et al. Primary pain palliation and local tumor control in bone metastases treated with magnetic resonance-guided focused ultrasound. *Investigative radiology.* 2013;48(6):351-8. PMID: 23571832
75. Masciocchi C, Zugaro L, Arrigoni F, et al. Radiofrequency ablation versus magnetic resonance guided focused ultrasound surgery for minimally invasive treatment of osteoid osteoma: a propensity score matching study. *European radiology.* 2016;26:2472-81. PMID: 26612546
76. Hynynen K, Pomeroy O, Smith DN, et al. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. *Radiology.* 2001;219(1):176-85. PMID: 11274554
77. Zippel DB, Papa MZ. The use of MR imaging guided focused ultrasound in breast cancer patients; a preliminary phase one study and review. *Breast Cancer.* 2005;12(1):32-8. PMID: 15657521
78. Huber PE, Jenne JW, Rastert R, et al. A new noninvasive approach in breast cancer therapy using magnetic resonance imaging-guided focused ultrasound surgery. *Cancer Res.* 2001;61(23):8441-7. PMID: 11731425
79. Gianfelice D, Khiat A, Amara M, et al. MR imaging-guided focused US ablation of breast cancer: histopathologic assessment of effectiveness-- initial experience. *Radiology.* 2003;227(3):849-55. PMID: 12714680
80. Gianfelice D, Khiat A, Amara M, et al. MR imaging-guided focused ultrasound surgery of breast cancer: correlation of dynamic contrast-enhanced MRI with histopathologic findings. *Breast Cancer Res Treat.* 2003;82(2):93-101. PMID: 14692653
81. Gianfelice D, Khiat A, Boulanger Y, et al. Feasibility of magnetic resonance imaging-guided focused ultrasound surgery as an adjunct to tamoxifen therapy in high-risk surgical patients with breast carcinoma. *Journal of vascular and interventional radiology : JVIR.* 2003;14(10):1275-82. PMID: 14551274
82. Merckel LG, Knuttel FM, Deckers R, et al. First clinical experience with a dedicated MRI-guided high-intensity focused ultrasound system for breast cancer ablation. *Eur Radiol.* 2016;26(11):4037-46. PMID: 26852219
83. McDannold N, Clement GT, Black P, et al. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery.* 2010;66(2):323-32; discussion 32. PMID: 20087132
84. Ghai S, Finelli A, Corr K, et al. MRI-guided Focused Ultrasound Ablation for Localized Intermediate-Risk Prostate Cancer: Early Results of a Phase II Trial. *Radiology.* 2021;299(2):E258. PMID: 33900880
85. Yuh B, Liu A, Beatty R, et al. Focal therapy using magnetic resonance image-guided focused ultrasound in patients with localized prostate cancer. *Journal of therapeutic ultrasound.* 2016;4:8. PMID: 26973790
86. Lindner U, Ghai S, Spensieri P, et al. Focal magnetic resonance guided focused ultrasound for prostate cancer: Initial North American experience. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada.* 2012;6(6):E283-6. PMID: 23283106

87. Napoli A, Anzidei M, De Nunzio C, et al. Real-time magnetic resonance-guided high-intensity focused ultrasound focal therapy for localised prostate cancer: preliminary experience. *European urology.* 2013;63(2):395-8. PMID: 23159454
88. Arrigoni F, Napoli A, Bazzocchi A, et al. Magnetic-resonance-guided focused ultrasound treatment of non-spinal osteoid osteoma in children: multicentre experience. *Pediatr Radiol.* 2019;49(9):1209-16. PMID: 31129699
89. Arrigoni F, Spiliopoulos S, de Cataldo C, et al. A Bicentric Propensity Score Matched Study Comparing Percutaneous Computed Tomography-Guided Radiofrequency Ablation to Magnetic Resonance-Guided Focused Ultrasound for the Treatment of Osteoid Osteoma. *Journal of vascular and interventional radiology : JVIR.* 2021;32(7):1044-51. PMID: 33775816
90. Geiger D, Napoli A, Conchiglia A, et al. MR-guided focused ultrasound (MRgFUS) ablation for the treatment of nonspinal osteoid osteoma: a prospective multicenter evaluation. *J Bone Joint Surg Am.* 2014;96(9):743-51. PMID: 24806011
91. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. *Obstetrics and gynecology.* 2008;112(2 Pt 1):387-400. PMID: 18669742
92. Knuttinen MG, Stark G, Hohenwalter EJ, et al. ACR Appropriateness Criteria((R)) Radiologic Management of Uterine Leiomyomas. *Journal of the American College of Radiology : JACR.* 2018;15(5S):S160-S70. PMID: 29724419
93. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. *The Journal of urology.* 2018;199(3):683-90. PMID: 29203269
94. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 2.2022. [cited 9/14/2022]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
95. Carranza-Mamane B, Havelock J, Hemmings R, et al. The management of uterine fibroids in women with otherwise unexplained infertility. *J Obstet Gynaecol Can.* 2015;37:277-88. PMID: 26001875

CODES

NOTE: There are no specific CPT codes for the use of magnetic resonance–guided high-intensity ultrasound ablation in certain cancers. In these situations an unlisted code would be used based on the anatomic location of the metastasis being treated (eg, 23929 for the clavicle) or perhaps one of the radiation oncology unlisted codes (eg, 77299 or 77499).

Codes	Number	Description
CPT	0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume of less than 200 cc of tissue
	0072T	;total leiomyomata volume greater or equal to 200 cc of tissue
	0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed
	23929	Unlisted procedure, shoulder
	55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance
	58578	Unlisted laparoscopy procedure, uterus
	58579	Unlisted hysteroscopy procedure, uterus
HCPCS	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance

Date of Origin: *October 2004*

Regence

Medical Policy Manual Surgery, Policy No. 145

Automated Percutaneous and Percutaneous Endoscopic Discectomy

Effective: November 1, 2023

Next Review: July 2024
Last Review: September 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Automated percutaneous and percutaneous endoscopic discectomy are techniques used to remove spinal disc material for treatment of herniated discs.

MEDICAL POLICY CRITERIA

Note: This policy does *not* address intradiscal electrothermal annuloplasty (IDET), percutaneous intradiscal radiofrequency thermocoagulation (PIRFT), or laser discectomy and radiofrequency disc decompression which are considered in separate medical policies (see Cross References below).

Automated percutaneous and percutaneous endoscopic discectomy are considered **investigational** as techniques for intervertebral disc decompression in patients with back pain and/or radiculopathy related to disc herniation in the lumbar, thoracic, or cervical spine.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Percutaneous Intradiscal Electrothermal Annuloplasty, Radiofrequency Annuloplasty, and Biacuplasty, Surgery, Policy No. 118
2. Decompression of Intervertebral Discs Using Laser Energy (Laser Discectomy) or Radiofrequency Energy (Nucleoplasty), Surgery, Policy No. 131
3. Image-Guided Minimally Invasive Spinal Decompression (IG-MSD) for Spinal Stenosis, Surgery, Policy No. 176

BACKGROUND

Back pain or radiculopathy related to herniated discs is an extremely common condition and a frequent cause of chronic disability. Surgical decompression is often considered when the pain is unimproved with conservative therapy and is clearly neuropathic in origin, resulting from irritation of the nerve roots.

This policy addresses automated percutaneous and percutaneous endoscopic removal of disc material as minimally invasive alternatives to open surgical excision for disc decompression. Automated percutaneous discectomy involves placement of a probe within the intervertebral disc and aspiration of disc material using a suction cutting device. Endoscopic discectomy involves the percutaneous placement of a working channel under image guidance, followed by visualization of the working space and instruments through an endoscope, and aspiration of disc material. Endoscopic discectomy may also be referred to as arthroscopic discectomy.

REGULATORY STATUS

The Stryker DeKompressor® Percutaneous Discectomy Probe (Stryker), Herniatome Percutaneous Discectomy Device (Gallini Medical Devices), and the Nucleotome® (Clarus Medical) are examples of percutaneous discectomy devices that received clearance from the U.S. Food and Drug Administration (FDA) through the 510(k) process. Both have the same labeled intended use, i.e., “for use in aspiration of disc material during percutaneous discectomies in the lumbar, thoracic and cervical regions of the spine.”

A variety of endoscopes and associated surgical instruments have received marketing clearance through the FDA’s 510(k) process.

EVIDENCE SUMMARY

The primary beneficial outcomes of interest for treatment of spinal pain are relief of pain and improved function. Both outcomes are subjective and can be influenced by nonspecific effects, placebo response, and the variable natural history of the disease. Therefore, large, blinded, randomized controlled trials (RCTs) with long-term follow-up are necessary to establish the safety and efficacy of automated percutaneous and percutaneous endoscopic discectomy compared with open surgical discectomy, the current standard of care for surgical removal of damaged intervertebral disc material. These comparisons are necessary to determine whether any beneficial treatment effects of percutaneous and endoscopic discectomy outweigh any risks and provide a significant advantage over conventional open discectomy techniques.

AUTOMATED PERCUTANEOUS DISCECTOMY (APD)

Systematic Reviews

Several systematic reviews (SRs) have been published since 2007.[1-7] Four comparative trials have been published on APD, two comparing APD to chymopapain chemonucleolysis[8, 9] and two comparing APD to microdiscectomy[10, 11]. These trials suggested that APD produced inferior results to either of the established procedures, though the patient selection criteria may have been inappropriate in the Revel (1993) trial[8]. The authors of the systematic reviews reached similar conclusions, that while there is considerable evidence of efficacy for conventional surgical discectomy, there is insufficient evidence on percutaneous discectomy techniques including APD to draw firm conclusions. “Trials of automated percutaneous discectomy and laser discectomy suggest that clinical outcomes following treatment are at best fair and certainly worse than after microdiscectomy, although the importance of patient selection is acknowledged.[1]” A 2015 network meta-analysis found that percutaneous discectomy was one of the least effective treatment strategies for sciatica of 21 assessed.[12]

The four RCTs reviewed in the SRs had several methodological limitations including small size, high loss to follow-up, inadequate randomization procedure, between-group heterogeneity, and other significant design flaws. For example, the LAPDOG study was initially designed to recruit 330 patients, but only was able to recruit 36 patients for reasons that were not readily apparent to the authors.[11] Of the evaluable 27 patients, 41% of the percutaneous discectomy patients and 40% of the conventional discectomy patients were assessed as having successful outcomes at six months. The authors concluded that this trial was unable to enroll sufficient numbers of patients to reach a definitive conclusion. The authors stated, “It is difficult to understand the remarkable persistence of percutaneous discectomy in the face of a virtually complete lack of scientific support for its effectiveness in treated lumbar disc herniation.”

In a 2013 review for their practice guideline[13], the American Society of Interventional Pain Physicians noted that “the available literature on Dekompressor illustrates the common shortcomings of observational studies of interventions. Even though Dekomporssor may be considered a new interventional modality, the early studies were published approximately eight years ago. Consequently, one would expect that the technique’s continued use would be supported by more recent, high quality evaluations. Even though all the studies are of moderate quality, they lack scientific rigor because of their observational, albeit prospective, design. Further, these studies do not include sufficiently large numbers of patients.”

Randomized Controlled Trials

No RCTs were identified after the search dates of the systematic review.

ENDOSCOPIC DISCECTOMY

Systematic Reviews

Li (2022) published a systematic review comparing endoscopic discectomy to non-endoscopic discectomy for the treatment of symptomatic lumbar disc herniation.[14] A total of 25 studies were added, with 20 studies comparing endoscopic discectomy to non-endoscopic discectomy and five studies comparing percutaneous endoscopic transforaminal discectomy (PETD) to percutaneous endoscopic interlaminar discectomy (PEID). Operation time was longer and intraoperative blood loss volume was lower for microendoscopic discectomy (MED) compared to open discectomy. Complication rates were lower for percutaneous endoscopic lumbar discectomy (PELD) compared to fenestration discectomy and also for full-endoscopic discectomy compared to microscopic discectomy. The authors reported that there are some

potential advantages to endoscopic discectomy procedures, however more high quality randomized trials with large sample sizes are needed.

Zhang (2022) published a systematic review comparing percutaneous transforaminal endoscopic discectomy (PTED) to open lumbar discectomy in patients with lumbar disc herniations.[15] Nine studies were included in the review with a total of 1679 patients. There were no significant difference in excellent rates (OR = 1.47, 95% CI: 0.94-2.28, P= 0.09), reoperation rates (OR = 0.96, 95% CI: 0.50-1.84, P = 0.90), length of operation (SMD = -17.97, 95% CI: -54.83-18.89, P = 0.34], and the amount of intraoperative blood loss (SMD = -128.05, 95% CI: -258.67-2.57, P = 0.05), respectively. There were significant differences in complication rates (OR = 0.22, 95% CI: 0.14-0.33, P < 0.001), length of incision (SMD = -2.76, 95%CI: -2.88--2.65, P < 0.001), and length of hospital stay (SMD = -5.19, 95%CI: -5.36--5.01, P < 0.001), respectively. The authors concluded that PTED shows better outcomes for complication rate, incision size, and length of hospital stay compared to standard discectomy, however there was heterogeneity in inclusion criteria, baseline characteristics, and follow-up time in the included studies. Additionally, comparisons for each outcome were not equal and some comparison of outcomes had relatively small numbers of trials.

Zhang (2022) published a systematic review of nine, nonrandomized trials evaluating the safety and efficacy of percutaneous endoscopic cervical discectomy (PECD) in patients with cervical disc herniation.[16] The pooled results demonstration that VAS scores at one week follow-up and at last follow-up (varying times) were significantly lower than baseline VAS scores. The authors also reported pooled results showing decreased operative time and hospital stays for PECD compared to anterior cervical discectomy and fusion (ACDF). There is a need for high quality randomized trials with long-term follow-up and comparison to standard of care procedures, such as ACDF, to establish the clinical utility of PECD in patients with cervical disc herniation.

Zhao (2022) published a systematic review comparing PELD to MED and traditional open surgery for the treatment of lumbar disc herniation.[17] A total of 6467 cases across 33 studies were included in the review which assessed several outcomes such as blood loss, recovery time, VAS for pain, ODI, and revision or recurrence rates. PELD showed superior results compared to MED in some outcomes (e.g., blood loss, postoperative bed time, hospital stay duration), but show inferior results in other outcomes like revision and recurrence rates. Other outcomes were similar across groups including operation times, postoperative VAS for leg pain, and operation success. Additional studies are needed to demonstrate superior efficacy and outcomes for PELD compared to existing standards of care.

Bai (2022) published a systematic review with meta-analysis of 14 studies (N=2,528) comparing PELD to other surgical approaches to lumbar disc herniation (LDH).[18] Outcomes evaluated were success rate, recurrence rate, complication rate, operation time, hospital stay, blood loss, visual analog scale (VAS) score for back pain and leg pain, 12-item Short Form Health Survey (SF12) physical component score and mental component score, Japanese Orthopaedic Association Score, and Oswestry Disability Index. PELD had favorable clinical outcomes for PELD compared to other surgical approaches, including shorter operation time (weight mean difference, WMD=-18.14 minutes, 95% CI -25.24, -11.05; p<0.001) and hospital stay (WMD = -2.59 days, 95% CI -3.87, -1.31; p<0.001), less blood loss (WMD = -30.14 ml, 95% CI -43.16, -17.13; p<0.001), and improved SF12- mental component score (WMD = 2.28, 95% CI 0.50, 4.06; p=0.01) and physical component score (WMD = 1.04, 95% CI 0.37, 1.71; p=0.02). No significant difference between the PELD group and other surgical group was found

in success rate, complication rate, or other clinical outcomes assessed. PELD was associated with a significantly higher rate of recurrent disc herniation (relative risk [RR] = 1.65, 95% CI 1.08, 2.52; p=0.02).

Chen (2020) published a SR with meta-analysis comparing complication rates of surgical treatments of symptomatic lumbar disc herniation which included discectomy/microdiscectomy (OD/MD), MED, PELD, percutaneous laser disc decompression (PLDD), and tubular discectomy.[19] The review included 17 RCTs and 20 cohort studies. Overall complication rates of 16.8% and 16.1%, 21.2%, 5.8%, 8.4%, and 25.8% were found for RCTs evaluating OD/MD, MED, PELD, PLDD, and tubular discectomies, respectively. Moderate-quality evidence was found suggesting that, compared to OD/MD, PELD had a lower risk of overall complications (RR = 0.52, 95% CI 0.29-0.91) and high-quality evidence suggesting a lower risk of Type I complications (RR = 0.37, 95% CI 0.16-0.81). Compared with the data from cohort studies, there was low-quality evidence reported suggesting a higher risk of reherniations (RR = 1.67,95% CI 1.05-2.64) and reoperations (RR = 1.75, 95% CI 1.20-2.55) for PELD compared to OD/MD.

A SR with meta-analysis published by Xu (2020) evaluated mid- and long-term outcomes in single-level lumbar disc herniation treated with PELD or MED.[20] One prospective RCT and eight retrospective nonrandomized comparative studies were included (PELD N=468, MED N=516). Although no difference between groups within 24 months were found, at 24 months postoperative, significantly better outcomes were found in the PELD group compared to MED for low back pain visual analog scale score and Oswestry Disability Index (ODI) score (OR=-0.856, 95% CI -1.488 to -0.224, p=0.008; OR=-0.425, 95% CI -0.724 to -0.127, p=0.005). No significant differences were found in complication, recurrence, or reoperation rates at any timepoint reported.

Yu (2019) compared PTED to MED in a SR of eight comparative studies with a total of 805 patients.[21] Hospital stay, time in bed, incision length were shorter with PTED, but there were not differences between the interventions in surgical time or intraoperative blood loss. Visual Analogue Scale (VAS) back and leg pain scores were similar between groups at most time points, with the exception of lower leg pain VAS score at one week in the PTED group.

A meta-analysis by Alvi (2018) included 14 RCTs or quasi-randomized trials (total n=1,707), and compared OD/MD to minimally invasive procedures including percutaneous discectomy, percutaneous endoscopic discectomy (PED), and tubular discectomy (TD) for lumbar disc herniation.[22] All of the studies were determined to have a serious risk of bias and were judged to be of low or very low quality. No differences were seen between groups for VAS score. ODI score was lower for TD than for other procedures at one year (mean difference 1.17, 95% confidence interval [CI] 0.10 to 2.24, p=0.03), and at last follow-up, ODI scores were worse with OD/MD compared to TD and PED (mean difference 2.61, 95% CI 0.88 to 4.65, p=0.03). Open procedures were also associated with longer hospital stays and greater blood loss. TD was associated with a greater rate of complications and recurrent herniations than the other procedures, while MD/OD had significantly lower rates of recurrent herniations and revision surgery than TD or PED.

A meta-analysis by Ding (2018) compared PTED to fenestration discectomy (FD) in patients with lumbar disc herniation.[23] There were 17 studies included in the analysis, and all were retrospective studies. There were 733 patients who had PTED and 657 who had FD. There was no difference between groups for VAS score, but the PTED group had shorter operation,

bed rest, and hospitalization times (all p<0.00001), less bleeding (p<0.00001), and a lower postoperative ODI score (p=0.02). Long-term outcomes were not assessed in this study.

Phan (2017) published a SR comparing full endoscopic discectomy (FED) and MED with open discectomy for the treatment of lumbar disc herniation.[24] A database search through February 2016 identified 23 studies for inclusion. FED was favorable compared with open discectomy in surgery duration, hospital length of stay (LOS), and blood loss. MED was favorable compared with open discectomy in LOS and blood loss. Both endoscopic procedures were comparable to open discectomy as measured on a VAS for leg pain and ODI score. In terms of patient satisfaction, FED was more favorable than open discectomy and MED was comparable to open discectomy. The authors concluded that FED and MED are safe alternatives to other procedures, but more RCTs are needed to investigate and validate these as options for discectomies.

Li (2016) published a SR comparing FED with traditional discectomy surgery.[25] The search was conducted in January 2015 and resulted in the inclusion of four RCTs and two non-RCTs. FED for herniation (both cervical and lumbar) was favorable compared with traditional discectomy in operative duration, blood loss, length of stay, and return to work days. Clinical outcomes were comparable between FED and traditional discectomy. The authors concluded FED is effective, but larger RCTs with long-term follow-up are needed.

A 2016 meta-analysis identified nine RCTs (total n=1,092 patients) that compared endoscopic to open discectomy for lumbar disc herniation.[26] Endoscopic discectomy resulted in clinical outcomes similar to open discectomy, but had significantly greater patient satisfaction, lower intraoperative blood loss, and shorter hospital lengths of stay.

He (2016) reported results from another meta-analysis of five RCTs (n=501 patients) comparing outcomes from MED and open discectomy for patients with lumbar herniation.[27] Pooled analysis found no difference in VAS, ODI, or complication between the two groups. MED was associated with less blood loss, shorter length of hospital stay, and longer operation time.

A Cochrane review (2014) of literature through 2013 evaluated 11 studies of minimally invasive discectomy compared with microdiscectomy/open discectomy. Seven of the studies reviewed[10, 28-33] were rated as having a high risk of bias and the remaining four studies[34-37] were rated as having a low risk of bias. Included in the review were eight RCTs or quasi-RCTs that evaluated percutaneous endoscopic lumbar discectomy.[38] Also included were three studies on transmuscular tubular microdiscectomy and automated percutaneous lumbar discectomy. The review concluded that minimally invasive discectomy may be inferior in terms of relief of leg pain, low back pain, and rehospitalization; however, differences in pain relief appeared to be small and may not be clinically important. In addition, potential advantages of minimally invasive discectomy are a lower risk of surgical site infection and shorter hospital stay. Because of these potential advantages, the authors concluded that more research was needed to define the indications for minimally invasive discectomy.

Smith (2013) published a SR of MED for lumbar disc herniation.[39] A search was conducted for controlled trials published after the 2007. The Gibson and Waddel (2007) Cochrane review through September 2012 identified four RCTs. None of the studies found a significant difference in ODI scores compared with open discectomy or microdiscectomy. In the largest study, which included 240 patients, Teli (2010) reported an increase in the number of severe complications in the microendoscopic discectomy group.[36] In another large study with 112

patients Garg (2011) found a shorter hospital stay with no significant changes in ODI or complication rates but recommended that microendoscopic discectomy should not be attempted without appropriate training.[28] The two other trials included in the review were small, with 22[29] and 40[30] patients.

Randomized Controlled Trials

The following is a summary of randomized or quasi-randomized trials that were not included in the above systematic reviews.

Cervical disc decompression

Ruetten (2009) compared anterior endoscopic discectomy with anterior cervical discectomy and fusion (ACDF) in 120 patients with mediolateral cervical disc herniations.[40] The duration of pain ranged from 4 to 128 days. The mean operating time was 32 minutes for the endoscopic discectomy compared to 62 minutes for ACDF. In the endoscopic discectomy group, bone resection was required to reach the epidural space or the foramen in 55% of cases. At 24 months, 103 patients (86%) were available for follow-up examinations. The revision rate was 6.1% for ACDF and 7.4% for endoscopic discectomy; these were not significantly different. Excluding four patients who were revised by ACDF, 85 patients (85.9%) had no arm pain; there were no significant differences in clinical outcomes between the two groups. Advantages and disadvantages of the anterior endoscopic approach were discussed, including a difficult learning curve.

Lumbar disc decompression

Gadradj (2022) published the results of a RCT in 613 patients who underwent percutaneous transforaminal endoscopic discectomy (PTED, n=179) or conventional open microdiscectomy (n=309) for the treatment of lumbar disc herniation.[41] The primary outcome was self-reported leg pain measured by a 0-100 visual analogue scale and secondary outcomes included complications, reoperations, self-reported functional status as measured with the Oswestry Disability Index, visual analogue scale (VAS) for back pain, health related quality of life, and self-perceived recovery. At 12 months post-procedure, VAS scores for leg pain were lower in the PTED group (median 7.0, IQR 1.0-30.0) compared to the open microdiscectomy group (16.0, 2.0-53.5) (between group difference 7.1, 95% CI 2.8 to 11.3). Within one year, nine (5%) in the PTED group compared with 14 (6%) in the open microdiscectomy group had repeated surgery. This study was limited by lack of blinding.

Ran (2021) published the results of a RCT in 68 patients with highly migrated lumbar disc herniation who were randomized to computerized tomography (CT) navigation percutaneous spinal endoscopy (n=35) or open discectomy (n=33).[42] Although at one week post-procedure, VAS sores for back pain were significantly lower in the endoscopic group (1.30 ± 1.07 versus 2.44 ± 0.72, p< 0.01), at 12 months post-procedure, VAS scores were not statistically different between groups (0.58 ± 0.90 versus 0.75 ± 0.84, p=0.58). Limitations to the study design include unclear allocation concealment, apparent lack of blinding, and no power calculations reported.

Wang (2019) compared PTED to MED in a trial of 90 patients with lumbar disc herniation at a single center in China.[43] Patients in the PTED group had significantly better surgical and immediate postoperative outcomes (length of surgical incision, bleeding, postoperative bedridden time and hospital stay), while the MED group had shorter surgical time. Both groups

improved from baseline on low back pain VAS scores at three days, three months, and six months. Both groups also improved on ODI scores and there were no differences between groups postoperatively or up to six months after surgery.

Gibson (2017) published a RCT comparing transforaminal endoscopic discectomy (TED) with microdiscectomy.[44] Patients with single-level lumbar prolapse and radiculopathy were randomized to TED under conscious sedation (n=70) or to microdiscectomy under general anesthesia (n=70). Both procedures resulted in comparable improvements in outcomes (ODI scores, VAS back pain, VAS leg pain, SF-36 scores) at three months, one year, and two years compared with baseline. The trial noted limitations including being non-blinded.

Hussein (2014) reported the outcomes of 200 patients randomized to either microendoscopic lumbar discectomy (n=95) or to a control group in which patients underwent open lumbar discectomy (n=90).[45] The patients and investigators were not blinded to the treatment assignments. By eight years follow-up, data was available for 185 patients; 15 patients were lost to follow-up, 10 due to subsequent same-level fusion, three due to death unrelated to surgery, and two who did not response to telephone calls. Relief of leg pain was statistically significant for both groups, with no significant between-group difference. Back pain was significantly improved in the endoscopic group throughout the entire follow-up period. However, in the control group the significant improvement in back pain following surgery deteriorated over time; by eight years follow-up, back pain scores in this group had worsened significantly from preoperative scores. There were no serious complications in either group.

Nonrandomized Studies

Yu (2021) published the results of a retrospective multicenter study that followed patients for two years after receipt of transforaminal percutaneous endoscopic discectomy (n=632) and microendoscopic discectomy (n=421) for lumbar disc herniation.[46] Mean blood loss ($p<0.001$) and mean duration of hospital stay ($p=0.018$) were significantly less with transforaminal percutaneous endoscopic lumbar discectomy compared to microendoscopic discectomy. Rates of complications, recurrence, and revisions were similar in both groups. Visual analogue pain scores did not differ between groups after the first postoperative day. At 1 month postoperatively there was a significant difference in ODI scores between groups ($p=0.016$) in favor of transforaminal percutaneous endoscopic discectomy, but there was no difference at other time points.

Song (2021) published a retrospective single-center study that compared percutaneous endoscopic lumbar discectomy (n=306) and microendoscopic discectomy (n=116) in patients undergoing same day ambulatory surgery for lumbar disc herniation.[47] Mean blood loss and mean duration of hospital stay were significantly less with percutaneous endoscopic lumbar discectomy (both $p<0.001$ compared to microendoscopic discectomy). After three years of follow-up, visual analogue pain scores for the back were also significantly lower in the percutaneous endoscopic lumbar discectomy group compared to the microendoscopic discectomy group ($p=.001$) but there was no difference between groups in pain scores for the legs ($p=0.224$). Overall recurrence rates ($p=0.201$) and ODI scores ($p=0.220$) were also similar between groups.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS (ASIPP)[13]

In 2013, a task force of the ASIPP published updated guidelines for interventional techniques in the management of chronic spinal pain. The evidence for APD and for percutaneous lumbar discectomy was rated as limited for short- and long-term relief based on all observational studies. An evidence rating of “limited” is defined as evidence insufficient to assess effects on health outcomes because of limited number or inadequate power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or execution, gaps in the chain of evidence, or lack of information on important health outcomes. The ASIPP concluded that this technique may be performed when indicated, but did not provide patient selection criteria. Nor was the recommendation graded; the authors indicated only that this recommendation was based on “individual experience and the large amount of literature.” Therefore, this recommendation is not considered evidence-based.

NORTH AMERICAN SPINE SOCIETY (NASS)[48]

The 2014 practice guidelines from the NASS on the diagnosis and treatment of lumbar disc herniation with radiculopathy recommended that endoscopic percutaneous discectomy or automated percutaneous discectomy could be considered for the treatment of these patients. Both recommendations were grade C recommendations (poor quality evidence). However, a separate recommendation stated that evidence is insufficient to recommend for or against use of automated percutaneous discectomy compared with open discectomy.

THE AMERICAN SOCIETY OF PAIN AND NEUROSCIENCE (ASPN)[49]

ASPN (2022) published clinical guidance for interventional treatments for low back pain. The guideline states that discectomy procedures (such as percutaneous and endoscopic disc procedures) have favorable safety and efficacy profiles for the treatment of lumbar disc herniation with persistent radicular symptoms; however, it is stated that further research is needed to evaluate complications rates in order for these procedures to supplant classic open microdiscectomy.

SUMMARY

There is not enough research to show that automated percutaneous or percutaneous endoscopic discectomy improves health outcomes for people with back pain and/or radiculopathy related to disc herniation in the lumbar, thoracic, or cervical spine. Therefore, automated percutaneous or percutaneous endoscopic discectomy is considered investigational for people with back pain and/or radiculopathy related to disc herniation in the lumbar, thoracic, or cervical spine.

REFERENCES

1. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse. *Cochrane Database Syst Rev.* 2007(2):CD001350. PMID: 17443505
2. Freeman BJ, Mehdian R. Intradiscal electrothermal therapy, percutaneous discectomy, and nucleoplasty: what is the current evidence? *Curr Pain Headache Rep.* 2008;12(1):14-21. PMID: 18417018

3. Hirsch JA, Singh V, Falco FJ, et al. Automated percutaneous lumbar discectomy for the contained herniated lumbar disc: a systematic assessment of evidence. *Pain Physician.* 2009;12(3):601-20. PMID: 19461826
4. Singh V, Benyamin RM, Datta S, et al. Systematic review of percutaneous lumbar mechanical disc decompression utilizing Dekompressor. *Pain Physician.* 2009;12(3):589-99. PMID: 19461825
5. Vorobeychik Y, Gordin V, Fuzaylov D, et al. Percutaneous mechanical disc decompression using Dekompressor device: an appraisal of the current literature. *Pain Med.* 2012;13(5):640-6. PMID: 22494347
6. Manchikanti L, Singh V, Calodney AK, et al. Percutaneous lumbar mechanical disc decompression utilizing Dekompressor(R): an update of current evidence. *Pain Physician.* 2013;16(2 Suppl):SE1-24. PMID: 23615884
7. Manchikanti L, Singh V, Falco FJ, et al. An updated review of automated percutaneous mechanical lumbar discectomy for the contained herniated lumbar disc. *Pain Physician.* 2013;16(2 Suppl):SE151-84. PMID: 23615890
8. Revel M, Payan C, Vallee C, et al. Automated percutaneous lumbar discectomy versus chemonucleolysis in the treatment of sciatica. A randomized multicenter trial. *Spine (Phila Pa 1976).* 1993;18(1):1-7. PMID: 8434309
9. Krugluger J, Knahr K. Chemonucleolysis and automated percutaneous discectomy--a prospective randomized comparison. *Int Orthop.* 2000;24(3):167-9. PMID: 10990391
10. Chatterjee S, Foy PM, Findlay GF. Report of a controlled clinical trial comparing automated percutaneous lumbar discectomy and microdiscectomy in the treatment of contained lumbar disc herniation. *Spine (Phila Pa 1976).* 1995;20(6):734-8. PMID: 7604351
11. Haines SJ, Jordan N, Boen JR, et al. Discectomy strategies for lumbar disc herniation: results of the LAPDOG trial. *J Clin Neurosci.* 2002;9(4):411-7. PMID: 12217670
12. Lewis RA, Williams NH, Sutton AJ, et al. Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses. *The spine journal : official journal of the North American Spine Society.* 2015;15(6):1461-77. PMID: 24412033
13. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain Physician.* 2013;16(2 Suppl):S49-283. PMID: 23615883
14. Li WS, Yan Q, Cong L. Comparison of Endoscopic Discectomy Versus Non-Endoscopic Discectomy for Symptomatic Lumbar Disc Herniation: A Systematic Review and Meta-Analysis. *Global Spine J.* 2022;12(5):1012-26. PMID: 34402320
15. Zhang J, Gao Y, Zhao B, et al. Comparison of percutaneous transforaminal endoscopic discectomy and open lumbar discectomy for lumbar disc herniations: A systematic review and meta-analysis. *Front Surg.* 2022;9:984868. PMID: 36439526
16. Zhang J, Zhou Q, Yan Y, et al. Efficacy and safety of percutaneous endoscopic cervical discectomy for cervical disc herniation: a systematic review and meta-analysis. *J Orthop Surg Res.* 2022;17(1):519. PMID: 36456964
17. Zhao XM, Chen AF, Lou XX, et al. Comparison of Three Common Intervertebral Disc Discectomies in the Treatment of Lumbar Disc Herniation: A Systematic Review and Meta-Analysis Based on Multiple Data. *J Clin Med.* 2022;11(22). PMID: 36431083
18. Bai X, Lian Y, Wang J, et al. Percutaneous endoscopic lumbar discectomy compared with other surgeries for lumbar disc herniation: A meta-analysis. *Medicine (Baltimore).* 2021;100(9):e24747. PMID: 33655938

19. Chen X, Chamoli U, Vargas Castillo J, et al. Complication rates of different discectomy techniques for symptomatic lumbar disc herniation: a systematic review and meta-analysis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2020;29:1752-70. PMID: 32274586
20. Xu J, Li Y, Wang B, et al. Minimum 2-Year Efficacy of Percutaneous Endoscopic Lumbar Discectomy versus Microendoscopic Discectomy: A Meta-Analysis. *World neurosurgery.* 2020;138:19-26. PMID: 32109644
21. Yu P, Qiang H, Zhou J, et al. Percutaneous Transforaminal Endoscopic Discectomy versus Micro-Endoscopic Discectomy for Lumbar Disc Herniation. *Medical science monitor : international medical journal of experimental and clinical research.* 2019;25:2320-28. PMID: 30927349
22. Alvi MA, Kerezoudis P, Wahood W, et al. Operative Approaches for Lumbar Disc Herniation: A Systematic Review and Multiple Treatment Meta-Analysis of Conventional and Minimally Invasive Surgeries. *World neurosurgery.* 2018;114:391-407 e2. PMID: 29548960
23. Ding W, Yin J, Yan T, et al. Meta-analysis of percutaneous transforaminal endoscopic discectomy vs. fenestration discectomy in the treatment of lumbar disc herniation. *Der Orthopade.* 2018;47(7):574-84. PMID: 29404628
24. Phan K, Xu J, Schultz K, et al. Full-endoscopic versus micro-endoscopic and open discectomy: A systematic review and meta-analysis of outcomes and complications. *Clinical neurology and neurosurgery.* 2017;154:1-12. PMID: 28086154
25. Li XC, Zhong CF, Deng GB, et al. Full-Endoscopic Procedures Versus Traditional Discectomy Surgery for Discectomy: A Systematic Review and Meta-analysis of Current Global Clinical Trials. *Pain Physician.* 2016;19(3):103-18. PMID: 27008284
26. Cong L, Zhu Y, Tu G. A meta-analysis of endoscopic discectomy versus open discectomy for symptomatic lumbar disk herniation. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2016;25(1):134-43. PMID: 25632840
27. He J, Xiao S, Wu Z, et al. Microendoscopic discectomy versus open discectomy for lumbar disc herniation: a meta-analysis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2016;25(5):1373-81. PMID: 27001138
28. Garg B, Nagraja UB, Jayaswal A. Microendoscopic versus open discectomy for lumbar disc herniation: a prospective randomised study. *J Orthop Surg (Hong Kong).* 2011;19(1):30-4. PMID: 21519072
29. Huang TJ, Hsu RW, Li YY, et al. Less systemic cytokine response in patients following microendoscopic versus open lumbar discectomy. *J Orthop Res.* 2005;23:406-11. PMID: 15734255
30. Righesso O, Falavigna A, Avanzi O. Comparison of open discectomy with microendoscopic discectomy in lumbar disc herniations: results of a randomized controlled trial. *Neurosurgery.* 2007;61:545-9; discussion 49. PMID: 17881967
31. Ruetten S, Komp M, Merk H, et al. Full-endoscopic cervical posterior foraminotomy for the operation of lateral disc herniations using 5.9-mm endoscopes: a prospective, randomized, controlled study. *Spine (Phila Pa 1976).* 2008;33:940-8. PMID: 18427313
32. Mayer HM, Brock M. Percutaneous endoscopic discectomy: surgical technique and preliminary results compared to microsurgical discectomy. *J Neurosurg.* 1993;78(2):216-25. PMID: 8267686

33. Ryang YM, Oertel MF, Mayfrank L, et al. Standard open microdiscectomy versus minimal access trocar microdiscectomy: results of a prospective randomized study. *Neurosurgery.* 2008;62:174-81; discussion 81-2. PMID: 18300905
34. Arts M, Brand R, van der Kallen B, et al. Does minimally invasive lumbar disc surgery result in less muscle injury than conventional surgery? A randomized controlled trial. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2011;20(1):51-7. PMID: 20556439
35. Hermantin FU, Peters T, Quartararo L, et al. A prospective, randomized study comparing the results of open discectomy with those of video-assisted arthroscopic microdiscectomy. *J Bone Joint Surg Am.* 1999;81(7):958-65. PMID: 10428127
36. Teli M, Lovi A, Brayda-Bruno M, et al. Higher risk of dural tears and recurrent herniation with lumbar micro-endoscopic discectomy. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2010;19(3):443-50. PMID: 20127495
37. Shin DA, Kim KN, Shin HC, et al. The efficacy of microendoscopic discectomy in reducing iatrogenic muscle injury. *Journal of neurosurgery Spine.* 2008;8(1):39-43. PMID: 18173345
38. Rasouli MR R-MV, Shokraneh F, et al. . Minimally invasive discectomy versus microdiscectomy/open discectomy for symptomatic lumbar disc herniation. *Cochrane Database Syst Rev 2014 CD010328.* 2014. PMID: 25184502
39. Smith N, Masters J, Jensen C, et al. Systematic review of microendoscopic discectomy for lumbar disc herniation. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2013;22(11):2458-65. PMID: 23793558
40. Ruetten S, Komp M, Merk H, et al. Full-endoscopic anterior decompression versus conventional anterior decompression and fusion in cervical disc herniations. *Int Orthop.* 2009;33(6):1677-82. PMID: 19015851
41. Gadjradj PS, Rubinstein SM, Peul WC, et al. Full endoscopic versus open discectomy for sciatica: randomised controlled non-inferiority trial. *BMJ.* 2022;376:e065846. PMID: 35190388
42. Ran B, Wei J, Yang J, et al. Quantitative Evaluation of the Trauma of CT Navigation PELD and OD in the Treatment of HLDH: A Randomized, Controlled Study. *Pain Physician.* 2021;24(4):E433-E41. PMID: 34213868
43. Wang F, Guo D, Sun T, et al. A comparative study on short-term therapeutic effects of percutaneous transforaminal endoscopic discectomy and microendoscopic discectomy on lumbar disc herniation. *Pakistan journal of medical sciences.* 2019;35(2):426-31. PMID: 31086527
44. Gibson JNA, Subramanian AS, Scott CEH. A randomised controlled trial of transforaminal endoscopic discectomy vs microdiscectomy. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2017;26(3):847-56. PMID: 27885470
45. Hussein M, Abdeldayem A, Mattar MM. Surgical technique and effectiveness of microendoscopic discectomy for large uncontained lumbar disc herniations: a prospective, randomized, controlled study with 8 years of follow-up. *European spine journal : official publication of the European Spine Society, the European Spinal*

Deformity Society, and the European Section of the Cervical Spine Research Society. 2014. PMID: 24736930
46. Yu P, Zan P, Zhang X, et al. Comparison of Percutaneous Transforaminal Endoscopic Discectomy and Microendoscopic Discectomy for the Surgical Management of Symptomatic Lumbar Disc Herniation: A Multicenter Retrospective Cohort Study with a Minimum of 2 Years' Follow-Up. *Pain Physician.* 2021;24(1):E117-e25. PMID: 33400445
47. Song Z, Ran M, Luo J, et al. Follow-up results of microendoscopic discectomy compared to day surgery using percutaneous endoscopic lumbar discectomy for the treatment of lumbar disc herniation. *BMC Musculoskelet Disord.* 2021;22(1):160. PMID: 33563264
48. North American Spine Society. Clinical guidelines for the diagnosis and treatment of lumbar disc herniation with radiculopathy. 2012. [cited 8/22/2023]. 'Available from:' https://www.spine.org/Documents/ResearchClinicalCare/Guidelines/LumbarDiscHerniation.pdf.
49. Sayed D, Grider J, Strand N, et al. The American Society of Pain and Neuroscience (ASPN) Evidence-Based Clinical Guideline of Interventional Treatments for Low Back Pain. *J Pain Res.* 2022;15:3729-832. PMID: 36510616

CODES

NOTE: CPT code 62287 specifically describes a percutaneous aspiration or decompression procedure of the lumbar spine. This code does not distinguish between an aspiration procedure (addressed in this policy) and a laser decompression procedure (addressed in separate medical policies). Also, note that this code is specifically limited to the lumbar region. Although the majority of percutaneous discectomies are performed on lumbar vertebrae, the FDA labeling of the Stryker DeKompressor Percutaneous Discectomy Probe includes the thoracic and cervical vertebrae.

Codes	Number	Description
CPT	62287	Decompression procedure, percutaneous, of nucleus pulposus of intervertebral disk, any method utilizing needle based technique to remove disc material under fluoroscopic imaging or other form of indirect visualization, with discography and/or epidural injection(s) at the treated level(s), when performed, single or multiple levels, lumbar
	62380	Endoscopic decompression of spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of herniated intervertebral disc, 1 interspace, lumbar
	64999	Unlisted procedure; nervous system
HCPCS	C2614	Probe, percutaneous lumbar discectomy

Date of Origin: *October 2005*

Regence

Medical Policy Manual Surgery, Policy No. 147

Ovarian, Internal Iliac, and Gonadal Vein Embolization, Ablation, and Sclerotherapy

Effective: July 1, 2023

Next Review: April 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Embolization involves occlusion of blood flow through the ovarian, internal iliac, and gonadal veins with coils, foam, or a chemical sclerosant as a treatment of pelvic congestion syndrome or varicoceles.

MEDICAL POLICY CRITERIA

Note: This policy does not address surgical ligation of the spermatic vein(s) or uterine artery embolization.

Embolization, ablation, and sclerotherapy of ovarian veins, internal iliac veins, or gonadal veins is considered **investigational** for the treatment of pelvic congestion syndrome and varicoceles.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Varicose Vein Treatment, Surgery, Policy No. 104

BACKGROUND

Enlarged ovarian and internal iliac veins can lead to pelvic congestion syndrome in women, and enlarged gonadal and internal iliac veins can lead to a varicoceles in men. Each are discussed separately below.

PELVIC CONGESTION SYNDROME

Pelvic congestion syndrome (PCS), also called pelvic venous incompetence, is a rare condition characterized by chronic pelvic pain. Although this condition is primarily found in women it can also be found in men. PCS is often aggravated by standing for long periods of time, and often manifests during or after pregnancy. The syndrome is thought to be associated with dilated and refluxing incompetent pelvic veins, similar to what happens in varicose veins of the legs. However, the cause of PCS is unclear. Furthermore, there are no definitive diagnostic criteria for PCS. Instead the diagnosis is generally based on a combination of symptoms, tenderness on physical exam, and documentation of pelvic vein dilation or incompetence after excluding all other causes for the nonspecific findings. Although imaging may show vein dilation or incompetence, these findings are common nonspecific findings and therefore no diagnostic.

There is no standard treatment approach for PCS, and the optimum treatment is unknown. Instead, therapy is individualized and based on symptoms. Medical therapy is generally the first line of treatment, as it is low risk and non-invasive. Other methods, such as embolization has been proposed as an alternative to surgical treatment for patients who fail medical therapy with analgesics. Embolization therapy involves the occlusion of blood flow through the ovarian and internal iliac veins with coils, glue, or chemical sclerosants. The internal iliac veins may be treated at the same time or a later date to prevent recurrence.

VARICOCELES

A varicocele is the dilation of the pampiniform plexus of the gonadal veins. Varicocele's are present in 15 to 20% of post-pubertal males, and generally get larger over time. Most varicoceles occur in the left hemiscrotum because the left gonadal vein is one of the longest veins in the body and it enters the left renal vein at a perpendicular angle increasing pressure which can dilate the veins and cause incompetence of the valves, similar to what happens in varicose veins of the legs. Although varicoceles on the left are more common, bilateral varicoceles can occur; however, this could be caused by a possible underlying pathology warranting more investigation. Symptoms of a varicocele include dull, aching, left scrotal pain, which is often aggravated by standing for long periods of time, testicular atrophy, and decreased fertility. Although there are no clear guidelines regarding the established treatment for varicoceles, surgical ligation is the preferred first-line treatment.

EVIDENCE SUMMARY

The primary beneficial outcomes of interest for treatments of pelvic pain in both men and woman are symptom reduction and improvement in the ability to function. These are subjective outcomes that are typically associated with a placebo effect. Therefore, data from adequately powered, randomized controlled trials (RCTs) with sufficient long-term follow-up are required to control for the placebo effect, determine its magnitude, and to determine whether any treatment effect from provides a significant advantage over placebo or other treatment options.

TREATMENT FOR PELVIC CONGESTION SYNDROME

Health Technology Assessments

In 2016, Champaneria published a health technology assessment from the National Institute for Health Research that examined the diagnosis and treatment of pelvic vein incompetence and chronic pelvic pain in women.[1] Forty studies were included in the review; six association studies, ten studies involving ultrasound, two studies involving magnetic resonance venography, 21 case series, and one poor-quality randomized trial of embolization. The authors found that there were no consistent diagnostic criteria for pelvic congestion syndrome (PCS). Although the studies have showed associations between chronic pelvic pain (CPP) and pelvic vein incompetence (PVI), the prevalence of PVI ranged widely. The authors identified that transvaginal ultrasound with doppler and magnetic resonance venography are both useful screening methods; however, there is limited data on the accuracy of these methods for PCS. Finally, although the research showed embolization provides symptomatic relief in the majority of women, these studies were small case series. The authors concluded that more research is needed to determine what the diagnostic criteria for PCS are, and the efficacy of embolization as a treatment for PCS.

Systematic Reviews

Sutanto (2022) published a systematic review to study the efficacy and safety of the use of percutaneous coil embolization (CE) in isolation for pelvic venous reflux (PVR).[2] A total of 970 patients (range, 3-218, 100% female) undergoing isolated ovarian vein or mixed veins embolization from 20 studies were included. Pooled analysis revealed mean improvements of 5.47 points (95% CI, 4.77-6.16) on the visual analogue scale. Common symptoms such as urinary urgency and dyspareunia reported significant improvements of 78-100% and 60-89.5% respectively. Two randomized controlled trials revealed improved clinical outcomes with CE as compared with vascular plugs and hysterectomy. While this data suggests that isolated CE is technically effective and can result in clinical improvement among patients with PVR, further trials are required to ascertain the long-term effects.

A 2016 systematic review by Mahmoud identified 20 case series (total N=1081 patients) who underwent vein embolization for pelvic congestion syndrome.[3] The authors did not require any particular diagnostic criteria for pelvic congestion syndrome. The length of follow-up in the studies ranged from one month to six years. Seventeen studies (n=648 patients) reported the proportion of patients who reported symptom relief. Overall, 571 (88.1%) patients reported short-term symptom relief and 77 (11.9%) reported little or no relief. Seventeen studies (n=721 patients) reported symptom relief at 12 months. A total of 88.6% had symptom improvement and 13.4% reported little or no relief. Only one study used a comparison group, but patients in it received conservative treatment because they were ineligible for vein embolization therapy, so outcomes after the two interventions cannot be compared.

A systematic review by Daniels (2016) assessed the effectiveness of sclerotherapy or embolization for the treatment of chronic pelvic pain.[4] The review included 21 case series and one poor-quality randomized trial. Due to the overall low quality and heterogeneity of the studies, a meta-analysis was not performed. However, the authors reported that approximately 75% of women who underwent embolization experienced early pain relief. Adverse events noted included, transient pain following foam embolization and a small (<2%) risk of coil migration.

In 2015 Hansrani published a systematic review that evaluated the effectiveness of trans-venous occlusion as a treatment of chronic pelvic pain.[5] Thirteen studies were included comprising 866 women. The authors noted that all 13 studies were of poor methodological quality, and most studies did not use objective outcome measures or have consistent follow-up of outcomes. Studies on embolization for treatment of PCS were rated as poor due to lack of randomization and control groups, unclear patient selection criteria, and heterogeneous outcome measures that did not permit between-study comparison or estimates of overall treatment effects. There was one RCT included in the review, in which embolization resulted in significantly better pain reduction than hysterectomy, but the study also had significant limitations, including but not limited to, the randomization protocol was not described, and the hysterectomy patients (bilateral compared to unilateral salpingo-oophorectomy) were not blinded to their treatment allocation, small sample size limits the ability to rule out the role of chance as an explanation of study findings, and a discrepancy between reported outcomes in text and data tables. The authors recommended that more high quality studies are needed that compare embolization, with other treatments, including surgical treatments, hormonal therapy, and other noninvasive treatments.

Randomized Controlled Trials

A randomized, prospective trial by Guirola (2018) compared the safety and efficacy of embolization with vascular plugs (VP) or fibered platinum coils (FPC) in women with pelvic congestion syndrome.[6] Patients were enrolled (N=100) and randomly assigned to each treatment group via block randomization (N=50). Diagnosis of pelvic congestion syndrome was accomplished through a symptom screening questionnaire followed by an ultrasound study. Patients with 3 or more positive symptom responses advanced to the ultrasound screening, and patients with pelvic veins >6 mm in diameter and/or venous reflux or dilated midline communicating veins were advanced to randomization. Follow-up screening occurred at 1, 3, 6, and 12 months. The primary outcome was clinical success assessed subjectively through patient responses regarding relief of symptoms and pain scores assessed with the visual analog scale. Clinical success was achieved in 89.7% of the FPC group and 90.6% of the VP group. Improvement in visual analog scale pain scores at the end of 12 months was 90.2% overall and improvement was seen in 95.9% of the FPC group and 96% of the VP group. A total of 11 (22%) complications were seen in the FPC group and 5 (10%) in the VP group. Minor adverse events included access site hematoma and ovarian vein extravasation. Device migrations were considered major complications. A major limitation in the study is the significant difference in age and pre-treatment visual analog scale pain score between groups, both of which were higher in the VP group despite randomization.

Nonrandomized Studies

The remainder of the published literature regarding the clinical outcomes of embolization therapy consists of nonrandomized studies, case series, and retrospective reviews.[7-29] Collectively, conclusions concerning safety and effectiveness cannot be reached from these studies due to significant limitations in the data, including but not limited to:

- Lack of established diagnostic criteria for pelvic congestion syndrome. Without consistent criteria for patient selection it is unknown which patients are most likely to benefit, or not benefit, from treatment. Furthermore, it is unknown how results from the various case series can be applied to the overall population of patients with this condition.

- Lack of randomization and comparison groups. Failure to randomize patients to different treatment groups may introduce bias on the part of both the study participant and researchers in favor of the new technology. As noted above, for pain treatments, a comparator (preferably sham treatment) is necessary, in order to guard against this bias and to distinguish treatment from placebo effects.
- Retrospective design and failure to control for other treatments. Retrospective study designs do not allow for control of co-treatments or confounding factors that may influence results. This design may also introduce bias to interpretation of results. Control for additional factors, such as other medical therapies, is necessary to isolate treatment response to embolization therapy.
- Failure to define relevant study endpoints. Bias may also be introduced by failure to define study endpoints and treatment success prior to commencement of the study.

Adverse Effects

The following adverse effects associated with embolization of the uterine and internal iliac veins, though uncommon, have been reported in the literature.[7, 15]

- Embolization of coils to the pulmonary circulation
- Embolization of coils to the renal circulation
- Accidental embolization of glue fragments
- Perforations of the ovarian vein with extravasation of contrast
- Transient cardiac arrhythmia

Treatment of Varicoceles

Systematic Reviews

Belczak (2021) published a systematic review regarding semen parameter improvement after varicocele coil embolization.[30] There were six retrospective studies and two observational studies included involving 701 patients where semen concentration and motility were the primary outcomes. The authors concluded that semen concentration was improved significantly in all five studies using that outcome and semen motility was significantly improved in seven studies. This review is limited by a small number of studies and no randomized or comparative studies being included.

In 2012 Kroese published results from a systematic review and meta-analysis that examined the effect of treatment, surgery or embolization, for varicoceles in subfertile men.[31] Ten studies were included in the review, which comprised 894 men. The authors concluded that there is evidence to suggest treatment improves a couple’s chance of pregnancy; however, findings are inconclusive. Furthermore, the available evidence is of low quality and limited to men from couples with subfertility problems. Therefore further research is needed to determine the efficacy of treatment, surgery or embolization, for the treatment of varicoceles.

Randomized-Controlled Trials

No randomized controlled trials have been published comparing embolization therapy for the treatment of varicoceles to an alternative or sham/placebo treatment. Randomized controlled trials are especially needed in situations such as this where the primary symptom is pain, a subjective outcome for which a placebo response to treatment is likely.

Nonrandomized studies

The remainder of the published literature regarding the clinical outcomes of embolization therapy consists of case series and retrospective reviews.[32-49] Collectively, conclusions concerning safety and effectiveness cannot be reached from these studies due to significant limitations in the data.

PRACTICE GUIDELINE SUMMARY

PELVIC CONGESTION SYNDROME

American Congress of Obstetricians and Gynecologists

No relevant policy positions on embolization for treating pelvic congestion syndrome were identified on the American Congress of Obstetricians and Gynecologists (ACOG) website.[50]

Society for Vascular Surgery (SVS) and the American Venous Forum

The 2011 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) guidelines for the care of patients with varicose veins and associated chronic venous diseases provided a Grade 2B recommendation in favor of coil embolization, plugs, or transcatheter sclerotherapy for treatment of PCS. A Grade 2B recommendation is defined as a weak recommendation based on medium quality evidence.[51]

SUMMARY

There is not enough research to show that embolization, ablation, or sclerotherapy improves long term health outcomes for people with pelvic congestion syndrome or varicoceles, compared to other forms of therapy. Therefore, embolization, ablation, or sclerotherapy of ovarian veins, internal iliac veins, or gonadal veins are considered investigational for the treatment of pelvic congestion syndrome or varicoceles.

REFERENCES

1. Champaneria R, Shah L, Moss J, et al. The relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness. *Health Technol Assess.* 2016;20(5):1-108. PMID: 26789334
2. Sutanto SA, Tan M, Onida S, et al. A systematic review on isolated coil embolization for pelvic venous reflux. *Journal of vascular surgery Venous and lymphatic disorders.* 2022;10(1):224-32 e9. PMID: 34358670
3. Mahmoud O, Vikatmaa P, Aho P, et al. Efficacy of endovascular treatment for pelvic congestion syndrome. *Journal of vascular surgery Venous and lymphatic disorders.* 2016;4(3):355-70. PMID: 27318059
4. Daniels JP, Champaneria R, Shah L, et al. Effectiveness of Embolization or Sclerotherapy of Pelvic Veins for Reducing Chronic Pelvic Pain: A Systematic Review. *J Vasc Interv Radiol.* 2016;27(10):1478-86 e8. PMID: 27397619
5. Hansrani V, Abbas A, Bhandari S, et al. Trans-venous occlusion of incompetent pelvic veins for chronic pelvic pain in women: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2015;185:156-63. PMID: 25590499

6. Guirola JA, Sánchez-Ballestin M, Sierre S, et al. A Randomized Trial of Endovascular Embolization Treatment in Pelvic Congestion Syndrome: Fibered Platinum Coils versus Vascular Plugs with 1-Year Clinical Outcomes. *J Vasc Interv Radiol.* 2018;29(1):45-53. PMID: 29174618
7. Maleux G, Stockx L, Wilms G, et al. Ovarian vein embolization for the treatment of pelvic congestion syndrome: long-term technical and clinical results. *J Vasc Interv Radiol.* 2000;11(7):859-64. PMID: 10928522
8. Venbrux AC, Chang AH, Kim HS, et al. Pelvic congestion syndrome (pelvic venous incompetence): impact of ovarian and internal iliac vein embolotherapy on menstrual cycle and chronic pelvic pain. *J Vasc Interv Radiol.* 2002;13(2 Pt 1):171-8. PMID: 11830623
9. Sichlau MJ, Yao JS, Vogelzang RL. Transcatheter embolotherapy for the treatment of pelvic congestion syndrome. *Obstet Gynecol.* 1994;83(5 Pt 2):892-6. PMID: 8159389
10. Venbrux AC, Lambert DL. Embolization of the ovarian veins as a treatment for patients with chronic pelvic pain caused by pelvic venous incompetence (pelvic congestion syndrome). *Curr Opin Obstet Gynecol.* 1999;11(4):395-9. PMID: 10498026
11. Tarazov PG, Prozorovskij KV, Ryzhkov VK. Pelvic pain syndrome caused by ovarian varices. Treatment by transcatheter embolization. *Acta Radiol.* 1997;38(6):1023-5. PMID: 9394662
12. Cordts PR, Eclavea A, Buckley PJ, et al. Pelvic congestion syndrome: early clinical results after transcatheter ovarian vein embolization. *J Vasc Surg.* 1998;28(5):862-8. PMID: 9808854
13. Kim HS, Malhotra AD, Rowe PC, et al. Embolotherapy for pelvic congestion syndrome: long-term results. *J Vasc Interv Radiol.* 2006;17(2 Pt 1):289-97. PMID: 16517774
14. Kwon SH, Oh JH, Ko KR, et al. Transcatheter ovarian vein embolization using coils for the treatment of pelvic congestion syndrome. *Cardiovasc Intervent Radiol.* 2007;30(4):655-61. PMID: 17468903
15. Creton D, Hennequin L, Kohler F, et al. Embolisation of symptomatic pelvic veins in women presenting with non-saphenous varicose veins of pelvic origin - three-year follow-up. *Eur J Vasc Endovasc Surg.* 2007;34(1):112-7. PMID: 17336555
16. Gandini R, Chiocchi M, Konda D, et al. Transcatheter foam sclerotherapy of symptomatic female varicocele with sodium-tetradecyl-sulfate foam. *Cardiovasc Intervent Radiol.* 2008;31(4):778-84. PMID: 18172712
17. Tropeano G, Di Stasi C, Amoroso S, et al. Ovarian vein incompetence: a potential cause of chronic pelvic pain in women. *Eur J Obstet Gynecol Reprod Biol.* 2008;139(2):215-21. PMID: 18313828
18. Pieri S, Agresti P, Morucci M, et al. Percutaneous treatment of pelvic congestion syndrome. *Radiol Med.* 2003;105(1-2):76-82. PMID: 12700549
19. Capasso P, Simons C, Trotteur G, et al. Treatment of symptomatic pelvic varices by ovarian vein embolization. *Cardiovasc Intervent Radiol.* 1997;20(2):107-11. PMID: 9030500
20. Asciutto G, Asciutto KC, Mumme A, et al. Pelvic venous incompetence: reflux patterns and treatment results. *Eur J Vasc Endovasc Surg.* 2009;38(3):381-6. PMID: 19574069
21. van der Vleuten CJ, van Kempen JA, Schultze-Kool LJ. Embolization to treat pelvic congestion syndrome and vulval varicose veins. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2012;118(3):227-30. PMID: 22727416
22. Edo Prades MA, Ferrer Puchol MD, Esteban Hernandez E, et al. Pelvic congestion syndrome: outcome after embolization with coils. *Radiologia.* 2012. PMID: 22633116

23. Meneses L, Fava M, Diaz P, et al. Embolization of incompetent pelvic veins for the treatment of recurrent varicose veins in lower limbs and pelvic congestion syndrome. *Cardiovasc Intervent Radiol.* 2013;36(1):128-32. PMID: 22547030
24. Laborda A, Medrano J, de Blas I, et al. Endovascular treatment of pelvic congestion syndrome: visual analog scale (VAS) long-term follow-up clinical evaluation in 202 patients. *Cardiovasc Intervent Radiol.* 2013;36(4):1006-14. PMID: 23456353
25. Nasser F, Cavalcante RN, Affonso BB, et al. Safety, efficacy, and prognostic factors in endovascular treatment of pelvic congestion syndrome. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* 2014;125(1):65-8. PMID: 24486124
26. Hocquelet A, Le Bras Y, Balian E, et al. Evaluation of the efficacy of endovascular treatment of pelvic congestion syndrome. *Diagnostic and interventional imaging.* 2014;95(3):301-6. PMID: 24183954
27. Siqueira FM, Monsignore LM, Rosa ESJC, et al. Evaluation of embolization for periuterine varices involving chronic pelvic pain secondary to pelvic congestion syndrome. *Clinics (Sao Paulo, Brazil).* 2016;71(12):703-08. PMID: 28076514
28. Pyra K, Wozniak S, Drelich-Zbroja A, et al. Evaluation of Effectiveness of Embolization in Pelvic Congestion Syndrome with the New Vascular Occlusion Device (ArtVentive EOS): Preliminary Results. *Cardiovasc Intervent Radiol.* 2016;39(8):1122-7. PMID: 27250353
29. Gavrilov SG, Sazhin A, Krasavin G, et al. Comparative analysis of the efficacy and safety of endovascular and endoscopic interventions on the gonadal veins in the treatment of pelvic congestion syndrome. *Journal of vascular surgery Venous and lymphatic disorders.* 2021;9(1):178-86. PMID: 32464289
30. Belczak SQ, Stefaniak V, Góes LG, et al. Improvement of semen parameters after coil embolization of varicoceles: a systematic review. *J Vasc Bras.* 2021;20:e20200137. PMID: 34093687
31. Kroese AC, de Lange NM, Collins J, et al. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database Syst Rev.* 2012;10:CD000479. PMID: 23076888
32. Zampieri N, Chironi C, Sulpasso M. Treatment of varicocele with transfemoral retrograde sclero-embolization in pediatric patients under local anesthesia. *Minerva Pediatr.* 2015;67:227-9. PMID: 25018081
33. Bechara CF, Weakley SM, Kougias P, et al. Percutaneous treatment of varicocele with microcoil embolization: comparison of treatment outcome with laparoscopic varicocelectomy. *Vascular.* 2009;17 Suppl 3:S129-36. PMID: 19919803
34. Hawkins CM, Racadio JM, McKinney DN, et al. Varicocele retrograde embolization with boiling contrast medium and gelatin sponges in adolescent subjects: a clinically effective therapeutic alternative. *J Vasc Interv Radiol.* 2012;23(2):206-10. PMID: 22177844
35. Heye S, Maleux G, Wilms G. Pain experience during internal spermatic vein embolization for varicocele: comparison of two cyanoacrylate glues. *European radiology.* 2006;16(1):132-6. PMID: 15999214
36. Kim J, Shin JH, Yoon HK, et al. Persistent or recurrent varicocoele after failed varicocoelectomy: outcome in patients treated using percutaneous transcatheter embolization. *Clin Radiol.* 2012;67(4):359-65. PMID: 22142501
37. Lord DJ, Burrows PE. Pediatric varicocele embolization. *Tech Vasc Interv Radiol.* 2003;6(4):169-75. PMID: 14767848

38. Puche-Sanz I, Flores-Martin JF, Vazquez-Alonso F, et al. Primary treatment of painful varicocoele through percutaneous retrograde embolization with fibred coils. *Andrology.* 2014;2(5):716-20. PMID: 25073877
39. Reiner E, Pollak JS, Henderson KJ, et al. Initial experience with 3% sodium tetradecyl sulfate foam and fibered coils for management of adolescent varicocele. *J Vasc Interv Radiol.* 2008;19(2 Pt 1):207-10. PMID: 18341950
40. Storm DW, Hogan MJ, Jayanthi VR. Initial experience with percutaneous selective embolization: A truly minimally invasive treatment of the adolescent varicocele with no risk of hydrocele development. *Journal of pediatric urology.* 2010;6(6):567-71. PMID: 20149980
41. Urbano J, Cabrera M, Alonso-Burgos A. Sclerosis and varicocele embolization with N-butyl cyanoacrylate: experience in 41 patients. *Acta Radiol.* 2014;55(2):179-85. PMID: 23888063
42. Vanlangenhove P, Everaert K, Van Maele G, et al. Tolerance of glue embolization under local anesthesia in varicoceles: a comparative study of two different cyanoacrylates. *European journal of radiology.* 2014;83(3):559-63. PMID: 24374263
43. Gat Y, Bachar GN, Everaert K, et al. Induction of spermatogenesis in azoospermic men after internal spermatic vein embolization for the treatment of varicocele. *Hum Reprod.* 2005;20(4):1013-7. PMID: 15618245
44. Jargiello T, Drelich-Zbroja A, Falkowski A, et al. Endovascular transcatheter embolization of recurrent postsurgical varicocele: anatomic reasons for surgical failure. *Acta Radiol.* 2015;56(1):63-9. PMID: 24413222
45. Vanlangenhove P, De Keukeleire K, Everaert K, et al. Efficacy and safety of two different n-butyl-2-cyanoacrylates for the embolization of varicoceles: a prospective, randomized, blinded study. *Cardiovasc Intervent Radiol.* 2012;35(3):598-606. PMID: 21638147
46. Keene DJ, Cervellione RM. Antegrade sclerotherapy in adolescent varicocele patients. *Journal of pediatric urology.* 2017. PMID: 28215837
47. Bilreiro C, Donato P, Costa JF, et al. Varicocele embolization with glue and coils: A single center experience. *Diagnostic and interventional imaging.* 2017. PMID: 28185841
48. Paradiso FV, Mason EJ, Nanni L. Antegrade Sclerotherapy to Treat All Types of Varicoceles in the Pediatric Population: Experience of a Single Center. *Urology.* 2016;98:149-53. PMID: 27374731
49. Malekzadeh S, Fraga-Silva RA, Morere PH, et al. Varicocele percutaneous embolization outcomes in a pediatric group: 7-year retrospective study. *International urology and nephrology.* 2016;48(9):1395-9. PMID: 27363981
50. The American Congress of Obstetricians and Gynecologists (ACOG). [cited 04/21/2023]. 'Available from:' http://www.acog.org/.
51. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(5 Suppl):2S-48S. PMID: 21536172

CODES

NOTE: There are no specific codes for ovarian and internal iliac vein embolization; however, the following codes may be used:

Codes	Number	Description
CPT	36012	Selective catheter placement, venous system: second order or more selective, branch (eg, left adrenal vein, petrosal sinus)
	37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
HCPCS	None	

Date of Origin: *October 2005*

Regence

Medical Policy Manual Surgery, Policy No. 153

Balloon Ostial Dilation for Treatment of Sinusitis

Effective: November 1, 2023

Next Review: August 2024
Last Review: September 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Balloon ostial dilation is proposed as a less invasive alternative to traditional endoscopic sinus surgery. In this procedure, a balloon catheter is placed in the opening of the sinus and inflated to widen the opening, allowing for better drainage of secretions.

MEDICAL POLICY CRITERIA

I. The use of a catheter-based inflatable device for the treatment of chronic sinusitis may be considered **medically necessary** when all of the following Criteria are met:

   A. Patient has chronic sinusitis that interferes with lifestyle and has persisted for at least 12 weeks; and

   B. Documentation of abnormal findings from diagnostic evaluation including at least one of the following:

      1. CT findings suggestive of obstruction or infection of the sinus including but not limited to air fluid levels, air bubbles, significant mucosal thickening of greater than 3 mm, pansinusitis, or diffuse opacification documented by a formal CT scan report from an independent radiologist; or

      2. Nasal endoscopy findings suggestive of significant sinus ostial obstruction disease; and

C. Inadequate response to maximal medical therapy that included all of the following:

1. Saline nasal irrigations or saline nasal spray; and
2. Two or more antibiotic courses or one prolonged course of at least 21 days; and
3. A trial of nasal steroids.

II. The use of a catheter-based inflatable device for the treatment of chronic sinusitis is considered **investigational** when Criterion I. is not met.

III. The use of a catheter-based inflatable device for the treatment of recurrent acute rhinosinusitis may be considered **medically necessary** when all of the following Criteria are met:

A. Four or more documented and treated episodes of acute rhinosinusitis over a period of 12 months; and

B. CT findings performed during the fourth episode should demonstrate obstruction or infection of the sinus including but not limited to air fluid levels, air bubbles, significant mucosal thickening of greater than 3 mm, pansinusitis, or diffuse opacification documented by a formal CT scan report from an independent radiologist.

IV. The use of a catheter-based inflatable device for the treatment of recurrent acute rhinosinusitis is considered **investigational** when Criterion III. is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Indication for the requested service
- If indication is chronic rhinosinusitis:
  - Documentation of chronic rhinosinusitis including length of time present and interference with lifestyle;
  - CT and/or nasal endoscopy report;
  - Failure of maximum medical therapy including saline nasal irrigations/nasal spray, two or more antibiotic courses or one minimum 21 day course, and nasal steroid trial.
- If indication is recurrent acute rhinosinusitis:
  - Documentation of four or more documented and treated episodes of acute rhinosinusitis over 12 months;
  - CT report.

CROSS REFERENCES

1. Implantable Sinus Devices for Postoperative Use Following Endoscopic Sinus Surgery and for Recurrent Sinonasal Polyposis, Surgery, Policy No. 198
2. Balloon Dilation of the Eustachian Tube, Surgery, Policy No. 206
3. Cryoablation for Chronic Rhinitis, Surgery, Policy No. 224

BACKGROUND

Balloon ostial dilation (BOD, also known as balloon sinuplasty, balloon catheter dilation, or sinus ostial dilation) for the treatment of sinusitis involves placement and inflation of a balloon catheter within an obstructed frontal, sphenoid, or maxillary sinus ostium. The balloon catheter is placed using transnasal endoscopy, or a transantral approach may be used for direct access to the maxillary sinus. Inflation of the balloon is intended to enlarge the sinus ostium by compressing mucosa and displacing local bony structures. This technique has been used as an alternative or adjunct to functional endoscopic sinus surgery (FESS) which involves surgical excision of the mucosa and bone. When performed in combination with FESS, it is sometimes referred to as a hybrid procedure.

REGULATORY STATUS

In March 2008, the “Relieva Sinus Balloon Catheter” (Acclarent, Menlo Park, CA) device was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in dilating the sinus ostia and paranasal spaces in adults and maxillary sinus spaces in children. Subsequent devices developed by Acclarent have also been granted 510(k) approval. These include the Relieva Spin Sinus Dilation System®, approved in August 2011, and the Relieva Seeker Balloon Sinuplasty System®, approved in November 2012.

In June 2008, the FinESS™ Sinus Treatment (Entellus Medical, Inc, Maple Grove, MN) device was cleared for marketing by the FDA through the 510(k) process. The indication noted is to access and treat the maxillary ostia/ethmoid infundibulum in adults using a transantral approach. The bony sinus outflow tracts are remodeled by balloon displacement of adjacent bone and paranasal sinus structures. Two other balloon sinuplasty devices by Entellus Medical, Inc. also received 510(k) approval in August, 2012. These are the ENTrigue® Sinus Dilation System, and the XprESS® Multi-Sinus Dilation Tool.

In 2013, a sinus dilation system (Medtronic Xomed, Jacksonville, FL), later named the NuVent™ EM Balloon Sinus Dilation System, was cleared for marketing by the FDA through the 510(k) process for use in conjunction with a Medtronic computer-assisted surgery system when surgical navigation or image-guided surgery may be necessary to locate and move tissue, bone, or cartilaginous tissue surrounding the drainage pathways of the frontal, maxillary, or sphenoid sinuses.

Also in 2013, a sinus dilation system (ArthroCare, San Antonio, TX), later named the Ventera™ Sinus Dilation System, was cleared for marketing through the 510(k) process to access and treat the frontal recesses, sphenoid sinus ostia, and maxillary ostia/ethmoid infundibula in adults using a transnasal approach.

EVIDENCE SUMMARY

To determine the benefits and harms of BOD as a stand-alone procedure for the treatment of

sinusitis, it must be compared with standard functional endoscopic sinus surgery (FESS) which involves excision of ostial tissues. Well-designed prospective comparative studies, preferably randomized controlled trials (RCTs), are needed to compare health outcomes between the two procedures and determine whether balloon dilation is as effective and durable as excision.

The most important clinical outcomes to compare for treatment of sinusitis are:

- Symptom relief
- Durability of any beneficial effects
- Adverse event rate and severity
- Rate and type of reoperations including repeat dilation procedures

The focus of this evidence review is on systematic reviews, randomized controlled trials, and nonrandomized comparative trials.

ADULT PATIENTS

Systematic Reviews

Sinha (2023) published a systematic review comparing BOD to FESS which included 18 studies and a subset of seven studies were used to conduct a meta-analysis.[1] The primary outcome was post-operative Sinonasal Outcome Test-20 scores and the pooled difference in means between BOD and FESS was 0.44, which was below the clinically meaningful difference of 0.8 set out in the study. The authors conclude that BOD is an appropriate choice and shows positive outcomes in patients with chronic rhinosinusitis while calling for additional high-quality studies comparing BOD to other treatment options.

Levy (2016) reported on a systematic review and meta-analysis of studies of paranasal BOD for chronic rhinosinusitis.[2] The review included 17 studies, only three of which were RCTs. Two of the RCTs reported on differences in the change in 20-Item Sinonasal Outcome Test (SNOT-20) scores between patients treated with BOD or FESS (n = 110; standard mean difference [SMD] -0.42, 95% CI -1.39 to 0.55, I^2=76%).[3, 4] However, the reviewers found no significant differences in outcome in patients treated with BOD compared to those treated with conventional FESS (p=0.07). The reviewers did report improvements in SNOT-20 score and sinus opacification after BOD, but these conclusions were not drawn from comparative studies, but from five cohort studies.

A BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment was completed in 2012 titled “Balloon Ostial Dilation for Treatment of Chronic Rhinosinusitis”.[5] This Assessment reviewed evidence from one RCT, three non-randomized comparative studies, and nine case series. The following conclusions were made concerning the adequacy of this evidence for determining the effect of balloon sinuplasty on health outcomes:

> “The evidence is insufficient to determine the effect of the technology on health outcomes. One randomized clinical trial comparing balloon sinuplasty to FESS was inadequately powered and did not evaluate differences in outcomes between the two treatments. While most nonrandomized comparative studies of balloon sinuplasty and FESS show no difference in health outcomes between the two treatments, confounding factors may bias the comparison of the two treatments. Several case series show improvement in symptoms of rhinosinusitis over baseline measures, and such improvement appears durable up to 2 years. Case series do not allow conclusions

regarding the comparative efficacy of balloon sinuplasty to FESS."

A 2011 Cochrane systematic review on balloon sinuplasty for chronic rhinosinusitis concentrated on RCTs.[6] One small RCT[7] met the inclusion criteria. Patients were randomized to a "hybrid approach" that included balloon sinuplasty of the affected frontal recess along with traditional FESS of other paranasal sinuses (n = 16), or to traditional FESS (n = 16). At 12-months follow-up, both groups reported improvements in symptoms, but there were no significant differences between the two groups. The authors of the Cochrane review rated this study as having a low risk for bias for most parameters, but a high risk for bias in reporting of the outcomes. Specifically, symptom scores were not presented systematically and details of statistical testing were not reported. The overall conclusion of this review was that there is no convincing evidence supporting the use of balloon sinuplasty in chronic rhinosinusitis (CRS).

Batra (2011) performed a comprehensive review of the literature regarding balloon catheter technology (BCT) in rhinology.[8] The authors noted significant study design flaws in the studies, including lack of comparator group in most, lack of randomization in the single comparative study, unclear selection criteria, and use of patient-reported symptom improvement.

The authors reached the following conclusions:

> "The accrued data attests to its safety, whereas the largest published observational cohort studies have demonstrated the ability to achieve ostia patency for up to 2 years. However, because the selection criteria for these studies were not clearly defined, it is unclear if this data can be extrapolated to the general population with chronic rhinosinusitis (CRS). Is BCT superior or equivalent to the existing devices employed in FESS for the management of CRS? Will the use of BCT translate into improvements in patient outcomes, overall health, and/or quality of life? The many unsettled questions "will be best answered by prospective randomized trials that directly compare FESS to BCT, or directly compare medical to surgical treatment."

Randomized Controlled Trials (RCTs)

The REMODEL Study

The REMODEL (Randomized Evaluation of Maxillary antrostomy versus Ostial Dilation Efficacy through Long-term follow-up) study was an industry-sponsored RCT that compared BOD as a stand-alone procedure with FESS.[4] A total of 105 patients with recurrent acute sinusitis or chronic sinusitis and failure of medical therapy were randomized to BOD or FESS. BOD was performed with the Entellus device, which is labeled for a transantral approach. FESS consisted of maxillary antrostomy and uncinectomy with or without anterior ethmoidectomy. Thirteen patients withdrew consent prior to treatment, 11 in the FESS group (21%) and two in the BOD group (4%). The primary outcomes were the change in the SNOT-20 score at six-month follow-up, and the mean number of debridements performed postoperatively. Secondary outcomes included recovery time, complication rates, and rates of revision surgery. Both superiority and noninferiority analyses were performed on these outcomes.

A total of 91 patients were available at six-month follow-up. The improvement in the SNOT-20 score was 1.67 ± 1.10 in the balloon dilation group and 1.60 ± 0.96 in the FESS arm (p=0.001

for noninferiority). Postoperative debridements were more common in the FESS group compared with balloon dilation (1.2 ± 1.0 vs. 0.1 ± 0.6 in the FESS arm, p<0.001 for superiority). Patients in the balloon dilation arm returned to normal daily activities earlier (1.6 days vs. 4.8 days, p=0.002 for superiority), and required fewer days of prescription pain medications (0.9 days vs. 2.8 days, p=0.002 for superiority). There were no major complications in either group, and one patient in each group required revision surgery. This study was likely to have adequate power to detect group differences; however, there were some methodologic limitations. The study was unblinded and did not have blinded outcome assessment for the symptom-based outcomes or the secondary clinical outcomes. There was also evidence of differential dropout, with larger numbers of patients withdrawing from the FESS group following randomization (21% vs 4%).

Bikhazi (2014) reported one-year outcomes in the REMODEL study. A total of 92 patients (balloon dilation n = 50, FESS n = 42) were treated and 89 (96.7%) completed one-year follow-up.[9] Both groups showed clinically meaningful and statistically significant (p<0.0001) improvement in mean overall SNOT-20 scores and in all four SNOT-20 subscales. Ostial patency was 96.7 and 98.7% after balloon dilation and FESS, respectively, and each group reported significant reductions (p<0.0001) in rhinosinusitis episodes (mean decrease 4.2 for balloon dilation and 3.5 for FESS) during the follow-up period of one year. Overall work productivity and daily activity impairment due to chronic sinusitis were significantly improved (p<0.001) in both groups. There were no complications, and the revision surgery rate was 2% in each arm through one year. The authors concluded that stand-alone balloon dilation was as effective as FESS in the treatment of CRS in patients with maxillary sinus disease, with or without anterior ethmoid disease, who failed medical therapy, and met the criteria for medically necessary FESS. The study included the use of self-reported quality of life questionnaires, which are subject to recall bias.

Chandra (2015) published final results of the REMODEL study[10], which indicated that patients in the balloon sinus dilation groups experienced significantly faster recovery (1.7 vs. 5.0 days, p<0.0001), less nasal bleeding (32% vs. 56%; p=0.009), and less need for prescription pain medication (1.0 vs. 2.8 days, p<0.0001). Study authors also reported results of a meta-analyses of several stand-alone balloon sinus dilation studies. The meta-analysis was based on five studies that included non-randomized studies and two studies were reportedly unpublished. Based on results of the meta-analyses, FESS and balloon dilation were not significantly different for mean SNOT-20 symptom scores and revisions rates assessed at 12 months.

Other Randomized Controlled Trials

Sikand (2019) published results from a trial where the primary outcome was the difference between arms in change in Chronic Sinusitis Survey (CSS) score from baseline to 24 weeks.[11] The change in CSS was significantly greater in the BOD group compared to the control group (mean change 37.3 vs 21.8). Patients in the BOD group had a lower mean number of sinus infections through the 24-week followup period (0.2 vs 0.95). Durability of the outcome measure differences was demonstrated up to 48 weeks. After the 24-week followup period, 18 of 30 patients who were randomized to the control arm elected to receive BOD. Of those who crossed over at 24 weeks, none reported no change or worsening of symptoms, three reported improved symptoms but still used nasal sprays at high rates, four had improved symptoms to varying degrees but were not eliminated, and one reported a sinus infection just before their 24-week visit. There was one procedure-related serious adverse event in the BOD

group, two possibly procedure-related nonserious adverse events, and no device-related adverse events.

Bizaki (2014) reported results from an RCT that compared BOD to FESS among patients with symptomatic chronic or recurrent rhinosinusitis.[12] The trial enrolled 46 subjects, four of whom withdrew; the analysis included 42 patients (n = 21 in each group; statistical power calculations reported). Both groups demonstrated significant improvements in SNOT-22 scores from baseline to postprocedure. There were no differences in change in total SNOT-22 scores between groups at three months postprocedure. As a 2016 follow-up publication, trialists reported on nasal airway resistance and sinus symptoms between FESS- and BOD-treated groups.[13] For this analysis, 62 patients were included (32 from the FESS group, 30 from the balloon dilation group). Patients in the BOD group had significant improvements in nasal volume from pre- to postoperative measurements, but there were no significant differences between groups pre- or postoperatively in nasal volume.

Another RCT by Bizaki (2016) compared BOD to FESS, with a focus on mucociliary clearance.[14] It was conducted at the same institution as the previously reported Bizaki RCT; however, it was not specified whether it included the same patients. This trial enrolled 36 patients who were randomized to BOD (n=17) or FESS (n=19); seven patients dropped out (three in the FESS group, four in the balloon dilation group) and were not included in analyses. SNOT-22 scores improved in both groups from pre- to postoperative analyses. However, changes in total SNOT-22 scores did not differ significantly between groups. There was no significant change in mucociliary clearance before and after either treatment, nor was there a significant between-group difference in mucociliary clearance.

Marzetti (2014) reported results of a small RCT that compared BOD with an unspecified device (or devices) with FESS in the treatment of sinus headache.[15] The study included 83 patients with sinus headache, based on the American Academy of Otolaryngology-Head and Neck Surgery criteria, 44 of whom were randomized to conventional FESS and 35 to BOD. In the balloon dilation group, 23 patients were “only frontal sinus balloon” patients, in which balloon catheters were the only tools used for frontal sinus sinusotomy, and 12 were “hybrid,” in which balloon catheters and traditional endoscopic sinus surgery were used concurrently. It was not specified how patients were selected for these groups. FESS treatment was administered on participants in both groups, but specific data was not reported by study authors. At six months of follow up, scores on the SNOT-22 improved from 28.6 at baseline to 7.8 in the FESS group and 27.3 at baseline to 5.3 in the BOD group, with a statistically significant reduction in both groups ($p<0.001$). At six months of follow up, headache scores based on the visual analog score (VAS) improved from 6.5 to 5.4 in the FESS group and from 7.1 at baseline to 1.2 in the BOD group ($p<0.001$). Study authors did not report other patient-relevant outcomes, such as the number of headache days or use of pain medications following treatment. Limitations of this study included the small number of patients who received BOD, which limits the generalizability of study results, and the lack of blinding of both patients and clinical assessors. In addition, there were various concurrent surgical procedures conducted in both treatment and control groups, which made it difficult to properly assess the treatment effects of BOD.

Another small RCT published by Achar (2012) enrolled 24 patients with chronic sinusitis who had failed medical therapy and were scheduled for surgery.[3] Patients were randomized to balloon dilation or FESS and followed for a total of 24 weeks. The primary outcome measures were changes in the SNOT-20 score and the saccharine clearance time test. Both groups improved significantly on both outcome measures. The degree of improvement was greater for

the functional endoscopic dilatation sinus surgery group compared to the FESS group on both the SNOT-20 score (43.8 ± 15.2 vs. 29.7 ± 12.3, p<0.03) and on the saccharine clearance score (7.5 ± 5.1 vs. 3.5 ± 4.3, p=0.03). Adverse events were not reported.

A small RCT was published in 2011 that reported on physiologic outcomes.[16] Twenty patients were randomly assigned to removal of the uncinate process via FESS or balloon sinus ostial dilation as a stand-alone procedure. The main outcome measures were CO_2 concentration in the sinuses and maximum sinus pressure, both intended to be surrogate measures for sinus ventilation. The CO_2 concentration decreased in both study arms to a similar degree. The mean maxillary sinus pressure on inspiration decreased in the FESS group but did not change in the balloon sinus ostial dilation group.

Bozdemir (2011) published a small study of 10 patients with nasal polyposis, in which one side was treated with FESS and the other with balloon sinus ostial dilation.[17] All procedures were performed by the same surgeon, and polypectomy was performed prior to FESS or balloon sinus ostial dilation in all patients. Outcome measures included sinus patency, as measured by computed tomography (CT) scan (Lund-McKay classification) or repeat endoscopy (McKay grading). At 10 days following the procedure, there were improvements in both groups on measures of patency, but there were no differences between groups.

Nonrandomized Studies

Gould (2014) assessed the one-year changes in sinonasal symptoms and health care use after office-based, multi-sinus balloon dilation in an industry-sponsored prospective, multicenter study.[18] A total of 313 ostial dilations were attempted and 307 were successfully completed (98.1%) in 81 subjects. Seventy-six of the 81 patients completed the one-year follow-up. Mean procedure tolerance was 2.8 ± 2.2 (0 = no pain, 10 = severe pain). SNOT-20 symptom improvement was observed at one and six months and sustained through one year. The RSI questionnaire that rates five major and seven minor rhinosinusitis symptoms measured a treatment effect for all major rhinosinusitis symptoms. Compared with the previous one-year period, patients reported an average of 2.3 fewer acute sinus infections (p<0.0001), 2.4 fewer antibiotic courses taken (p<0.0001), and 3.0 fewer sinus-related physician visits (p<0.0001) after balloon dilation. No serious device or procedure-related adverse events occurred. One subject underwent revision surgery. The authors reported that patients reported significant reductions in both sinonasal symptoms and health care use after balloon dilation. Methodological limitations included the implementation of self-reported SNOT-20 and RSI questionnaires, which may lead to recall bias; lack of a comparison group, which precludes the ability to isolate any reported treatment effects; and the uncertain timing between the preoperative CT scan and failure of medical management.

Brodner (2013) reported a prospective, multi-center study to evaluate outcomes for the XprESS device for the treatment of the frontal recesses, maxillary ostia, and/or sphenoid sinus ostia in 175 adults who had previously been scheduled for conventional FESS.[19] The criteria for previously-scheduled conventional FESS are not specified. There were a mean 2.7 sinuses per patient treated; of the targeted sinuses, 479/497 (96.4%) were successfully accessed and treated. One-year follow up was planned in the first 50 subjects, who only underwent dilation of frontal recesses and sphenoid ostia; at one year, in the 41 subjects with one-year follow-up available, 76/83 (91.6%) of the ostia dilated with the study device were patent. At one year, in 44 subjects who completed follow-up, the average overall SNOT-20 score was 0.8 (vs 1.9 at baseline; p<0.0001 for change), which was considered a clinically meaningful improvement

(change ≥ 0.8).

Albritton (2012) reported results of a prospective, nonrandomized evaluation of the feasibility of in-office balloon sinus dilation with the Relieva device who were enrolled in the ORIOS trial.[20] The study included 37 subjects (59 sinuses) who had a diagnosis of chronic rhinosinusitis (>12 weeks of symptoms including but not restricted to nasal obstruction, sinus/facial pressure, nasal discharge, and congestion) that was unresponsive to maximal medical management. Successful access and dilation of all targeted sinuses occurred in 33/37 subjects (89%). Follow up was available for 32 (86.5%), 31 (83.8%), 26 (70.2%), and 21 (56.8%) at 1-, 4-, 24-, and 52-weeks post-procedure, respectively. Symptoms were assessed based on the change in SNOT-20 score from baseline to follow up, with a mean reduction from baseline of -0.98 (95% CI -1.27 to -0.70), -1.32 (95% CI -1.65 to -1.00), -1.25 (95% CI -1.65 to -0.85), and -1.42 (95% CI -1.87 to -0.90) at 1-, 4-, 24-, and 52-weeks post-procedure, respectively. For the 29 subjects who had CT scans available at baseline and 24 weeks of follow up, Lund-Mackay score improved from 6.62 preprocedure to 2.79 postprocedure (p<0.0001).

In the ORIOS2 study, Karanfilov (2013) reported results of a prospective, nonrandomized, multicenter evaluation of office-based balloon sinus dilation with the Relieva device in 203 patients who required FESS for medically refractory chronic sinusitis.[21] Three cohorts were enrolled, a lead-in cohort which consisted of each investigator's first cases where all targeted sinuses were successfully dilated (n = 36), a standard enrollment cohort which consisted of up to approximately 15 cases (n = 84), and an extended enrollment cohort which included subjects after the first 15 cases (n = 83). Dilation technically successful in 552 of 592 attempted sinuses (93.2%). Matched baseline and twenty-four week follow up was available for 112 patients, who demonstrated a mean improvement in SNOT-20 scores of -1.1 (p<0.0001). In the 110 patients with 24 week CT scans available, Lund-Mackay score improved by -4.3 compared with baseline (p<0.0001 for change).

Levine (2013) reported results of a prospective, nonrandomized, multicenter evaluation of office-based balloon sinus dilation with the FinESS device in 74 patients with chronic rhinosinusitis (n = 52) or recurrent acute sinusitis (n = 17).[22] Balloon dilation was successful in 69 patients, and analyses are reported per protocol. The overall technical success rate in patients was 91.9% (124 of 135 ostia) but it was not specified if this was in overall sample of 74 patients or in analysis sample of 69 patients. Mean SNOT-20 scores improved from a mean 2.3 at baseline to 1.1 at six months and 12 months in the 66 patients with follow up data available (mean change -1.2, p<0.0001). There were no significant differences in improvements reported between the chronic rhinosinusitis and recurrent acute sinusitis patients.

A number of additional nonrandomized studies have been identified, which do not allow conclusions concerning the impact of BSD on primary health outcomes compared with FESS. These studies have methodological limitations such as a limited number of patients,[20, 23] a heterogenous study population,[24] no primary health outcomes reported,[25] limited follow-up,[20, 23, 24, 26] retrospective study design[26, 27 , 28, 29], or implementation of self-reported questionnaires.[18, 25, 27] The exception is a single-arm study by Tomazic (2013), in which the authors planned to evaluate a cohort of 200 patients with BOD or a hybrid procedure, but ended the study early after 45 patients after a high technical failure rate was noted, with 44/68 sinuses in a planned BOD group and 29/44 sinuses in a planned hybrid procedure group failing.[30]

Retrospective studies are limited by the accuracy of the medical records reviewed or the recall ability of patients when filling out a study questionnaire. In addition, there is no randomization or blinding in a retrospective study design and therefore it is difficult to control for bias and confounders.

PEDIATRIC PATIENTS

Nonrandomized Studies

Wang (2015) reported on a perspective nonrandomized controlled study of 79 pediatric patients (age 7-12) with chronic sinusitis resistant to medical therapy, including 42 patients treated with sinus balloon catheter dilation balloon (SBCD) and 37 control patients treated conservatively (including oral antibiotics, local nasal steroid spray, and nasal saline irrigation).[31] At one-year posttreatment, the SN-5 scores were significantly better in the SBCD group (22 patients [52%] had marked improvement, 11 [26%] had moderate improvement, and six [14%] had mild improvement) than in the control group (five [14%], seven [19%], and four [11%], respectively) ($p < 0.05$ for all comparisons).

In a retrospective comparative study, Thottam (2012) evaluated the incremental value of Relieva balloon catheter sinuplasty when combined with FESS in 31 children (mean age 9.3 years) who had persistent chronic sinusitis despite standard maximal medical therapy.[32] The authors performed a blinded chart review of 15 children who underwent balloon catheter sinuplasty with ethmoidectomy and 16 children who underwent FESS. Thirteen children had prior adenoidectomy. A total symptom score was constructed for the number of complaints presurgery, postsurgery, and at the final postsurgical examination (> four months) including facial pain, sinus congestion, postnasal drip, rhinorrhea, headache, and low-grade fever. Success and improvement were defined as a decrease in the total complaint score of ≥ 1 point at the last visit, while total improvement was defined as total resolution of all complaints (i.e., symptom score of 0). Compared with baseline values, significant posttreatment reductions in overall sinusitis symptoms and needed interventions were observed in both treatment groups. In the Relieva balloon catheter sinuplasty group, 80% of the patients reported improvements in their overall sinus symptoms at an average of 37 weeks, versus 62.5% of the FESS patients. This difference between groups was not significant. No serious complications occurred.

In a prospective, nonrandomized controlled study, Ramadan (2010) compared the efficacy and safety of Relieva balloon sinuplasty combined with adenoidectomy (n=30) with that of adenoidectomy alone (n = 19) in 49 children (mean age 6.6 years, range 2-11) with chronic sinusitis that was refractory to medical therapy for at least six months.[33] The patients were followed at regular intervals for up to one year. Twenty-four of the 30 (80%) patients in the Relieva plus adenoidectomy group showed symptom improvement at one year compared with 10 of 19 (52.6%) children in the adenoidectomy alone group. Two (6%) patients with hypoplastic sinuses failed balloon sinuplasty and required revision FESS. One patient was lost to follow-up, and another had no improvement in SN-5 scores. Three (15%) children who did not improve after adenoidectomy had balloon sinuplasty. Overall, the mean SN-5 score for all participants decreased from a baseline value of 4.1 to 2.9 after surgery. In the Relieva plus adenoidectomy group, the mean SN-5 score decreased from 4.2 to 3.0, while in the adenoidectomy alone group, the score decreased from 3.8 to 2.9. No major complications occurred in either treatment group.

Prospective, multicenter single-arm studies have reported outcomes in pediatric patients with chronic sinusitis. In one study of 32 children, 24 had one-year follow-up data.[34] Of the 32

children enrolled, 24 were studied at one-year follow-up. Significant improvements in quality of life outcomes were reported using the SN-5 score ($p<0.0001$). Twelve (50%) children had a significant improvement of their SN-5 score, seven children (29%) had moderate improvement, two (8%) had mild improvement, one (4%) remained the same, and two children (8%) had worsening scores. A similar study with 50 participants and 157 total attempted dilations also reported significant improvement in SN-5 scores at six months ($p<0.0001$).[35] No adverse procedure-related events were reported in either study However, these studies lacked a comparison group, limiting conclusions regarding the efficacy of the procedure.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY (AAO-HNS)

In 2018, the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) published a clinical consensus statement on balloon dilation of the sinuses.[36] Participating subgroups included the Triologic Society, the American Rhinologic Society, the American Academy of Otolaryngic Allergy, and the American Academy of Allergy, Asthma & Immunology. The following statements met consensus:

Patient Criteria:

- Balloon dilation is not appropriate for patients who are without both sinonasal symptoms and positive findings on CT. (Strong consensus)
- Balloon dilation is not appropriate for the management of headache in patients who do not otherwise meet the criteria for chronic sinusitis or recurrent acute sinusitis. (Strong consensus)
- Balloon dilation is not appropriate for the management of sleep apnea in patients who do not otherwise meet the criteria for chronic sinusitis or recurrent acute sinusitis. (Strong consensus)
- CT scanning of the sinuses is a requirement before balloon dilation can be performed. (Strong consensus)
- Balloon dilation is not appropriate for patients with sinonasal symptoms and a CT that does not show evidence of sinonasal disease.
- Balloon dilation can be appropriate as an adjunct procedure to FESS in patients with chronic sinusitis without nasal polyps.
- There can be a role for balloon dilation in patients with persistent sinus disease who have had previous sinus surgery.
- There is a role for balloon sinus dilation in managing patients with recurrent acute sinusitis as defined in the AAO-HNSF guideline based on symptoms and CT evidence of ostial occlusion and mucosal thickening.

Perioperative Considerations:

- Surgeons who consider reusing devices intended for dilation of the sinuses should understand the regulations set forth by the FDA for reprocessing such devices and ensure that they are followed. (Strong consensus)
- Balloon dilation can be performed under any setting as long as proper precautions are taken and appropriate monitoring is performed.
- Balloon dilation can be performed under local anesthesia with or without sedation.

Outcome:

- Balloon dilation can improve short-term quality-of-life outcomes in patients with limited CRS without polyposis.
- Balloon dilation can be effective in frontal sinusitis

SUMMARY

There is enough research to show that balloon ostial dilation improves health outcomes for patients with sinusitis compared to functional endoscopic sinus surgery (FESS). In addition, there are clinical practice guidelines that address balloon ostial dilation for the treatment of sinusitis. Therefore, balloon ostial dilation as a treatment for sinusitis, either as a stand-alone procedure or in conjunction with FESS, may be considered medically necessary when policy criteria are met.

There is not enough research to show that balloon ostial dilation improves health outcomes for patients with chronic or acute sinusitis when policy criteria are not met. Therefore, balloon ostial dilation as a treatment for sinusitis, either as a stand-alone procedure or in conjunction with FESS, is considered investigational when policy criteria are not met.

REFERENCES

1. Sinha P, Tharakan T, Payne S, et al. Balloon Sinus Dilation Versus Functional Endoscopic Sinus Surgery for Chronic Rhinosinusitis: Systematic Review and Meta-Analysis. *The Annals of otology, rhinology, and laryngology.* 2023;132(5):578-88. PMID: 35703383
2. Levy JM, Marino MJ, McCoul ED. Paranasal Sinus Balloon Catheter Dilation for Treatment of Chronic Rhinosinusitis: A Systematic Review and Meta-analysis. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2016;154:33-40. PMID: 26519456
3. Achar P, Duvvi S, Kumar BN. Endoscopic dilatation sinus surgery (FEDS) versus functional endoscopic sinus surgery (FESS) for treatment of chronic rhinosinusitis: a pilot study. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* 2012;32(5):314-9. PMID: 23326011
4. Cutler J, Bikhazi N, Light J, et al. Standalone balloon dilation versus sinus surgery for chronic rhinosinusitis: A prospective, multicenter, randomized, controlled trial. *American journal of rhinology & allergy.* 2013. PMID: 23920419
5. TEC Assessment 2012. "Balloon Ostial Dilation for Treatment of Chronic Rhinosinusitis." BlueCross BlueShield Association Technology Evaluation Center, Vol. 27, Tab 9.
6. Ahmed J, Pal S, Hopkins C, et al. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2011(7):CD008515. PMID: 21735433
7. Plaza G, Eisenberg G, Montojo J, et al. Balloon dilation of the frontal recess: a randomized clinical trial. *The Annals of otology, rhinology, and laryngology.* 2011;120(8):511-8. PMID: 21922974

8. Batra PS, Ryan MW, Sindwani R, et al. Balloon catheter technology in rhinology: Reviewing the evidence. *Laryngoscope.* 2011;121(1):226-32. PMID: 20824793
9. Bikhazi N, Light J, Schwartz M, et al. Standalone balloon dilation versus sinus surgery for chronic rhinosinusitis: A prospective, multicenter, randomized, controlled trial with 1-year follow-up. *American journal of rhinology & allergy.* 2014. PMID: 24823902
10. Chandra RK, Kern RC, Cutler JL, et al. REMODEL larger cohort with long-term outcomes and meta-analysis of standalone balloon dilation studies. *Laryngoscope.* 2015. PMID: 26228589
11. Sikand A, Ehmer DR, Jr., Stolovitzky JP, et al. In-office balloon sinus dilation versus medical therapy for recurrent acute rhinosinusitis: a randomized, placebo-controlled study. *International forum of allergy & rhinology.* 2019;9(2):140-48. PMID: 30452127
12. Bizaki AJ, Taulu R, Numminen J, et al. Quality of life after endoscopic sinus surgery or balloon sinuplasty: a randomized clinical study. *Rhinology.* 2014;52(4):300-5. PMID: 25479206
13. Bizaki AJ, Numminen J, Taulu R, et al. Decrease of nasal airway resistance and alleviations of symptoms after balloon sinuplasty in patients with isolated chronic rhinosinusitis. A prospective, randomized clinical study. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2015. PMID: 26548697
14. Bizaki AJ, Numminen J, Taulu R, et al. A Controlled, Randomized Clinical Study on the Impact of Treatment on Antral Mucociliary Clearance: Uncinectomy Versus Balloon Sinuplasty. *The Annals of otology, rhinology, and laryngology.* 2016;125:408-14. PMID: 26611244
15. Marzetti A, Tedaldi M, Passali FM. The role of balloon sinuplasty in the treatment of sinus headache. *Otolaryngologia polska The Polish otolaryngology.* 2014;68(1):15-9. PMID: 24484944
16. Kutluhan A, Salviz M, Bozdemir K, et al. The effects of uncinectomy and natural ostial dilatation on maxillary sinus ventilation: a clinical experimental study. *Eur Arch Otorhinolaryngol.* 2011;268(4):569-73. PMID: 21110035
17. Bozdemir K, Kutluhan A, Cetin H, et al. Comparison of outcomes of simple polypectomy plus balloon catheter dilatation versus functional endoscopic sinus surgery in nasal polyposis: a preliminary study. *American journal of rhinology & allergy.* 2011;25(3):198-200. PMID: 21679533
18. Gould J, Alexander I, Tomkin E, et al. In-office, multisinus balloon dilation: 1-Year outcomes from a prospective, multicenter, open label trial. *American journal of rhinology & allergy.* 2014;28:156-63. PMID: 24598043
19. Brodner D, Nachlas N, Mock P, et al. Safety and outcomes following hybrid balloon and balloon-only procedures using a multifunction, multisinus balloon dilation tool. *International forum of allergy & rhinology.* 2013;3(8):652-8. PMID: 23424023
20. Albritton FDt, Casiano RR, Sillers MJ. Feasibility of in-office endoscopic sinus surgery with balloon sinus dilation. *American journal of rhinology & allergy.* 2012;26(3):243-8. PMID: 22449614
21. Karanfilov B, Silvers S, Pasha R, et al. Office-based balloon sinus dilation: a prospective, multicenter study of 203 patients. *International forum of allergy & rhinology.* 2013;3(5):404-11. PMID: 23136057
22. Levine SB, Truitt T, Schwartz M, et al. In-office stand-alone balloon dilation of maxillary sinus ostia and ethmoid infundibula in adults with chronic or recurrent acute rhinosinusitis: a prospective, multi-institutional study with-1-year follow-up. *The Annals of otology, rhinology, and laryngology.* 2013;122(11):665-71. PMID: 24358625

23. Stankiewicz J, Truitt T, Atkins J, Jr. One-year results: Transantral balloon dilation of the ethmoid infundibulum. *Ear Nose Throat J.* 2010;89(2):72-7. PMID: 20155675
24. Stankiewicz J, Tami T, Truitt T, et al. Transantral, endoscopically guided balloon dilatation of the ostiomeatal complex for chronic rhinosinusitis under local anesthesia. *American journal of rhinology & allergy.* 2009;23(3):321-7. PMID: 19419611
25. Stankiewicz J, Tami T, Truitt T, et al. Impact of chronic rhinosinusitis on work productivity through one-year follow-up after balloon dilation of the ethmoid infundibulum. *International forum of allergy & rhinology.* 2011;1(1):38-45. PMID: 22287306
26. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. *Laryngoscope.* 1990;100(1):79-84. PMID: 2293704
27. Koskinen A, Penttila M, Myller J, et al. Endoscopic sinus surgery might reduce exacerbations and symptoms more than balloon sinuplasty. *American journal of rhinology & allergy.* 2012;26(6):e150-6. PMID: 23232189
28. Matthews BL, Smith LE, Jones R, et al. Endoscopic sinus surgery: outcome in 155 cases. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 1991;104(2):244-6. PMID: 1901154
29. Laury AM, Bowe SN, Stramiello J, et al. Balloon dilation of sinus ostia in the Department of Defense: Diagnoses, actual indications, and outcomes. *Laryngoscope.* 2017;127(3):544-49. PMID: 27659163
30. Tomazic PV, Stammberger H, Braun H, et al. Feasibility of balloon sinuplasty in patients with chronic rhinosinusitis: the Graz experience. *Rhinology.* 2013;51(2):120-7. PMID: 23671892
31. Wang F, Song Y, Zhang X, et al. Sinus balloon catheter dilation in pediatric chronic rhinosinusitis resistant to medical therapy. *JAMA Otolaryngol Head Neck Surg.* 2015;141:526-31. PMID: 25835158
32. Thottam PJ, Haupert M, Saraiya S, et al. Functional endoscopic sinus surgery (FESS) alone versus balloon catheter sinuplasty (BCS) and ethmoidectomy: a comparative outcome analysis in pediatric chronic rhinosinusitis. *Int J Pediatr Otorhinolaryngol.* 2012;76:1355-60. PMID: 22770596
33. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. *The Annals of otology, rhinology, and laryngology.* 2010;119(9):578-82. PMID: 21033023
34. Ramadan HH, McLaughlin K, Josephson G, et al. Balloon catheter sinuplasty in young children. *American journal of rhinology & allergy.* 2010;24(1):e54-6. PMID: 20109327
35. Soler ZM, Rosenbloom JS, Skarada D, et al. Prospective, multicenter evaluation of balloon sinus dilation for treatment of pediatric chronic rhinosinusitis. *International forum of allergy & rhinology.* 2017;7(3):221-29. PMID: 27888649
36. American Academy of Otolaryngology-Head and Neck Surgery. Statement on Balloon Dilation. Reviewed January 2, 2014. [cited 9/16/2023]. 'Available from:' http://www.entnet.org/Practice/Balloon-Dilation.cfm.

CODES

Codes	Number	Description
CPT	31295	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); maxillary sinus ostium, transnasal or via canine fossa
	31296	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); frontal sinus ostium

Codes	Number	Description
	31297	;sphenoid sinus ostium
	31298	Nasal/sinus endoscopy, surgical; with dilation of frontal and sphenoid sinus ostia (eg, balloon dilation)
	31299	Unlisted procedure, accessory sinuses
HCPCS	C1726	Catheter, balloon dilatation, non-vascular

Date of Origin: *August 2006*

Regence

Medical Policy Manual Surgery, Policy No. 165

Surgical Treatments for Hyperhidrosis

Effective: May 1, 2023

Next Review: March 2024
Last Review: March 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

This policy addresses surgical treatments for hyperhidrosis, excessive sweating beyond a level required to maintain normal body temperature.

MEDICAL POLICY CRITERIA

Note: This policy only addresses the surgical treatment of hyperhidrosis.

I. Surgical treatment of hyperhidrosis, including craniofacial hyperhidrosis, via endoscopic transthoracic sympathectomy or excision of axillary sweat glands may be considered **medically necessary** when there is clinical documentation that all of the following Criteria (A. – C.) are met:

   A. Primary medical conditions causing hyperhidrosis have been identified and treated where possible; and

   B. The hyperhidrosis is persistent and severe, and has resulted in one or more of the significant medical complications below (see Policy Guidelines):

      1. Acrocyanosis of the hands; or

      2. Recurrent skin maceration with secondary bacterial or fungal infection; or

3. Recurrent secondary infections; or
4. Persistent eczematous dermatitis; or
5. Documentation of inability to perform critical activities of daily living or demands of employment (such as impaired grip and writing ability for employment, or impaired walking) due to symptoms of hyperhidrosis; and

C. A trial of all of the following nonsurgical treatments has been ineffective, not tolerated, or are contraindicated:

1. Prescription antiperspirants (e.g. aluminum chloride hexahydrate 20%) and/or anticholinergics (e.g. glycopyrrolate or oxybutynin); and
2. If the treatment is for axillary or palmar hyperhidrosis and the patient is age 18 years or older, a trial of botulinum toxin type A [Botox] injection is completed OR the patient does not have axillary or palmar hyperhidrosis.

II. Tympanic neurectomy may be considered **medically necessary** for the treatment of severe gustatory hyperhidrosis if a trial of nonsurgical treatments failed or is contraindicated.

III. Surgical treatment of hyperhidrosis via endoscopic transthoracic sympathectomy, excision of axillary sweat glands, or tympanic neurectomy is considered **not medically necessary** when the Criteria in I. or II. above are not met (see Policy Guidelines).

IV. All other surgical treatments of hyperhidrosis are considered **investigational**, including but not limited to lumbar sympathectomy; axillary liposuction or curettage performed alone or in combination with any other procedure; subdermal laser-assisted axillary hyperhidrosis treatment; percutaneous radiofrequency sympathicolysis or sympathectomy; and radiofrequency ablation for palmar hyperhidrosis.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Medical treatment of persistent hyperhidrosis is considered not medically necessary in the absence of significant medical complications associated with the condition. Skin irritation, skin maceration without secondary infection, need for frequent changing of clothing, or psychosocial distress alone are not considered to be significant medical complications.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes including the following:
  - Type of hyperhidrosis
  - Documentation primary medical conditions causing hyperhidrosis have been identified and treated where possible

- Documentation hyperhidrosis is persistent and severe and has resulted in significant medical complications including inability to perform critical activities of daily living or demands of employment, if relevant
- Documentation of specific nonsurgical treatments trialed and documented response including use of prescription antiperspirants and/or anticholinergics, and botulinum toxin type A [Botox] injection trial when appropriate per policy.

CROSS REFERENCES

1. Botulinum toxin Type A injection, Medication Policy Manual, Drugs, Policy No. 006

BACKGROUND

HYPERHIDROSIS

Hyperhidrosis may be defined as excessive sweating, beyond a level required to maintain normal body temperature in response to heat exposure or exercise. Hyperhidrosis can be classified as either primary or secondary.

Primary Hyperhidrosis

Primary focal hyperhidrosis is defined as idiopathic bilateral, relatively symmetric, excessive sweating of at least six months' duration induced by sympathetic hyperactivity in selected areas that is not associated with an underlying disease process. The most common locations are underarms (axillary hyperhidrosis), palms (palmar hyperhidrosis), soles of the feet (plantar hyperhidrosis) or face and scalp (craniofacial hyperhidrosis). The second (T2) and third (T3) thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglia controls axillary hyperhidrosis, and the first (T1) thoracic ganglia controls facial hyperhidrosis.

Secondary Hyperhidrosis

Secondary generalized hyperhidrosis is a type of excessive sweating that is caused by another medical condition or is a side effect of a medication. Secondary hyperhidrosis can result from a variety of drugs, [e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs)], olfactory stimuli, or underlying diseases/conditions, such as febrile diseases, diabetes mellitus, anxiety, menopause, neurologic lesions, intrathoracic neoplasms, and Raynaud's disease.

Secondary gustatory hyperhidrosis is excessive sweating related to ingesting or thinking about the ingesting food. This trigeminovascular reflex typically occurs symmetrically on scalp or face and predominately over forehead, lips and nose and can include flushing, redness, and general discomfort felt at the cheek level. This phenomenon is associated with conditions including encephalitis, syringomyelia, diabetic neuropathies, and, most commonly, conditions resulting from damage to the parotid gland (sometimes referred to as Frey's syndrome) including herpes zoster parotitis and parotid abscess. Other conditions and diseases also can cause hyperhidrosis, including those listed at sweathelp.org.[1]

Frey's syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to, or surgery near, the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve. After injury, these fibers regenerate and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in

gustatory sweating and facial flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial in nature. Excessive sweating may be socially embarrassing or may interfere with certain professions. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the minor starch iodine test, which is a simple qualitative measure to identify specific sites of involvement.

A variety of medical therapies have been investigated for treating primary hyperhidrosis, including topical therapy with aluminum chloride or tanning agents, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, and microwave treatment. Treatment of secondary hyperhidrosis naturally focuses on treatment of the underlying cause.

SURGICAL TREATMENT

This medical policy addresses only surgical treatment of hyperhidrosis. Surgical treatments for axillary hyperhidrosis include transthoracic sympathectomy and surgical excision of axillary sweat glands. Transthoracic sympathectomy may also be used for palmar hyperhidrosis. Surgical removal of axillary sweat glands has been performed in patients with severe isolated axillary hyperhidrosis. Removal may involve removal of the subcutaneous sweat glands without removal of any skin, limited excision of skin and removal of surrounding subcutaneous sweat glands, or a more radical excision of skin and subcutaneous tissue en bloc.

A variety of approaches have been reported for sympathectomy. For transthoracic sympathectomy, transthoracic endoscopic techniques have emerged as minimally invasive alternatives to transaxillary, supraclavicular, or anterior thoracic approaches. Percutaneous radiofrequency (RF) sympathicolysis has also been proposed as a sympathectomy technique in which RF lesions are made in the thoracic sympathetic chain under fluoroscopic guidance without the need for general anesthesia, intubation, or risk of lung collapse. Lumbar sympathectomy may be performed as a surgical treatment of plantar hyperhidrosis and may also be done endoscopically.

While accepted as an effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner's syndrome, compensatory sweating on the trunk can occur in up to 55% of patients, reducing patient satisfaction with the procedure. Gustatory sweating may also occur. Sympathectomy also results in cardiac sympathetic denervation, which in turn can lead to a 10% reduction in the heart rate. In addition to the complications associated with transthoracic sympathectomy, lumbar sympathectomy for plantar hyperhidrosis may have the additional risk of permanent sexual dysfunction in men and women. Medical researchers have investigated whether certain approaches, e.g., T3 versus T4 sympathectomy, result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this side effect.

Tympanic neurectomy is a surgical technique that may be used for treatment of severe gustatory hyperhidrosis. The nerves are transected in the middle ear through a flap created in the ear drum. Possible risks from this surgery include rupture of the tympanic membrane, infection, hearing loss, and loss of taste in certain parts of the tongue.

EVIDENCE SUMMARY

In order to determine whether surgical treatment of hyperhidrosis results in sustained improvements in clinically meaningful health outcomes, comparisons to conventional therapies in well-designed comparative studies (ideally randomized controlled trials) are needed using standardized functional measurement tools.

For individuals who have primary axillary or palmar hyperhidrosis, a high rate of clinical efficacy after endoscopic transthoracic sympathectomy has been demonstrated,[2-10] although the rate of postoperative compensatory sweating was substantial.[11] Surgical excision of axillary sweat glands in individuals who have primary axillary hyperhidrosis has been shown to be highly effective. The evidence is sufficient to determine that endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands results in a meaningful improvement in the net health outcome for individuals who have primary axillary or palmar hyperhidrosis. These procedures are considered standard of care for these indications when a trial of non-surgical treatment has failed.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, this treatment has been shown to have high success rates, without the need for repeated interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome and this treatment is considered standard of care for this indication when a trial of non-surgical treatment has failed.

The focus of the following evidence summary is on systematic reviews (SRs), technology assessments (TAs), randomized controlled trials (RCT), and comparative nonrandomized studies for the investigational indications listed in the policy criteria.

LUMBAR SYMPATHECTOMY

Systematic Review

Chudry (2022) published a systematic review (SR) evaluating the effectiveness of interventions for primary palmar hyperhidrosis (PH).[12] Six studies were included in the review. Two of these studies addressed the use of endoscopic thoracic sympathectomy (ETS) in PH, and both reported over 95% patient symptom improvement. The authors conclude that ETS was reported as successful as other interventions in the reduction of PH, however, ETS carries significant adverse effects such as compensatory sweating and the potential of complications associated with surgery.

Lima (2020) conducted a SR and meta-analysis of lumbar sympathectomy for plantar hyperhidrosis.[13] Eight studies were identified, including a total of 517 patients. One RCT met inclusion criteria; the other studies were case series. In all of the studies, lumbar sympathectomy was conducted following transthoracic sympathectomy. Resolution of symptoms occurred in 92% of patients when mechanical sympathectomy was used with clipping or resection of the lymph nodes between L2 and L5, with similar results regardless of resection level, Overall, 44% of patients had mild to severe compensatory sweating after a mean of six months of follow-up. The RCT was conducted in 30 women at a single hospital in Brazil. The primary outcome measure was a quality-of-life questionnaire that was developed for use in patients undergoing thoracic sympathectomy. After six months, patients in the intervention group had a greater improvement in quality of life relative to the control group patients; 53% reported worsening compensatory sweating. This study was limited by its small

sample size, use of an unvalidated outcome measure, and lack of blinded outcome assessment.

Lima (2017) published a SR evaluating the efficacy of lumbar sympathectomy in plantar hyperhidrosis. Among the nine studies included, eight were retrospective studies, and one was a RCT.[14] None of the eight retrospective studies were considered to be of high quality, assessed by the Newcastle Ottawa Scale. The protocol was highly variable across trials, with respect to intervention site (ranging from L2/L3 to L5) and surgical technique (seven studies used mechanical clipping or resection sympathectomy, two used chemical sympathectomy). Across all studies, the percent of patients with resolution of symptoms ranged from 5 to 98%. There was a high variation in the incidence of complications across studies, including neuralgia (range, 3% to 42.2%), compensatory sweating, (1.5% to 90%), and sexual dysfunction (not reported by all studies). There is not enough evidence of the safety or long-term clinical outcomes of lumbar sympathectomy in the treatment of plantar hyperhidrosis. Additional RCTs with standardized protocols are needed.

Randomized Controlled Trials

No RCTs beyond those summarized in the SR above were identified.

Nonrandomized Studies

In addition to the nonrandomized studies summarized in the SR above, there have been case series published, however, these observations are not generalizable due to lack of randomization, lack of a control group for comparison, heterogeneous patient characteristics, lack of long-term follow-up, subjective outcomes, and the use of different surgical techniques.[15-17] In addition to low success rates, concerns have been reported for side effects in sexual functioning in both males and females.

REMOVAL OF AXILLARY SWEAT GLANDS BY LIPOSUCTION OR CURETTAGE

There is insufficient evidence to determine whether liposuction or curettage of sweat glands is safe or effective as a treatment of axillary hyperhidrosis. In a SR of treatments available in secondary care for the management of primary hyperhidrosis, Wade (2018) evaluated studies on curettage for axillary hyperhidrosis.[18] Nine studies were identified including four RCTs and five nonrandomized studies. All were considered to be at high risk for bias. Meta-analysis was not possible due to methodological differences. In four studies, curettage was compared to botulinum treatment and only one small RCT found a statistically significant improvement in symptoms, favoring botulinum.[19] No differences were found in sweating, quality-of-life or satisfaction outcomes, although, where reported, the incidence of adverse events was higher with curettage than with botulinum. Although this procedure has been performed for several decades, only scattered reports regarding its effectiveness were identified in a PubMed literature search.[20-25]

AXILLARY SUBDERMAL LASER TREATMENT

Systematic Reviews and Technology Assessments

In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a rapid response review on the clinical effectiveness of laser therapy in axillary hyperhidrosis.[26] Five publications were included in the review, three RCTs and two nonrandomized studies. No relevant evidence-based guidelines were identified for inclusion. The authors reported that

although the evidence suggests laser therapy may reduce sweating in cases of axillary hyperhidrosis, these results should be interpreted with caution due to the methodological limitations of the studies, which include but are not limited to, small sample sizes, a lack of reporting on efficacy and safety outcomes, potential selection bias, and a lack of long term follow-up data.

Randomized Controlled Trials

No RCTs beyond those summarized in the review above were identified.

Nonrandomized Studies

No studies beyond those summarized in the review above were identified.

PERCUTANEOUS RADIOFREQUENCY TREATMENTS

Systematic Reviews

Hasimoto (2020) published a SR with meta-analysis of nine studies (N=378) evaluating the effectiveness of radiofrequency (RF) treatment of primary hyperhidrosis, including radiofrequency ablation (RFA) sympathectomy (N=238) and fractionated microneedle radiofrequency (FMRF) of the axillary (N=75) compared to video-assisted thoracic sympathectomy (VATS) (N=65).[27] In seven of the nine studies, patients were subjected to RF only, and in two of nine studies RF was compared to VATS. Across the three studies evaluating FMRF, there was a reduction in the severity of hyperhidrosis (mean difference -1.24, 95% CI -1.44 to -1.03) and minor improvement in reported quality of life (QoL) (-9.0, 95% CI -9.15 to -8.85). There was improvement in QoL found after RFA (two studies, mean difference -15.92, 95% CI -17.61 to -14.24), although the one study comparing QoL improvement after RFA or VATS found that VATS showed superior results. In the one study that evaluated symptom recurrence between VATS and RF found higher recurrence rates in RF (5% vs. 25%, respectively, $p<0.01$). There were no RCTs identified for inclusion, and of the two studies comparing RFA to VATS, one was a non-randomized controlled study and the other was a retrospective observational study. The authors concluded that there is a need for high-quality prospective studies comparing RF to current standard practice, particularly VATS.

Randomized Controlled Trials

Mostafa (2019) conducted a randomized controlled trial (RCT) of radiofrequency ablation compared to botulinum toxin type A in 80 patients with primary palmar hyperhidrosis.[28] Both groups showed improvements from baseline in HDSS scores at one week, one month, and two months after treatment, but scores in the radiofrequency ablation group were significantly lower (indicating more improvement with RFA) than in the botulinum toxin group at one week, one month, and two, six, and 12 months after treatment.

Rummaneethorn (2019) compared RFA to botulinum toxin A in 20 patients with primary axillary hyperhidrosis.[29] At the endpoint visit (week 12), the botulinum toxin A group had significantly greater reduction of mean HDSS score than the RFA group with 1.60 (0.59) versus 2.05 (0.68), respectively (p=0.0332). At week 12, the botulinum toxin A group also had significantly higher satisfaction score by quartile rating scale than the microneedle RF group (2.55 + 0.69 versus 1.70 + 1.03, respectively, p=0.004).

Nonrandomized Studies

No studies beyond those summarized in the SR above were identified.

PRACTICE GUIDELINE SUMMARY

In 2011, an expert consensus statement on the surgical treatment of hyperhidrosis was published by a task force of the Society of Thoracic Surgeons.[30] The document stated that endoscopic thoracic sympathectomy is the treatment of choice for patients with primary hyperhidrosis. They further recommend the following treatment strategies (with R referring to rib and the number to the specific rib):

- R3 interruption for palmar hyperhidrosis; an R4 interruption is also reasonable. The authors note a slightly higher rate of compensatory sweating with an R3, but R3 is also more effective at treating hyperhidrosis.
- R4 or R5 interruption for palmar-axillary, palmar-axillary-plantar or axillary hyperhidrosis alone; R5 interruption is also an option for axillary hyperhidrosis alone.
- R3 interruption for craniofacial hyperhidrosis without blushing; an R2 and R3 procedure is an option but may lead to a higher rate of compensatory sweating, and also increases the risk of Horner's syndrome.

SUMMARY

There is enough evidence to determine that endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands results in a meaningful improvement in the net health outcome for individuals who have primary axillary, craniofacial, or palmar hyperhidrosis. These procedures are considered standard of care for these indications when a trial of non-surgical treatment has failed. Clinical guidelines based on research recommend surgical treatment for primary hyperhidrosis. Therefore, endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands is considered medically necessary when policy criteria are met.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, this treatment has been shown to have high success rates without the need for repeated interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome and this treatment is considered standard of care for this indication when a trial of non-surgical treatment has failed. Therefore, tympanic neurectomy is considered medically necessary for the treatment of secondary gustatory hyperhidrosis when policy criteria are met.

There is not enough research to show surgical treatment for hyperhidrosis improves health outcomes for all other conditions and/or complications. Therefore, surgical treatment for hyperhidrosis is considered not medically necessary when policy criteria are not met.

There is not enough research to show that surgical treatments of hyperhidrosis including, but not limited to lumbar sympathectomy, axillary liposuction or curettage performed alone or in combination with any other procedure, subdermal laser-assisted axillary hyperhidrosis treatment, percutaneous radiofrequency sympathicolysis or sympathectomy and radiofrequency ablation for palmar hyperhidrosis improves health outcomes for people with hyperhidrosis. There are no evidence-based clinical practice guidelines recommending these

procedures for the treatment of hyperhidrosis. Therefore, these techniques are considered investigational.

REFERENCES

1. Society IH. Diseases and Conditions that Can Cause Hyperhidrosis. [cited 03/13/2023]. 'Available from:' https://www.sweathelp.org/pdf/Diseases_2009.pdf.
2. Deng B, Tan QY, Jiang YG, et al. Optimization of sympathectomy to treat palmar hyperhidrosis: the systematic review and meta-analysis of studies published during the past decade. *Surg Endosc.* 2011;25(6):1893-901. PMID: 21136103
3. Youssef T, Soliman M. Unilateral sequential endoscopic thoracic sympathectomy for palmar hyperhidrosis: a proposed technique to overcome compensatory hyperhidrosis and improve plantar hyperhidrosis. *J Laparoendosc Adv Surg Tech A.* 2015;25(5):370-4. PMID: 25768057
4. Heidemann E, Licht PB. A comparative study of thoracoscopic sympathicotomy versus local surgical treatment for axillary hyperhidrosis. *Ann Thorac Surg.* 2013;95(1):264-8. PMID: 23200232
5. Yuncu G, Turk F, Ozturk G, et al. Comparison of only T3 and T3-T4 sympathectomy for axillary hyperhidrosis regarding treatment effect and compensatory sweating. *Interact Cardiovasc Thorac Surg.* 2013;17:263-7. PMID: 23644731
6. Ibrahim M, Menna C, Andreetti C, et al. Two-stage unilateral versus one-stage bilateral single-port sympathectomy for palmar and axillary hyperhidrosis. *Interact Cardiovasc Thorac Surg.* 2013;16:834-8. PMID: 23442937
7. Baumgartner FJ, Reyes M, Sarkisyan GG, et al. Thoracoscopic sympathicotomy for disabling palmar hyperhidrosis: a prospective randomized comparison between two levels. *Ann Thorac Surg.* 2011;92(6):2015-9. PMID: 22115211
8. Ishy A, de Campos JR, Wolosker N, et al. Objective evaluation of patients with palmar hyperhidrosis submitted to two levels of sympathectomy: T3 and T4. *Interact Cardiovasc Thorac Surg.* 2011;12(4):545-8. PMID: 21233258
9. Inan K, Goksel OS, Ucak A, et al. Thoracic endoscopic surgery for hyperhidrosis: comparison of different techniques. *Thorac Cardiovasc Surg.* 2008;56(4):210-3. PMID: 18481239
10. Wait SD, Killory BD, Lekovic GP, et al. Thoracoscopic sympathectomy for hyperhidrosis: analysis of 642 procedures with special attention to Horner's syndrome and compensatory hyperhidrosis. *Neurosurgery.* 2010;67(3):652-6; discussion 56-7. PMID: 20647968
11. de Andrade Filho LO, Kuzniec S, Wolosker N, et al. Technical difficulties and complications of sympathectomy in the treatment of hyperhidrosis: an analysis of 1731 cases. *Annals of vascular surgery.* 2013;27(4):447-53. PMID: 23406790
12. Chudry H. The treatment of palmar hyperhidrosis - a systematic review. *Int J Dermatol.* 2022;61(11):1303-10. PMID: 34653261
13. Lima SO, Santos RS, Moura AMM, et al. A systematic review and meta-analysis to evaluate the efficacy of lumbar sympathectomy for plantar hyperhidrosis. *Int J Dermatol.* 2019;58(8):982-86. PMID: 31099425
14. Loureiro Mde P, de Campos JR, Kauffman P, et al. Endoscopic lumbar sympathectomy for women: effect on compensatory sweat. *Clinics (Sao Paulo).* 2008;63:189-96. PMID: 18438572

15. Coelho M, Kondo W, Stunitz LC, et al. Bilateral retroperitoneoscopic lumbar sympathectomy by unilateral access for plantar hyperhidrosis in women. *J Laparoendosc Adv Surg Tech A.* 2010;20(1):1-6. PMID: 19943777
16. Reisfeld R, Pasternack GA, Daniels PD, et al. Severe plantar hyperhidrosis: an effective surgical solution. *The American surgeon.* 2013;79(8):845-53. PMID: 23896256
17. Singh S, Kaur S, Wilson P. Early experience with endoscopic lumbar sympathectomy for plantar hyperhidrosis. *Asian journal of endoscopic surgery.* 2016. PMID: 26822187
18. Wade R, Llewellyn A, Jones-Diette J, et al. Interventional management of hyperhidrosis in secondary care: a systematic review. *The British journal of dermatology.* 2018;179(3):599-608. PMID: 29573391
19. Ibrahim O, Kakar R, Bolotin D, et al. The comparative effectiveness of suction-curettage and onabotulinumtoxin-A injections for the treatment of primary focal axillary hyperhidrosis: a randomized control trial. *J Am Acad Dermatol.* 2013;69(1):88-95. PMID: 23591103
20. Park S. Very superficial ultrasound-assisted lipoplasty for the treatment of axillary osmidrosis. *Aesthetic Plast Surg.* 2000;24(4):275-9. PMID: 10954790
21. Tsai RY, Lin JY. Experience of tumescent liposuction in the treatment of osmidrosis. *Dermatol Surg.* 2001;27(5):446-8. PMID: 11359491
22. Swinehart JM. Treatment of axillary hyperhidrosis: combination of the starch-iodine test with the tumescent liposuction technique. *Dermatol Surg.* 2000;26(4):392-6. PMID: 10759833
23. Shenaq SM, Spira M, Christ J. Treatment of bilateral axillary hyperhidrosis by suction-assisted lipolysis technique. *Ann Plast Surg.* 1987;19(6):548-51. PMID: 3439770
24. Ong WC, Lim TC, Lim J, et al. Suction-curettage: treatment for axillary hyperhidrosis and hidradenitis. *Plast Reconstr Surg.* 2003;111(2):958-9. PMID: 12560743
25. Chern E, Yau D, Chuang FC, et al. Arthroscopic shaver with refinement for axillary osmidrosis. *Int J Dermatol.* 2010;49(7):813-7. PMID: 20618505
26. Laser Therapy for Hyperhidrosis: A Review of the Clinical Effectiveness and Guidelines [Internet]. 2015. PMID: 26180877
27. Hasimoto FN, Cataneo DC, Hasimoto EN, et al. Radiofrequency in the treatment of primary hyperhidrosis: systematic review and meta-analysis. *Clin Auton Res.* 2020;30(2):111-20. PMID: 31552511
28. Mostafa TAH, Hamed AA, Mohammed BM, et al. C-Arm Guided Percutaneous Radiofrequency Thoracic Sympathectomy for Treatment of Primary Palmar Hyperhidrosis in Comparison with Local Botulinum Toxin Type A Injection, Randomized Trial. *Pain Physician.* 2019;22(6):591-99. PMID: 31775406
29. Rummaneethorn P, Chalermchai T. A comparative study between intradermal botulinum toxin A and fractional microneedle radiofrequency (FMR) for the treatment of primary axillary hyperhidrosis. *Lasers Med Sci.* 2020;35(5):1179-84. PMID: 31939036
30. Cerfolio RJ, De Campos JR, Bryant AS, et al. The Society of Thoracic Surgeons expert consensus for the surgical treatment of hyperhidrosis. *Ann Thorac Surg.* 2011;91(5):1642-8. PMID: 21524489

CODES

NOTE: Codes 11450 and 11451 should not be reported when there is a diagnosis of hyperhidrosis.

Codes	Number	Description
CPT	32664	Thoracoscopy, surgical; with thoracic sympathectomy

Codes	Number	Description
	64818	Sympathectomy, lumbar
	69676	Tympanic neurectomy
HCPCS	None	

Date of Origin: *November 1999*

Regence

Medical Policy Manual Surgery, Policy No. 166

Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome

Effective: January 1, 2024

Next Review: October 2024
Last Review: November 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

When conservative therapies for obstructive sleep apnea or upper airway resistance syndrome fail, established surgical interventions may be indicated.

MEDICAL POLICY CRITERIA

Note: Contract language takes precedent over medical policy. Some member contracts have specific benefit limitations for orthognathic and telegnathic surgery.

Pediatric Patients

I. In pediatric patients (age 17 years and younger), surgical treatment for obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) may be considered **medically necessary** when the request is not for any of the investigational procedures listed in Criterion III. below.

II. In pediatric patients, surgical treatment of snoring in the absence of documented obstructive sleep apnea is considered **not medically necessary**.

III. In pediatric patients, surgical treatment of obstructive sleep apnea (OSA) and upper

airway resistance syndrome (UARS) using any one or more of the following procedures is considered **investigational**:

A. Laser-assisted uvulopalatoplasty (LAUP) or volumetric tissue reduction

B. Palatal stiffening procedures, including but not limited to the following: Cautery-assisted palatal stiffening operation (CAPSO), injection of sclerosing agent (also known as snoreplasty), and implantation of palatal implants (also known as the pillar procedure)

C. Radiofrequency volumetric tissue reduction of the tongue base or palatal tissues

D. Tongue base suspension procedures, including but not limited to the AIRvance™ and the Encore™ tongue suspension systems

E. Uvulectomy

Adult Patients

IV. Surgical procedures for the treatment of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients (age 18 years and older) may be considered **medically necessary** when all of the criteria below (A. - E.) are met:

A. There is documentation of a sleep study performed within the last 3 years; and

B. One or more of the following procedures are requested:

a. Hyoid myotomy and suspension

b. Mandible osteotomy with or without genioglossus advancement

c. Maxillo-mandibular advancement (MMA)

d. Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty [UPPP], uvulopharyngoplasty)

e. Partial Glossectomy

C. Evidence, documented in the medical records, of exam findings that demonstrate upper airway collapse or obstruction as a reasonable cause of obstructive sleep apnea (e.g., palatine tonsils, epiglottis collapse, arytenoid collapse, lateral pharyngeal, craniofacial deficits).

D. The patient meets criteria for clinically significant obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS) as defined by Criteria 1. or 2. below:

1. Clinically significant obstructive sleep apnea (OSA) defined as Criteria a. or b. below:

a. An AHI equal to or greater than 15 per hour; or

b. An AHI equal to or greater than 5 per hour with at least one of the following associated symptoms:

i. Excessive daytime sleepiness that is not better explained by other factors

ii. Documented unexplained hypertension

iii. Ischemic heart disease or congestive heart failure

iv. Atrial fibrillation

v. History of stroke

vi. Obesity

vii. Diabetes and glucose intolerance

viii. Two or more of the following that are not better explained by other factors:

a.) Choking or gasping during sleep

b.) Recurrent awakenings during sleep

c.) Unrefreshing sleep with daytime fatigue

d.) Impaired concentration or cognition

e.) Insomnia

2. Upper airway resistance syndrome (UARS) that is clinically significant is defined as greater than 10 alpha EEG arousals per hour.

E. All of the following conservative medical therapies have failed to improve apnea/hypopnea including associated conditions such as excess daytime sleepiness:

1. Adjustment in sleep position when the sleep study shows improvement of sleep apnea when non-supine; and

2. An adequate trial (at least 3 consecutive months [90 days] of continuous [at least 5 nights per week]) of a custom-made mandibular repositioning appliance has failed OR the patient is not an appropriate mandibular repositioning appliance candidate (see Policy Guidelines); and

3. An adequate positive airway pressure (PAP, continuous or bi-level) trial that is a minimum of 4 hours per night for 3 weeks of PAP usage has failed OR the patient is not an appropriate PAP candidate (see Policy Guidelines).

V. Surgical treatment of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients is considered **not medically necessary** when Criterion IV. is not met, including PAP therapy refusal, or to treat snoring in the absence of documented obstructive sleep apnea in adult patients.

VI. Surgical treatments of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients not listed in Criterion IV.B. are considered **investigational** including, but not limited to the following:

A. Laser-assisted uvulopalatoplasty (LAUP) or volumetric tissue reduction

B. Palatal stiffening procedures, including but not limited to cautery-assisted palatal stiffening operation (CAPSO), injection of sclerosing agent (also known as snoreplasty), or implantation of palatal implants (also known as the pillar procedure)

C. Radiofrequency volumetric tissue reduction of the tongue base or palatal tissues

D. Tongue base suspension procedures, including but not limited to the AIRvance™ and the Encore™ tongue suspension systems

E. Uvulectomy

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

MANDIBULAR REPOSITIONING DEVICE

Not all patients are candidates for a mandibular repositioning device. Patients with tonsil hypertrophy criteria grade 3 or 4 on the Friedman scale, severe psychiatric diseases or dementia, untreated caries or periodontal disease, few teeth for anchoring a device, temporomandibular joint disorder, inadequate mandibular protrusive capacity, and class III malocclusion are examples of conditions that are contraindications to mandibular repositioning appliances.

POSITIVE AIRWAY PRESSURE (PAP)

PAP failure: defined as AHI greater than 20 events per hour while using PAP.

Not an appropriate PAP candidate: defined as being unable to use PAP therapy for at least 4 hours per night for 5 nights or more per week, with reasonable attempts having been made to address any medical, mechanical, or psychological problems associated with PAP, e.g., adjustment of pressure settings, appropriate medication and humidification, refitting of the mask, trial of alternative pressure delivery systems such as auto-adjusting positive airway pressure or bi-level positive airway pressure.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Conservative Medical Therapies failed
- PAP Trial results
- Sleep Study results
- Documentation of an adequate trial of a mandibular repositioning device or documentation that the patient is not an appropriate appliance candidate with clinical rationale
- Evidence of airway obstruction or narrowing consistent with the procedure requested

CROSS REFERENCES

1. Prefabricated Oral Appliances for Obstructive Sleep Apnea, Allied Health, Policy No. 36
2. Orthognathic Surgery, Surgery, Policy No. 137
3. Absorbable Nasal Implant for Treatment of Nasal Valve Collapse, Surgery, Policy No. 209
4. Phrenic Nerve Stimulation for Central Sleep Apnea, Surgery, Policy No. 212
5. Hypoglossal Nerve Stimulation, Surgery, Policy No. 215
6. Cryoablation for Chronic Rhinitis, Surgery, Policy No. 224

BACKGROUND

OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep. The hallmark symptom of OSA is excessive daytime sleepiness, and the typical clinical sign of OSA is snoring, which can abruptly cease and be followed by gasping associated with a brief arousal from sleep. The snoring resumes when the patient falls back to sleep, and the cycle of snoring/apnea/arousal may be repeated as frequently as every minute throughout the night.

Sleep fragmentation associated with the repeated arousal during sleep can impair daytime activity. For example, adults with OSA-associated daytime somnolence are thought to be at higher risk for accidents involving motorized vehicles (i.e., cars, trucks, heavy equipment). OSA in children may result in neurocognitive impairment and behavioral problems. In addition, OSA affects the cardiovascular and pulmonary systems. For example, apnea leads to periods of hypoxia, alveolar hypoventilation, hypercapnia, and acidosis. This, in turn, can cause systemic hypertension, cardiac arrhythmias, and cor pulmonale. Systemic hypertension is common in patients with OSA. Severe OSA is associated with decreased survival, presumably related to severe hypoxemia, hypertension, or an increase in automobile accidents related to overwhelming sleepiness.

A polysomnogram performed in a sleep laboratory and, in adults, home sleep apnea testing with a technically adequate device (see Appendix 1), are considered the gold standard tests used to diagnose OSA in adults.[1] Objective measures of OSA are compiled using polysomnography monitors, which document the number of apneic and hypopneic events per hour and combine them into the apnea-hypopnea index (AHI). The respiratory disturbance index (RDI) may be defined as the number of apneas, hypopneas and respiratory effort-related arousals (RERAs) per hour of sleep. The final diagnosis of OSA rests on a combination of objective and subjective criteria (e.g. AHI or RDI and excessive daytime sleepiness) that seek to identify those levels of obstruction which are clinically significant. When sleep onset and offset are unknown (e.g., in home sleep studies) the AHI or RDI may be calculated based on the number of apneas, hypopneas, and/or RERAs per hour of recording time.

An increase in mortality is associated with an AHI greater than 15. More difficult to evaluate is the clinical significance of patients with mild sleep apnea. Mortality has not been shown to be increased in these patients, and frequently the most significant manifestations reported by the patient are snoring, excessive daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, nocturia, morning headaches, memory loss, irritability, or hypertension.[2, 3] The hallmark clinical symptom of OSA is excessive snoring, although it is important to note that snoring can occur in the absence of OSA. Isolated snoring in the absence of medical complications, while troubling to the patient's bed partner, is not considered a medical problem requiring surgical intervention.

There are racial and ethnic health disparities seen for OSA, impacting the prevalence of disease and accessibility to treatment options, particularly affecting children. Black children are four to six times more likely to have OSA than white children.[4] Among young adults younger than 26 years, African American individuals are 88% more likely to have OSA compared to white individuals. Another study found that African American individuals 65 years of age and older were 2.1 times more likely to have severe OSA than white individuals of the same age group. These health disparities may affect accessibility of treatment for OSA and impact health

outcomes. One analysis of insurance claims data, including over 500,000 patients with a diagnosis of OSA, found that increased age above the 18- to 29- year range (p<0.001) and Black race (p=.020) were independently associated with decreased likelihood for receiving surgery for sleep apnea.[5] Lee (2022) found that Black men had a continuous mortality increase specifically related to OSA over the study period (1999 to 2019; annual percentage change 2.7%; 95% confidence interval, 1.2 to 4.2) compared to any other racial group.[6]

Table 1. Definitions of Terms for Obstructive Sleep Apnea

Terms	Definition
Apnea	The frequency of apneas and hypopneas is measured from channels assessing oxygen desaturation, respiratory airflow, and respiratory effort. In adults, apnea is defined as a drop in airflow by ≥90% of pre-event baseline for at least 10 seconds. Due to faster respiratory rates in children, pediatric scoring criteria define an apnea as ≥2 missed breaths, regardless of its duration in seconds.
Hypopnea	Hypopnea in adults is scored when the peak airflow drops by at least 30% of pre-event baseline for at least 10 seconds in association with either at least 3% arterial oxygen desaturation or an arousal or at least 4% arterial oxygen desaturation (depending on the scoring criteria). Hypopneas in children are scored by a ≥50% drop in nasal pressure and either a ≥3% decrease in oxygen saturation or an associated arousal.
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Obstructive sleep apnea (OSA)	Repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep
Mild OSA	In adults: AHI of 5 to <15 In children: AHI ≥1 to <5
Moderate OSA	In adults: AHI of 15 to <30 In children: AHI ≥5 to <10
Severe OSA	Adults: AHI ≥30 Children: AHI ≥10
Continuous positive airway pressure (CPAP)	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP) or Bi-level (Bi-PAP). CPAP is a more familiar abbreviation and will refer to all types of PAP devices.
PAP Failure	Usually defined as an AHI greater than 20 events per hour while using PAP (continuous or bi-level)
PAP Intolerance	PAP use for less than 4 h per night for 5 nights or more per week, or refusal to use PAP (continuous or bi-level). PAP intolerance may be observed in patients with mild, moderate, or severe OSA

UPPER AIRWAY RESISTANCE SYNDROME (UARS)

Upper airway resistance syndrome (UARS) was initially used to describe a variant of OSA which is characterized by a partial collapse of the airway resulting in increased resistance to airflow. This resistance does not result in apnea, but the increased respiratory effort required to move air into the lungs results in fragmented sleep. These sleep fragmentations (RERAs) can be measured using an electroencephalogram (EEG). Diagnosis of UARS rests on documentation of more than 10 EEG arousals per hour of sleep along with documented episodes of abnormally negative intrathoracic pressure (i.e., more negative than -10 cm) associated with the EEG arousals. The drop in intrathoracic pressure can be measured by a variety of tests including use of an esophageal manometer, if available, as part of a polysomnogram. RERAs can also be detected absent manometry during polysomnography. It

has been proposed that UARS is a distinct syndrome from OSA that may be considered a disease of arousal.

See Appendix 1 for additional information on diagnostic tests for OSA and UARS.

SURGICAL TREATMENTS FOR OSA AND UARS

Medical therapy is considered the first-line treatment for OSA and UARS. These therapies include weight loss, various continuous positive airway pressure (CPAP) devices, or orthodontic repositioning devices in appropriate patients. See Appendix 2 for a description of medical devices used in the treatment of OSA and UARS. Most guidelines consider surgical intervention only after all appropriate medical treatments for OSA or UARS have failed. Conventional surgeries for OSA include uvulopalatopharyngoplasty (UPPP) and a variety of maxillofacial surgeries such as maxillo-mandibular advancement (MMA).

Uvulopalatopharyngoplasty (UPPP)

UPPP involves surgical modification of the oropharynx and/or velopharynx by resection or reconstruction of the associated structures (soft palate, uvula, and associated muscles).[7, 8] The UPPP procedure enlarges the oropharynx but cannot correct obstructions in the hypopharynx. Therefore, if hypopharynx obstruction is identified, then alternate procedures are considered. In addition, patients who fail UPPP may be candidates for additional procedures, depending on the site of obstruction. Additional or alternate procedures include hyoid suspensions, maxillary and mandibular osteotomies, and mandibular and maxillary advancement surgery.

Mandibular and maxillary advancement (MMA) surgery

Mandibular and maxillary advancement (MMA) surgery (may also be referred to as telegnathic surgery) is more extensive and is proposed for patients who do not have an adequate response to UPPP or other procedures, or who have mandibular or maxillary deficiency. These surgeries may be used to correct obstruction of the hypopharynx, oropharynx, or velopharynx; the areas of the full length of the throat.

Laser assisted uvuloplasty (LAUP)

LAUP is an outpatient procedure that has been proposed as a treatment of snoring with or without associated OSA. In this procedure, the tissues of the soft palate (palatal tissues) are reshaped using a laser. The extent of the surgery is typically different than standard UPPP, since only part of the uvula and associated soft-palate tissues are reshaped. The procedure, as initially described, does not remove or alter tonsils or lateral pharyngeal wall tissues. The patient undergoes from 3 to 7 sessions at 3- to 4-week intervals. LAUP cannot be considered an equivalent procedure to the standard UPPP, with the laser simply representing a surgical tool that the physician may opt to use. LAUP is considered a unique procedure, raising unique issues of safety and effectiveness.

Palatal stiffening procedures and radiofrequency tissue reduction

<u>Radiofrequency ablation of the soft palate and radiofrequency volumetric reduction of the tongue base (RFTBR)</u>

Radiofrequency energy is used to produce thermal lesions within the tissues. Radiofrequency devices transmit low frequency energy that causes ionic friction, which leads to coagulation necrosis, inflammation, and fibrosis.[9] These procedures may reduce the volume of soft tissue and may stiffen the tissue due to the creation of a submucosal scar. Radiofrequency based treatments to modify tissues of the soft palate have historically been referred to as somnoplasty.

Cautery assisted palatal stiffening procedure (CAPSO)

This palatal stiffening procedure uses cautery (electrically heated probes) to induce a midline palatal scar designed to stiffen the soft palate to eliminate excessive snoring.

Other palatal stiffening procedures

Other palatal stiffening procedures in use include injection sclerotherapy (also known as injection snoreplasty) and the pillar procedure, which involves the permanent implantation of braided polyester filaments into the soft palate through a needle.

Suspension of the tongue base and hyoid bone

Tongue or hyoid bone suspension is performed through a small incision under the chin. A titanium screw is inserted under the chin in the posterior aspect of the lower jaw at the floor of the mouth. For tongue suspension, a loop of suture is passed through the tongue base and attached to the mandibular bone screw. For hyoid suspension a suspension loop is placed around the hyoid bone and anchored to the mandibular screw or to the thyroid cartilage. Once the suspension loop is attached to the screw it is pulled forward to advance the tongue base out of the airway, making it less likely for the base of the tongue to drop backward during sleep.

Uvulectomy

This procedure surgically removes the uvula, the small tissue hanging from the soft palate at the back of the throat above the tongue. The uvula, which helps stiffen and shape the back of the throat and prevents food from going down the airway, is believed to be associated with excessive snoring.

Partial Glossectomy

This procedure, also referred to as midline glossectomy, surgically removes a portion of the tongue in an effort to reduce tongue volume and open the oropharynx and/or hypopharynx.

REGULATORY STATUS

The Somnoplasty® device has been cleared for marketing by FDA for RFA of palatal tissues for simple snoring and for the base of the tongue for OSA. FDA product code: GEI.

AIRvance® (Medtronic; formerly the Repose™ Bone Screw System from Influence) was cleared for marketing through the FDA 510(k) process in 1999 with intended use for anterior tongue base suspension by fixation of the soft tissue of the tongue base to the mandible bone using a bone screw with prethreaded suture. It is indicated for the treatment of OSA and/or snoring.

The Encore™ Tongue Suspension System (Siesta Medical) received clearance for marketing by FDA in 2011, citing the PRELUDE III Tongue Suspension System (Siesta Medical) as a predicate device.

The Pillar® Palatal Implant System (originally Restore Medical, St. Paul, MN, acquired by Medtronic, Minneapolis, MN) is an implantable device that has been cleared for marketing through the FDA 510(k) process. The labeled indication of the device is as follows: “The Pillar™ Palatal Implant System is intended for the reduction of the incidence of airway obstructions in patients suffering from mild to moderate OSA (obstructive sleep apnea).” FDA product code: LRK.

EVIDENCE SUMMARY

Positive airway pressure (PAP, continuous or bi-level) is the most widely accepted medical therapy for treatment of obstructive sleep apnea (OSA) in adults and improvement of primary health outcomes such as cardiovascular disease, type 2 diabetes, and overall mortality associated with OSA.[8] Surgical interventions are being proposed as a second line treatment for patients who have experienced PAP failure or intolerance.

Appropriately controlled and adequately powered, long-term randomized controlled trials (RCTs) are needed to determine the safety and effectiveness of various surgical interventions for treatment of OSA.

The evidence suggests conventional uvulopalatopharyngoplasty (UPPP), hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as maxillo-mandibular advancement (MMA), may improve health outcomes for some patients with OSA who have failed medical therapies for OSA.

- The available evidence does not currently support the widespread use of surgical interventions in the management of unselected patients with obstructive sleep apnea. Given the proven safety and efficacy of CPAP in patients with moderate and severe symptoms and significant sleep disordered breathing, surgery cannot be recommended as a first line therapy, ahead of positive airways pressure systems.[8, 10]
- While studies on UPPP and hyoid suspension procedures were not randomized, data from ten studies which included more than 750 patients consistently reported improved outcomes for patients with OSA as measured by postoperative polysomnographic assessment of sleep disturbance and compared with concurrent groups being treated with CPAP.[11]
- UPPP, hyoid suspension, mandible osteotomy, partial glossectomy and MMA procedures are widely practiced among surgeons in the United States. These procedures have been considered a standard of care in the medical community.[11]

Evidence is uncertain for use of other surgical interventions in the treatment of OSA, including but not limited to uvulectomy and minimally invasive surgical procedures such as laser-assisted uvuloplasty (LAUP), radiofrequency tongue base reduction (RFTBR), pillar stiffening procedures, and pillar implants. Therefore, the following evidence review will be focused on the investigational indications in this policy.

SURGICAL TREATMENTS FOR OSA

Technology Assessments and Systematic Reviews

Maniaci (2022) compared the efficacy and success rates of lateral pharyngoplasty techniques (LP) vs. uvulopalatopharyngoplasty (UPPP) among adult patients surgically treated for obstructive sleep apnea.[12] Nine articles for a total of 312 surgically treated patients with OSA were included in this systematic review. LP techniques for obstructive sleep apnea were used on 186 (60%) subjects, while 126 patients (40%) were treated with UPPP. Both surgical procedures resulted in significant improvements in apnea-hypopnea index (AHI), Epworth Sleepiness Scale (ESS) score, and lowest oxygen saturation (LOS) ($p<0.001$ in all cases). Although better outcomes were reported with lateral pharyngoplasty, the differences were not significant compared to UPPP post-operative results ($p>0.05$ in all cases). The authors further say, “Further evidence comparing the surgical effect on patients with OSA is needed to discriminate post-operative outcomes”.

A 2011 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review entitled “Diagnosis and Treatment of Obstructive Sleep Apnea in Adults” included studies conducted only in adults, defined as over 16 years of age. The authors state the following regarding the available evidence for surgical interventions for the treatment of OSA:[8]

- *The strength of evidence is insufficient to evaluate the relative efficacy of surgical interventions for the treatment of OSA.*
- *The strength of evidence is insufficient to determine the relative merits of surgical treatments versus CPAP.*
- *Due to the heterogeneity of interventions and outcomes examined, the variability of findings across studies, and the inherent bias of all but one study regarding which patients received surgery, it is not possible at this time to draw useful conclusions comparing surgical interventions with CPAP in the treatment of patients with OSA.*

The review cited the lack of comparative trials between CPAP and proposed surgical modalities and the lack of trial data providing long-term health outcomes associated with OSA treatment as limitations to available evidence.

Earlier evidence-based systematic reviews on the use of surgical therapies in OSA cited the lack of well-designed randomized controlled trials (RCTs) assessing different surgical techniques with inactive and active control treatments.[10, 13] These reviews were not able to make the highest-level recommendation supporting the use of any one surgical intervention. Limitations of studies include heterogeneous patient populations with mixed OSA severity, as measured by AHI; and lack of long-term followup. These reviews state that long-term follow-up of patients who undergo surgical correction of upper airway obstruction would help to determine whether surgery is curative, or whether the signs and symptoms of sleep apnea return, prompting patients to seek further treatment.

The 2009 systematic review by Franklin evaluated benefits and adverse effects of surgery for snoring and OSA.[14] The authors found only a small number of randomized controlled trials (RCTs) that assessed surgical procedures for snoring or sleep apnea. Key findings are as follows:

- Results from 45 studies reporting adverse events revealed persistent side effects after uvulopalatoplasty (UPP) and uvulopalatopharyngoplasty (UPPP) in about half the patients. Difficulty swallowing, globus sensation, and voice changes were especially common. The authors concluded that additional research with RCTs of surgery other

than UPP and UPPP is needed, as these surgical procedures are related to a high risk of adverse effects, especially difficulty swallowing.

- Four RCTs, rated as high quality, were identified for laser-assisted palatoplasty (LAUP) and radiofrequency ablation (RFA).[15-18] Study results were mixed and inconclusive for Apnea/Hypopnea Index (AHI), and showed no benefit on daytime sleepiness or quality of life. Interpretation of this result is limited by the inclusion of studies with one-stage procedures and subjects whose main symptom was disruptive snoring.[17] The relevant trials are described in greater detail below.

RADIOFREQUENCY VOLUMETRIC TISSUE REDUCTION OF THE TONGUE BASE OR PALATAL TISSUES

Systematic Reviews

Baba (2015) performed a systematic review and meta-analysis that addressed the efficacy of temperature controlled radiofrequency tissue ablation (TCRFTA) to alleviate symptoms of OSA.[19] The analyses included three small nonrandomized comparative trials comparing TCRFTA with three different nonsurgical or surgical interventions and seven prospective case series (of which all but one were small). TCRFTA was categorized based on location: base of tongue, soft palate and multilevel. Analysis showed significant reductions in respiratory disturbance index (RDI), Epworth Sleep Scale (ESS), lowest oxygen saturation (LSAT), and snoring for procedures performed at the base of the tongue. TCRFTA at the soft palate showed limited efficacy, although there was a paucity of studies in this area. Multilevel TCFFTA did show a significant reduction in RDI, in the short term. Analysis of AHI was not completed as this outcome was not consistently reported within the studies. The authors reported that the studies were generally of low quality and there was significant heterogeneity which did not allow for strong conclusions. Studies with longer-term outcomes would be useful in evaluating the benefits of this procedure.

In 2008, Farrar published a meta-analysis of RFA for the treatment of OSA in patients with a RDI of 5 or more.[9] Sixteen studies met the inclusion criteria; three were randomized and 13 were nonrandomized. Six studies treated both the base of the tongue and the soft palate, two treated the soft palate only, and eight ablated the base of the tongue only. The population was in the overweight, but not obese, category, with a mean BMI of 28.5. In half of the studies, the average baseline RDI was less than 30, and in six of the studies, the average baseline ESS was less than 10. The meta-analysis indicated a 31% reduction in both ESS and RDI. The lowest oxygen saturation level was not improved by RFA. The mean number of treatments required for patient satisfaction was 3.7 for the soft palate, 4.3 for the base of the tongue, and 4.8 for both sites (range, 3-7). Complications were noted in 4% of patients; two tongue abscesses progressed to airway obstruction requiring tracheotomy. Only two of the studies provided 2-year follow-up, with a 32% reduction in ESS and a 45% reduction in RDI. The number of patients who were successfully treated (e.g., 50% reduction in RDI) was not reported. This meta-analysis is limited by the inclusion of poor-quality uncontrolled studies.

Randomized Controlled Trials

McKay (2020) published the results of a randomized controlled trial (RCT, multicenter, parallel-group, open-label) that compared multilevel surgery (modified uvulopalatopharyngoplasty and radiofrequency tongue volume reduction; n=51) and ongoing medical management (e.g., advice on sleep positioning, weight loss; n=51) for the treatment of OSA.[20] There was a statistically significantly greater improvement from baseline to six months in AHI in the surgery

group (47.9 vs. 20.8) than in the ongoing medical management group (45.3 vs. 34.5, mean baseline-adjusted between-group difference,−17.6 events/h of sleep [95%CI, −26.8 to −8.4]; p<0.001) and in the ESS in the surgery group (12.4 vs 5.3) compared with the ongoing medical management group (11.1 vs 10.5, mean baseline adjusted between-group difference,−6.7 [95%CI,−8.2 to−5.2]; p<0.001). There were six serious adverse events in four participants in the surgery group and no serious adverse events in the ongoing medical management group. Although the results of this study did surpass the minimal clinically important difference for AHI, they did not meet the sufficiently important difference for AHI (the amount needed to account for the cost and potential morbidity of surgery), indicating that further studies are needed to establish the long-term effectiveness, safety, and cost-effectiveness of this surgical treatment for OSA. In addition, women were underrepresented in the trial and the study cohort was limited to a select population that excluded patients with severe obesity (BMI of 38 or greater), patients older than 70 years, and patients with retrognathia and significant comorbidities, limiting generalizability of the outcomes. No comparison of UPPP alone to RF tongue reduction alone or of these procedures alone compared to medical management was provided. Ultimately, the authors conclude “further research is needed to confirm these findings in additional populations and to understand clinical utility, long-term efficacy, and safety of multilevel upper airway surgery for treatment of patients with OSA.”

A single-blinded RCT of single-stage radiofrequency surgery of the soft palate was reported in 2009 by Back.[21] Thirty-two patients with mild OSA (AHI between 5 and 15), habitual snoring, and excessive daytime sleepiness according to subjective patient history, were randomized to a single session of RFA or sham ablation. There was no difference between the groups for baseline to posttreatment (4-6 months) changes in the Epworth Sleepiness Scale (ESS) (3-point improvement in ESS for both groups), reports of snoring (1-point improvement in both groups), AHI (no clinically significant change), or any other outcome measure. None of the patients reported any treatment-related symptoms or complications four months after treatment. Results of this small single-blinded RCT indicate that single-stage RFA of the soft palate is not effective for the treatment of mild OSA.

A RCT from 2009 by Fernandez-Julian compared efficacy and adverse effects of two tongue-based procedures (RFA or tongue-base suspension) when combined with UPPP in 57 patients with moderate-to-severe sleep apnea (AHI ≥15).[22] Patients with a BMI of 35 kg/m^2 or greater were excluded. Although interpretation of results is limited by the lack of a control group treated with UPPP alone, the success rate for combined RFA + UPPP (defined as a ≥50% reduction and final AHI <15) was 51%. BMI was the main predictor of success, with success rates of only 12.5% in patients with a BMI between 30 and less than 35 kg/m^2.

A 2003 two-site RCT study by Woodson compared the use of multilevel RFA with the current criterion standard of CPAP.[16] The study included patients with mild obesity levels (BMI ≥34 kg/m^2) who had mild to moderate sleep apnea with an AHI between 10 and 30. Statistically significant improvement was noted with RFA and CPAP over placebo in OSA-specific quality of life using the Functional Outcomes of Sleep Questionnaire. However, the small size of the trial resulted in most outcomes not being statistically significant. The same group of authors reported a further subgroup analysis from the same trial, focusing on the 26 patients randomized to the RFA arm of the trial to determine whether additional treatments improved outcomes.[23] Specifically, the authors focused on multilevel treatments on various combinations of palatal and tongue tissues. Greater improvements in quality of life were reported for those patients who had a total of five treatments compared with 3. Another subgroup analysis focused on multilevel treatments in 26 patients.[24] This subgroup likely

contains overlapping patients with the previous report, and the results were similar (i.e., greater improvements were reported in those patients who had a total of five treatments).

Nonrandomized Studies

Herman et al (2023) published a prospective, open-label, single-arm, nonrandomized trial that investigated multilevel RFA as an alternative therapy for patients with mild-to-moderate OSA (AHI 10 to 30) with intolerance or inadequate adherence to CPAP.[25] Patients were treated with three sessions of office-based RFA to the soft palate and tongue base. Of the 56 patients recruited for the study, 43 completed the protocol. Overall, 22/43 (51%) were considered complete responders with a ≥50% reduction in baseline AHI and an overall AHI <20 at study completion. A reduction in mean and median AHI was observed at six months follow-up (p=.001 for both); the mean AHI decreased from 19.7 to 9.86 and the median AHI decreased from 17.8 to 7.5. Likewise, ODI scores were significantly reduced at 6 months follow-up; the mean ODI score decreased from 12.79 to 8.36 (p=.006) and the median ODI score decreased from 11.65 to 6.23 (p=.008).

A 2008 retrospective cohort study assessed the incremental value of RFA of the tongue in combination with UPPP.[26] All patients with both palatal and retroglossal obstruction, an RDI between 5 and 50, and no previous OSA surgery were included in the study. Seventy-five patients meeting the inclusion criteria had been treated with UPPP during the three year period, 38 had UPPP alone, 37 had UPPP plus RFA. The groups were comparable for age, sex, BMI, AHI, and mean arterial oxygen saturation (Sa_{O_2}); however, no details were provided regarding the choice of procedure. With surgical success rate defined as more than 50% reduction of the AHI and AHI below 20, the success rate was 42% with UPPP alone and 49% with RFA (not significantly different). Two patients had an additional RFA treatment. No major complications were observed. The study concluded that the addition of RFA to UPPP resulted in only limited improvement, but there was no major downside to it.

Two earlier case series have been published by Steward (2005) and Stuck (2004) on the use of radiofrequency ablation of both tongue base and soft palate tissue, referred to as a combined or multi-level radiofrequency tissue ablation technique.[27, 28] Both case series reported significant improvements, including reductions in mean respiratory disturbance and apnea-hypopnea indexes, and in one case series these improvements persisted for a median of 23 months. However, both case series are limited by size, including 29 and 20 patients, respectively, and potential selection bias among the included participants. In addition, the ability to detect true long-term efficacy of this treatment is limited by the case series study design with lack of control group.

Radiofrequency Volumetric Tissue Reduction of the Tongue Base or Palatal Tissues Section Summary

The evidence for the use of radiofrequency volumetric tissue reduction of the tongue base or palatal tissues for the treatment of obstructive sleep apnea or upper airway resistance syndrome includes two systematic reviews, three randomized controlled trials, and four non-randomized studies. The considerable heterogeneity of outcomes tested across studies does not allow for conclusions about the potential benefit of these procedures. Additional appropriately controlled studies are needed to inform the clinical outcomes of these procedures alone or in addition to standard of care, as well as to evaluate the long-term benefits of these procedures.

TONGUE BASE SUSPENSION PROCEDURES

Systematic Reviews

In 2013, Handler reported a systematic review of tongue suspension versus hypopharyngeal surgery for the treatment of OSA.[29] The review included 27 studies reporting on four separate procedures; tongue suspension alone, tongue suspension + UPPP, genioglossus advancement (GA) + UPPP, and genioglossus advancement + hyoid suspension (GAHM) + UPPP. A successful treatment was defined as a 50% decrease in the RDI or AHI and a postoperative RDI or AHI less than 20. Tongue suspension alone (six studies, 82 patients) had a success rate of 36.6%, while the success rate of tongue suspension + UPPP (eight studies, 167 patients) was 62.3%. A success rate of 61.1% was found for GA + UPPP (seven studies, 151 patients) and for GAHM + UPPP (12 studies, 467 patients). The adverse effects of tongue suspension appear to be milder than GA or GAHM and are reversible. Most of the studies identified in this review were level IV evidence (case series).

Randomized Controlled Trial

One level II RCT by Fernandez-Julian (2009) included in the systematic review compared two tongue base surgeries (RFA or tongue-base suspension) combined with UPPP for moderate to severe sleep apnea (AHI ≥15).[22] In the tongue suspension plus UPPP group (n=28), the mean AHI decreased from 33.1 to 15.1 events per hour. The success rate for the combined procedure (defined as a ≥50% reduction, final AHI <15, and ESS <11) was 57.1%, compared with a success rate of 51.7% in the UPPP plus RFA group (p=0.79). BMI was the main predictor of success, with a success rate for tongue base suspension plus UPPP of only 10% in patients with a BMI between 30 and 35 kg/m^2. Morbidity and complications were higher with the tongue suspension procedure compared with RFA.

Nonrandomized Studies

In 2013, Li conducted a nonrandomized comparative study to evaluate the use of the Repose system in conjunction with UPPP to treat patients with obstructive sleep apnea hypopnea syndrome (OSAHS) caused by suspected glossoptosis.[30] Seventy-eight patients with OSAHS caused by suspected glossoptosis were non-randomly divided into two groups. The 45 patients in the first group received UPPP and tongue-base suspension (Repose). The 33 patients in the second group received UPPP alone. Follow-up was conducted over six months, and polysomnography was used to determine the effects of treatment. Follow-up results at six months revealed that the degree of improvement in patients treated with UPPP + Repose was significantly greater than that seen in patients treated with UPPP alone. In the UPPP + Repose group, 17 patients were cured, 23 showed marked improvement, and five did not improve. In the UPPP alone group, one patient was cured, 16 showed marked improvement, and 16 did not improve. The marked improvement rates of the two groups were 88.9 and 51.5 %, respectively, a significant difference.

In a 2010 multicenter, prospective case series, Woodson assessed the safety and effectiveness of an adjustable lingual suspension device (Advance System) for treating OSA.[31] Forty two surgically naive patients with moderate to severe OSA and tongue base obstruction underwent surgical insertion of a midline tissue anchor into the posterior tongue and connected to an adjustable mandibular bone anchor with a flexible tether. Outcomes included changes in AHI, sleepiness, sleep-related quality-of-life, snoring, swallowing, speech and pain. After six months, all patients noted improvement for AHI, sleepiness and sleep-

related quality of life. Post implant pain scores were mild to moderate at day one and resolved by day five. Device related adverse events included wound infection (7%) and edema or seroma (5%), which resolved. However, in 31 percent of patients, asymptomatic tissue anchor barb fractures were observed radiographically. The tissue anchor failure rate of the tested device precludes its clinical use. Further investigation is warranted.

In 2002, Miller conducted a retrospective analysis of the Repose System for the treatment of OSA to describe preliminary experience using the system in conjunction with UPPP in the multilevel surgical approach.[32] The authors evaluated 19 consecutive patients undergoing UPPP and the Repose System tongue base suspension for the management of OSA during a one-year period. Fifteen patients had complete preoperative and postoperative PSG data. A 46% reduction in RDI was demonstrated at a mean of 3.8 months after surgery. The apnea index demonstrated a 39% reduction. The authors concluded that the Repose System in conjunction with UPPP has been shown to produce significant reductions in the RDI and apnea index, as well as a significant increase in oxygen saturation. Despite the improvement in these objective parameters, the overall surgical cure rate was only 20% (three of 15 patients) in this retrospective series. Further research is warranted to define the role of the Repose System in the management of obstructive sleep apnea patients.

In 2000, DeRowe performed minimally invasive technique for tongue-base suspension with the Repose system in 16 patients with sleep-disordered breathing.[33] Fourteen patients reported an improvement in daytime sleepiness, and their bed partners reported an improvement in snoring. The mean respiratory distress index before surgery was 35. Two months after surgery, the mean respiratory distress index was 17, an improvement of 51.4%. These preliminary results show the initial efficacy and safety of this new surgical procedure. Similar improvements were reported in other small case series (n=8-14 patients with OSA) who underwent the same procedure.[34-36]

Tongue Base Suspension Procedures Section Summary

Evidence for the tongue base suspension procedures for the treatment of sleep apnea or upper airway resistance syndrome includes one systematic review, one randomized controlled trial, and four non-randomized studies. These studies report low success rates of the procedure, particularly in obese individuals, and adverse events including wound infection, edema, pain, and tissue anchor barb fractures are reported. Long-term outcomes of the procedure are not well characterized. Additional studies with longer end-points including those addressing safety and efficacy are needed.

LASER-ASSISTED PALATOPLASTY

Systematic Reviews

Wischhusen (2019) published a SR evaluating the complications and side effects of laser-assisted uvulopalatoplasty (LAUP) across 42 studies (N=3,093). Mean follow-up was 16.1 months (median six months, range of 0.5 – 134 months).[37] Across all 42 studies, the total number of LAUP complications based on a population of 1,000 patients with a 95% CI was reported as 255.71 ± 23.33. The authors also calculated relative risk of specific complications compared to published population studies and found significant effects for complications of globus sensation and velopharyngeal (VP) insufficiency with 95% CI of 1.07–2.06 and 1.29–3.94, respectively. In the four studies with the longest follow-up duration with a mean of 100.5 months, these complications were 12.2% and 10.8%, respectively, suggesting that these may

be long-term complications of the procedure. The authors conclude “based on the findings of this systematic review, we recommend that LAUP be performed with caution using the tissue-sparing approach or avoided altogether, given the potential for complications identified in the current literature.”

Randomized Controlled Trials

Ferguson (2003) reported a trial that randomized 45 subjects with mild-to-moderate sleep apnea (defined as an AHI ranging between 10-27 per hour) to either uvulopalatoplasty (LAUP) or no treatment.[15] The LAUP procedure was repeated at 1- to 2-month intervals until either the snoring was significantly reduced, no more tissue could safely be removed, or the patient refused further procedures. The primary outcome measurement was the reduction in AHI in the LAUP group versus the control group. An AHI of less than 10 was considered a successful treatment. In the treatment group, 24% were considered treatment successes and 76% were failures. In the control group (who received no therapy), 16.7% were considered treatment successes. The authors concluded that LAUP can be effective in some patients, but the reduction in AHI and the level of symptomatic improvement were minor overall.

Nonrandomized Studies

In 1995, Walker prospectively evaluated the outcomes of 65 patients who underwent LAUP for the treatment of OSA.[38] Of the 65 OSAS patients treated with LAUP, postoperative polysomnograms were obtained in 33 patients (51%). Surgical success was achieved in 16 (48%) of the 33 patients. However, seven patients (21%) had repeat polysomnograms that were worse than their preoperative polysomnograms, and five patients (15%) had no significant change.

CAUTERY-ASSISTED PALATAL STIFFENING OPERATION

Systematic Reviews

Iannella (2021) performed a systematic review that discusses the state of the art and evolution on the barbed reposition pharyngoplasty (BRP) in the velo-pharyngeal surgery.[39] Fifteen studies for a total of 1531 patients, out of which 1061 underwent barbed reposition pharyngoplasty. Five trials were uncontrolled prospective studies (215 patients, 14% of total), nine were retrospective studies (1266 patients, 82,6% of total), and one randomized prospective clinical trial (RCT) (50 patients, 3,32% of total). The authors commented that “Barbed reposition pharyngoplasty has proven to be an easy to learn, quick, safe and effective new palatopharyngeal procedure, that can be used in a single level surgery or as a part of multilevel procedures”.

Llewellyn (2018) published a SR with meta-analysis of outcomes for cautery-assisted palatal stiffening operation (CAPSO) as a treatment for adult OSA. This SR included eight studies (N=307) conducted in adult patients with sleep disordered breathing.[40] Additional inclusion criteria for the SR were: “outcomes for sleep study information, snoring and/or sleepiness; anterior palatoplasty *or* palatal stiffening operation *or* CAPSO *or* modified CAPSO with or without tonsillectomy/expansion pharyngoplasty (plication of palatopharyngeus);” and no other surgical procedures performed at the same time. Among these studies, four were considered to have high risk of bias in patient selection per QUADAS-2. The authors reported the following improvements (mean ± standard deviation [M ± SD] events per hour, percent change) in AHI: CAPSO alone (N=80 patients), (16.8 ± 11.9) to (9.9 ± 10.9), a 41.1% decrease; mixed CAPSO

with/without tonsillectomy (N=92), (24.8 ± 12.6) to (10.6 ± 9.5), a 61.7% decrease; CAPSO with expansion pharyngoplasty (N=78), (26.3 ± 17.7) to (12.6 ± 5.8), a 52.1% decrease. The authors also reported the following improvement in lowest oxygen saturation (LSAT): CAPSO alone (N=90), 5.4 point improvement; mixed CAPSO with/without tonsillectomy (N=77), 10.6 point improvement; and CAPSO with expansion pharyngoplasty (N=78), 5.2 point improvement. Although the authors reported effect sizes for pre- and post-surgery outcomes across all data, for none of the above analyses evaluating effects of CAPSO alone or in combination with other interventions were assessments of statistical significance (p values) reported. This SR included studies by Mair (2000) and Pang (2007), which focused on patients with simple snoring (AHI <5) or mild sleep apnea (AHI <15).[41, 42] A study with long-term follow-up reported in this SR found that 38% of patients with mild to moderate OSA had globus sensation and inability to clear phlegm 2 years after the operation.[43] Future RCTs evaluating the specific and long-term benefit of CAPSO in OSA are needed.

Randomized Controlled Trials

No additional RCTs beyond those addressed in the SR above on the use of cautery-assisted palatal stiffening operation in the treatment of OSA or UARS have been identified.

PALATAL IMPLANTS

Systematic Reviews

No SRs for the use of palatal implants for the treatment of OSA or UARS have been identified.

Randomized Controlled Trials

In 2012, Maurer reported a randomized double-blind, sham-controlled trial of the Pillar palatal implant in 20 patients with mild to moderate OSA because of palatal obstruction.[44] At 90 days, the AHI in the treatment group improved from 19.1 to 8.2 events per hour and lowest oxygen saturation improved from 82.8% to 88.3%. These measures did not improve significantly in the control group, and there was no significant difference in outcomes between the implant and control groups in this small trial. The ESS did not improve significantly in either group.

In a 2008 trial by Steward, 100 patients with mild to moderate OSA and suspected retropalatal obstruction were randomly assigned to palatal implants or sham placebo.[45] Patients with BMI greater than 32 kg/m^2 were excluded from the study. About 1000 patients were evaluated to identify the 100 study patients. At three-month follow-up, the average AHI increased in both groups from a baseline of about 17, although the increase was greater in the placebo group (8.9 vs 2.9, respectively). A reduction in AHI by at least 50% or to below 20 was more common in the implant group (26% vs 10%, respectively; p=0.05). Improvement in ESS did not differ from that of sham (p=0.62). Partial implant extrusion occurred in two patients (4%).

In 2008, Friedman reported an industry-sponsored randomized double-blind, sham-controlled trial of palatal implants in 62 patients with symptoms of OSA.[46] Other inclusion criteria included: Friedman tongue position I, II, or III; diagnosis of mild to moderate OSA (AHI ≥5 and <40) on baseline polysomnography (PSG); a soft palate of 2 cm or more but less than 3.5 cm; and BMI less than 32 kg/m^2. AHI at baseline was 23.8 events per hour in the implant group and 20.1 in controls. Seven patients did not return for repeat PSG and were considered treatment failures in the intention-to-treat analysis. At three-month follow-up, the AHI improved to 15.9 events per hour in the implant group but did not change significantly in the controls (21.0). The ESS improved from 12.7 to 10.2 in the implant group and did not change

significantly in the controls (11.7 to 11.1). With success defined as an AHI reduction of 50% or more and AHI less than 20, palatal implantation resulted in the successful treatment of 41.9% of implanted patients compared with 0% of controls. Two patients had partial implant extrusion.

Nonrandomized Studies

Neruntarat (2011) reported a case series with a minimum of 24-month follow-up.[47] This study included 92 patients with mild to moderate OSA (AHI ≤30 with daytime sleepiness or disturbed sleep) who had received palatal implants after failed medical management. At baseline, the mean AHI was 21.7 events per hour, and the lowest oxygen saturation was 87.4%. At mean 28.9-month follow-up, the AHI had decreased to 10.8, and the lowest oxygen saturation improved to 89.2%. Sleep efficiency improved from 80.6% to 87.2%, and the ESS score improved from a mean of 12.3 to 7.9. Implant extrusion occurred in seven patients (7.6%), and palatal abscess occurred in one patient (1.1%). Confounding factors, such as significantly lower BMI in “responders” may have affected the interpretation of the efficacy of this procedure in this patient population.

Walker published 90-day and 15-month follow-up from a multicenter study on palatal implants (Pillar System) in 63 subjects.[48, 49] The AHI decreased from a baseline of 25 to 22 in the 53 patients (84%) who were evaluated at 90 days. Twenty-two patients (35%) were available for the follow-up study; 13 had shown a decrease in AHI (from a baseline of 20 to 13) at 90 days. Of these, 10 (77% of the 13) maintained the decrease at 15 months. The nine patients whose AHI had not improved at 90 days had no subsequent improvement at the extended follow-up. Mean snoring was rated as eight at baseline (visual analog scale), and 4 at both 90 days and 15 months. Subjective daytime sleepiness measured by the ESS was reduced at 90 days (11 to 7) but returned to a score of 11 at the longer follow-up. In addition to the very large loss to follow-up, questions remain about the clinical significance of a three- to seven-point improvement in AHI.

In a prospective study, Nordgard (2007) assessed the long-term effectiveness of palatal implants for treatment of mild-to-moderate OSA.[50] A total of 26 referred patients with a pre-treatment AHI of 10 to 30 and a BMI of less than or equal to 30, representing an extended follow-up of a subset of 41 patients enrolled in previous short-term trials were included. Twenty-one of 26 patients (80.8 %) experienced a decrease in AHI. Fifteen of 26 patients (57.7 %) had a follow-up AHI less than 10 at one year, whereas 13 patients (50 %) had a 50 % or greater reduction to an AHI less than 10 at one year. Mean AHI was reduced from 16.5 +/- 4.5 at baseline to 12.5 +/- 10.5 at three months ($p < 0.014$) and to 12.3 +/- 12.7 at one year ($p < 0.019$). The authors concluded that patients initially responding to palatal implants with improved AHI maintained improvement through long-term follow-up at one year. The main limitation of this study was its small sample size. The authors noted that additional studies with longer follow-up would be appropriate.

Nordgard (2006) conducted a prospective nonrandomized study of 25 patients with untreated OSA with an AHI of 10–30, as determined by preoperative PSG, and BMI ≤ 30.[51] Three permanent implants were placed in the soft palate of each patient in an office setting under local anesthesia. A repeat PSG showed a mean decrease in AHI from 16.2 to 12.1 for the study group. Twenty of 25 patients demonstrated a reduced AHI, and 12 of 25 patients demonstrated an AHI of 10 or less 90 days post-implant. The mean ESS score decreased from 9.7 to 5.5. The authors concluded that palatal implants can significantly improve AHI and other sleep-related parameters in patients with mild to moderate OSA and BMI ≤ 30, with short-term

results comparable to those reported for UPPP. The authors acknowledged the lack of long-term outcomes in this study and the limited number of patients. As with other palatal procedures, reduction in effectiveness over time may be expected. The authors further concluded that while short-term durability and effectiveness have been established, longer-term research needs to be conducted.

In a retrospective, nonrandomized, controlled study, Friedman (2006) evaluated the Pillar implant system alone and in combination with other procedures for treatment of mild-to-moderate OSA/hypopnea syndrome (OSAHS).[52] A total of 125 patients who had mild-to-moderate OSAHS were assigned to palatal implantation alone (palatal group, n=29), or in combination with other procedures. Most of the procedures other than palatal implantation were not defined clearly. After a mean follow-up of eight months, mean AHI for the palatal group had decreased from 13.8 to 12.13; however, this difference was not statistically significant compared with baseline. Using the criteria of AHI < 20 and > 50% reduction of AHI as "cured," Friedman reported that seven (24%) palatal group patients and 43 (34%) of all patients were "cured." One of the study limitations was that many patients had an AHI < 20 at baseline, particularly in the Palatal Group, which had a baseline AHI of 13.8.

Three other small, uncontrolled studies have been performed to evaluate the Pillar Palatal Implant System for mild-to moderate OSA.[53, 54] These studies enrolled 16 to 26 patients who had an AHI score of 5 to 30. These studies reported that, compared with baseline, patients obtained small-to-moderate but statistically significant improvements in outcomes such as AHI and Epworth Sleepiness Scale (ESS) scores at up to one year of follow-up; however, these studies do not provide reliable evidence of efficacy since they did not involve any control or comparison groups.

Palatal Implants Section Summary

The literature on palatal implants consists of three moderately-sized RCTs and additional case series with medium-term follow-up. Evidence from sham-controlled trials shows a statistically significant but modest reduction in AHI and improvement in lowest oxygen saturation compared with placebo, with limited effects on daytime sleepiness. Additional studies are needed to determine whether there is a defined subset of patients who might benefit from this procedure. Studies with longer term follow-up are also needed to evaluate the potential for extrusion of the implants at longer time intervals.

THYROIDECTOMY

Masarwy (2022) performed an assessment of the impact of thyroidectomy on OSA to understand the intricate relationship between OSA and thyroid structure.[55] A systematic review of four electronic databases (PubMed (Medline), Embase, the Cochrane library, and ClinicalTrials.gov) was performed up to February 2022. The primary outcomes were preoperative and postoperative Apnea/Hypopnea Index (AHI), Epworth Sleepiness Scale (ESS), Berlin questionnaire scores, and continuous positive airway pressure (CPAP) use. Six cohort studies on 221 OSA patients who underwent thyroidectomies were included. The results showed that thyroidectomy was associated with significant reduction in postoperative AHI (Mean difference [MD], -6.39, 95% CI -12.46 to -0.32), however, no significant association was found with CPAP withdrawal (Odds ratio [OR], 0.38, 95% CI 0.12-1.18). The authors state that large-scale, well-designed prospective studies are necessary to validate these findings.

PRACTICE GUIDELINE SUMMARY

THE US DEPARTMENT OF VETERANS AFFAIRS AND THE DEPARTMENT OF DEFENSE

The 2019 US Department of Veterans Affairs and Department of Defense (VA/DoD) Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea provide the following recommendations regarding surgical treatment of OSA:[56]

> *For patients with severe obstructive sleep apnea who cannot tolerate or are not appropriate candidates for other recommended therapies, we suggest evaluation for alternative treatment with maxillomandibular advancement surgery. (Strength of recommendation: weak for. Category: new recommendation following review of the evidence)*

AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY

The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has published a number of consensus-based policy statements on various techniques for surgical management of obstructive sleep apnea.[7, 57-61] AAO-HNS position statements, by definition are “based on an informal process of expert or committee consensus that draws upon best available evidence and quality products.” thus each of the position statements may be supported to varying degrees by evidence. Procedures the AAO-HNS supports as effective and not considered investigational when part of a comprehensive approach in the medical and surgical management of adults with OSA include palatal advancement, uvulopalatopharyngoplasty, uvulopalatoplasty (including laser assisted and other techniques), genioglossal advancement, hyoid myotomy, midline glossectomy, tongue suspension, and maxillary and mandibular advancement.

No evidence-based practice guidelines from the AAO-HNS were identified.

AMERICAN ACADEMY OF SLEEP MEDICINE

The American Academy of Sleep Medicine (AASM, 2021) published practice guidelines on when to refer patients for surgical modifications of the upper airway for OSA.[62] These guidelines replaced the 2010 practice parameters for surgical modifications.[63] The AASM guidelines note that positive airway pressure (PAP) is the most efficacious treatment for OSA, but effectiveness can be compromised when patients are unable to adhere to therapy or obtain adequate benefit, which is when surgical management may be indicated. The AASM guideline recommendations are based on a systematic review and meta-analysis of 274 studies of surgical interventions, including procedures such as uvulopalatopharyngoplasty (UPPP), modified UPPP, MMA, tongue base suspension, and hypoglossal nerve stimulation.[64] The systematic review deemed most included data of low quality, consisting of mostly observational data. The AASM strongly recommend that clinicians discuss referral to a sleep surgeon with adults with OSA and body mass index (BMI) <40 kg/m2 who are intolerant or unaccepting of PAP. Clinically meaningful and beneficial differences in nearly all critical outcomes, including decrease in excessive sleepiness, improved quality of life (QOL), improved Apnea/Hypopnea Index (AHI) or respiratory disturbance index (RDI), and sleep quality, were demonstrated with surgical management in patients who are intolerant or unaccepting of PAP. The AASM makes a conditional recommendation that clinicians discuss referral to a sleep surgeon with adults with OSA, BMI <40 kg/m2, and persistent inadequate PAP adherence due to pressure-related side effects, as available data (very low-quality) suggests that upper airway surgery has a moderate effect in reducing minimum therapeutic PAP level and increasing PAP adherence. In adults with OSA and obesity (class II/III, BMI

>35) who are intolerant or unaccepting of PAP, the AASM strongly recommends discussion of referral to a bariatric surgeon, along with other weight loss strategies.

SUMMARY

There is enough research to suggest that uvulopalatopharyngoplasty (UPPP) and its variants, hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as maxillo-mandibular advancement (MMA) may improve health outcomes for some patients with obstructive sleep apnea (OSA) or airway resistance syndrome (UARS). These procedures have become a standard of care and may therefore be considered medically necessary when the policy criteria are met.

There is not enough research to support surgery as first-line treatment of obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS). Therefore, surgical treatments may be considered medically necessary only after failed medical therapy, including nasal continuous positive airway pressure (PAP) and a custom-made mandibular repositioning appliance. In addition, surgical treatments including uvulopalatopharyngoplasty (UPPP) and its variants, hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as maxillo-mandibular advancement (MMA) are considered not medically necessary when criteria are not met.

There is not enough research to determine the safety and efficacy of surgical interventions including but not limited to uvulectomy, and minimally invasive surgical procedures such as laser-assisted uvuloplasty (LAUP), radiofrequency tongue base or tissue volume reduction, palatal stiffening procedures, and palatal implants. The use of these interventions is considered investigational for the treatment of obstructive sleep apnea (OSA) or airway resistance syndrome (UARS).

Snoring in the absence of clinically significant obstructive sleep apnea (OSA) is not considered a medical condition. Therefore, any surgical intervention, including but not limited to uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty (LAUP), radiofrequency volumetric tissue reduction of the palate, or palatal stiffening procedures for snoring alone is considered not medically necessary.

REFERENCES

1. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017;13:479-504. PMID: 28162150
2. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.* 2009;5(3):263-76. PMID: 19960649
3. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep.* 1999;22(5):667-89. PMID: 10450601
4. Dudley KA, Patel SR. Disparities and genetic risk factors in obstructive sleep apnea. *Sleep Med.* 2016;18:96-102. PMID: 26428843

5. Cohen SM, Howard JJM, Jin MC, et al. Racial Disparities in Surgical Treatment of Obstructive Sleep Apnea. *OTO Open.* 2022;6(1):2473974X221088870. PMID: 35321423
6. Lee YC, Chang KY, Mador MJ. Racial disparity in sleep apnea-related mortality in the United States. *Sleep Med.* 2022;90:204-13. PMID: 35202926
7. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Uvulopalatopharyngoplasty. 2012. [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-Uvulopalatopharyngoplasty/.
8. Balk EM, Moorthy D, Obadan NO, et al. Diagnosis and Treatment of Obstructive Sleep Apnea in Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Jul. Report No.: 11-EHC052. *AHRQ Comparative Effectiveness Reviews.* 2011. PMID: 21977519
9. Farrar J, Ryan J, Oliver E, et al. Radiofrequency ablation for the treatment of obstructive sleep apnea: a meta-analysis. *Laryngoscope.* 2008;118(10):1878-83. PMID: 18806478
10. Sundaram S, Bridgman SA, Lim J, et al. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2005(4):CD001004. PMID: 16235277
11. TEC Assessment 1995. "Surgical Procedures for the Treatment of Obstructive Sleep Apnea Syndrome." BlueCross BlueShield Association Technology Evaluation Center, Vol. 10, Tab 31.
12. Maniaci A, Di Luca M, Lechien JR, et al. Lateral pharyngoplasty vs. traditional uvulopalatopharyngoplasty for patients with OSA: systematic review and meta-analysis. *Sleep & breathing = Schlaf & Atmung.* 2022. PMID: 34978022
13. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J.* 2011;37(5):1000-28. PMID: 21406515
14. Franklin KA, Anttila H, Axelsson S, et al. Effects and side-effects of surgery for snoring and obstructive sleep apnea--a systematic review. *Sleep.* 2009;32(1):27-36. PMID: 19189776
15. Ferguson KA, Heighway K, Ruby RR. A randomized trial of laser-assisted uvulopalatoplasty in the treatment of mild obstructive sleep apnea. *Am J Respir Crit Care Med.* 2003;167(1):15-9. PMID: 12502473
16. Woodson BT, Steward DL, Weaver EM, et al. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2003;128(6):848-61. PMID: 12825037
17. Larrosa F, Hernandez L, Morello A, et al. Laser-assisted uvulopalatoplasty for snoring: does it meet the expectations? *Eur Respir J.* 2004;24(1):66-70. PMID: 15293606
18. Stuck BA, Sauter A, Hörmann K, et al. Radiofrequency surgery of the soft palate in the treatment of snoring. A placebo-controlled trial. *28.* 2005;7:847-50. PMID:
19. Baba RY, Mohan A, Metta VV, et al. Temperature controlled radiofrequency ablation at different sites for treatment of obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep & breathing = Schlaf & Atmung.* 2015;19(3):891-910. PMID: 25643764
20. MacKay S, Carney AS, Catcheside PG, et al. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients With Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. *JAMA.* 2020;324(12):1168-79. PMID: 32886102
21. Back LJ, Liukko T, Rantanen I, et al. Radiofrequency surgery of the soft palate in the treatment of mild obstructive sleep apnea is not effective as a single-stage procedure: A

randomized single-blinded placebo-controlled trial. *Laryngoscope.* 2009;119(8):1621-7. PMID: 19504550
22. Fernandez-Julian E, Munoz N, Achiques MT, et al. Randomized study comparing two tongue base surgeries for moderate to severe obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2009;140(6):917-23. PMID: 19467415
23. Steward DL, Weaver EM, Woodson BT. A comparison of radiofrequency treatment schemes for obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2004;130(5):579-85. PMID: 15138424
24. Steward DL. Effectiveness of multilevel (tongue and palate) radiofrequency tissue ablation for patients with obstructive sleep apnea syndrome. *Laryngoscope.* 2004;114(12):2073-84. PMID: 15564825
25. Herman H, Stern J, Alessi DM, et al. Office-Based Multilevel Radiofrequency Ablation for Mild-to-Moderate Obstructive Sleep Apnea. *OTO Open.* 2023;7(1):e19. PMID: 36998558
26. van den Broek E, Richard W, van Tinteren H, et al. UPPP combined with radiofrequency thermotherapy of the tongue base for the treatment of obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol.* 2008;265(11):1361-5. PMID: 18347810
27. Steward DL, Weaver EM, Woodson BT. Multilevel temperature-controlled radiofrequency for obstructive sleep apnea: extended follow-up. *Otolaryngol Head Neck Surg.* 2005;132(4):630-5. PMID: 15806059
28. Stuck BA, Starzak K, Hein G, et al. Combined radiofrequency surgery of the tongue base and soft palate in obstructive sleep apnoea. *Acta Otolaryngol.* 2004;124(7):827-32. PMID: 15370568
29. Handler E, Hamans E, Goldberg AN, et al. Tongue suspension: an evidence-based review and comparison to hypopharyngeal surgery for OSA. *Laryngoscope.* 2014;124(1):329-36. PMID: 23729234
30. Li S, Wu D, Shi H. Treatment of obstructive sleep apnea hypopnea syndrome caused by glossoptosis with tongue-base suspension. *Eur Arch Otorhinolaryngol.* 2013;270(11):2915-20. PMID: 23649508
31. Woodson BT, Steward DL, Mickelson S, et al. Multicenter study of a novel adjustable tongue-advancement device for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2010;143:585-90. PMID: 20869572
32. Miller FR, Watson D, Malis D. Role of the tongue base suspension suture with The Repose System bone screw in the multilevel surgical management of obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2002;126(4):392-8. PMID: 11997779
33. DeRowe A, Gunther E, Fibbi A, et al. Tongue-base suspension with a soft tissue-to-bone anchor for obstructive sleep apnea: preliminary clinical results of a new minimally invasive technique. *Otolaryngol Head Neck Surg.* 2000;122(1):100-3. PMID: 10629491
34. Terris DJ, Kunda LD, Gonella MC. Minimally invasive tongue base surgery for obstructive sleep apnoea. *J Laryngol Otol.* 2002;116(9):716-21. PMID: 12437808
35. Woodson BT. A tongue suspension suture for obstructive sleep apnea and snorers. *Otolaryngol Head Neck Surg.* 2001;124(3):297-303. PMID: 11240995
36. Woodson BT, Derowe A, Hawke M, et al. Pharyngeal suspension suture with repose bone screw for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2000;122(3):395-401. PMID: 10699817
37. Wischhusen J, Qureshi U, Camacho M. Laser-assisted uvulopalatoplasty (LAUP) complications and side effects: a systematic review. *Nat Sci Sleep.* 2019;11:59-67. PMID: 31213936

38. Walker RP, Grigg-Damberger MM, Gopalsami C, et al. Laser-assisted uvulopalatoplasty for snoring and obstructive sleep apnea: results in 170 patients. *Laryngoscope.* 1995;105(9 Pt 1):938-43. PMID: 7666729
39. Iannella G, Lechien JR, Perrone T, et al. Barbed reposition pharyngoplasty (BRP) in obstructive sleep apnea treatment: State of the art. *Am J Otolaryngol.* 2022;43(1):103197. PMID: 34492427
40. Llewellyn CM, Noller MW, Camacho M. Cautery-assisted palatal stiffening operation for obstructive sleep apnea: A systematic review and meta-analysis. *World J Otorhinolaryngol Head Neck Surg.* 2019;5:49-56. PMID: 30775702
41. Mair EA, Day RH. Cautery-assisted palatal stiffening operation. *Otolaryngol Head Neck Surg.* 2000;122(4):547-56. PMID: 10740176
42. Pang KP, Terris DJ. Modified cautery-assisted palatal stiffening operation: new method for treating snoring and mild obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2007;136(5):823-6. PMID: 17478223
43. Ugur KS, Ark N, Kurtaran H, et al. Anterior palatoplasty for selected mild and moderate obstructive sleep apnea: preliminary results. *Eur Arch Otorhinolaryngol.* 2014;271(6):1777-83. PMID: 24264762
44. Maurer JT, Sommer JU, Hein G, et al. Palatal implants in the treatment of obstructive sleep apnea: a randomised, placebo-controlled single-centre trial. *Eur Arch Otorhinolaryngol.* 2012;269(7):1851-6. PMID: 22228439
45. Steward DL, Huntley TC, Woodson BT, et al. Palate implants for obstructive sleep apnea: multi-institution, randomized, placebo-controlled study. *Otolaryngol Head Neck Surg.* 2008;139(4):506-10. PMID: 18922335
46. Friedman M, Schalch P, Lin HC, et al. Palatal implants for the treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg.* 2008;138(2):209-16. PMID: 18241718
47. Neruntarat C. Long-term results of palatal implants for obstructive sleep apnea. *Eur Arch Otorhinolaryngol.* 2011;268(7):1077-80. PMID: 21298386
48. Walker RP, Levine HL, Hopp ML, et al. Palatal implants: a new approach for the treatment of obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2006;135(4):549-54. PMID: 17011415
49. Walker RP, Levine HL, Hopp ML, et al. Extended follow-up of palatal implants for OSA treatment. *Otolaryngol Head Neck Surg.* 2007;137(5):822-7. PMID: 17967653
50. Nordgard S, Hein G, Stene BK, et al. One-year results: palatal implants for the treatment of obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2007;136(5):818-22. PMID: 17478222
51. Nordgard S, Stene BK, Skjostad KW. Soft palate implants for the treatment of mild to moderate obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2006;134(4):565-70. PMID: 16564373
52. Friedman M, Vidyasagar R, Bliznikas D, et al. Patient selection and efficacy of pillar implant technique for treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg.* 2006;134(2):187-96. PMID: 16455363
53. Friedman M, Schalch P, Joseph NJ. Palatal stiffening after failed uvulopalatopharyngoplasty with the Pillar Implant System. *Laryngoscope.* 2006;116(11):1956-61. PMID: 17075397
54. Goessler UR, Hein G, Verse T, et al. Soft palate implants as a minimally invasive treatment for mild to moderate obstructive sleep apnea. *Acta Otolaryngol.* 2007;127(5):527-31. PMID: 17453480

55. Masarwy R, Kampel L, Ungar OJ, et al. The impact of thyroidectomy on obstructive sleep apnea: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol.* 2022. PMID: 35723730
56. VA/DoD clinical practice guideline for the management of chronic insomnia disorder and obstructive sleep apnea. [cited 10/31/2023]. 'Available from:' https://www.healthquality.va.gov/guidelines/CD/insomnia/VADoDSleepCPGFinal508.pdf .
57. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Submucosal Ablation of the Tongue Base for OSAS. 2012. [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-submucosal-ablation-of-the-tongue-base-for-osas/.
58. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Tongue Suspension. 2016. [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-tongue-suspension/.
59. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Midline Glossectomy for OSA. 2013 [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-midline-glossectomy-for-osa/.
60. American Academy of Otolaryngology Head and Neck Surgery. Position Statement: Treatment of Obstructive Sleep Apnea. 2017. [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-treatment-of-obstructive-sleep-apnea/.
61. American Academy of Otolaryngology Head and Neck Surgery. Position statement: Surgical Management of Obstructive Sleep Apnea. 2014. [cited 10/31/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-surgical-management-of-obstructive-sleep-apnea/.
62. Kent D, Stanley J, Aurora RN, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2021;17(12):2499-505. PMID: 34351848
63. Aurora RN, Casey KR, Kristo D, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep.* 2010;33(10):1408-13. PMID: 21061864
64. Kent D, Stanley J, Aurora RN, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2021;17(12):2507-31. PMID: 34351849
65. Crook S, Sievi NA, Bloch KE, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax.* 2019;74(4):390-96. PMID: 30100576
66. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. *Sleep.* 2006;29(2):240-3. PMID: 16494092
67. Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep.* 2006;29(2):244-62. PMID: 16494093

CODES

Codes	Number	Description
CPT	21121	Genioplasty; sliding osteotomy, single piece

Codes	Number	Description
	21122	Genioplasty; sliding osteotomies, two or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)
	21141	Reconstruction midface, LeFort 1; single piece, segment movement in any direction (eg, for Long Face Syndrome), without bone graft
	21145	Reconstruction midface, LeFort 1; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts)
	21196	Reconstruction of mandibular rami and /or body, sagittal split; with internal rigid fixation
	21198	Osteotomy, mandible, segmental
	21199	Osteotomy, mandible, segmental; with genioglossus advancement
	21685	Hyoid myotomy and suspension
	41120	Glossectomy; less than one-half tongue
	41512	Tongue base suspension, permanent suture technique
	41530	Submucosal ablation of the tongue base, radiofrequency, one or more sites, per session
	41599	Unlisted procedure, tongue, floor of mouth
	42140	Uvulectomy, excision of uvula
	42145	Palatopharyngoplasty (eg, Uvulopalatopharyngoplasty, Uvulopharyngoplasty)
	42160	Destruction of lesion, palate or uvula (thermal, cryo, or chemical)
	42299	Unlisted procedure, palate, uvula
HCPCS	S2080	Laser-assisted uvulopalatoplasty (LAUP)

Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing	
Polysomnography (PSG)	Full night PSG consists of five to eight hours of monitoring, supervised by a sleep technician, while the patient sleeps. It is performed in a sleep lab and involves the following monitoring modalities: electroencephalogram (EEG) (to stage sleep and detect arousals), electro-oculogram (EOG) (to detect arousal and REM sleep) submental electromyogram, (EMG), electrocardiogram (EKG), two-leg EMG, respiratory airflow and effort (to detect apnea), snoring, oxygen saturation, time and position. In addition, a full night PSG may include additional monitoring modalities as indicated, such as esophageal pressure monitoring, blood pressure monitoring, carbon dioxide trends, and pulse transit time. The first three elements listed above (EEG, submental electromyogram, and electro-oculogram) are required for sleep staging. By definition, a polysomnogram always includes sleep staging, while a “sleep study” does not include sleep staging. The actual components of the study will be dictated by the clinical situation. Typically, the evaluation of obstructive sleep apnea would include respiratory airflow and effort, electro-oculogram, and oxygen desaturation. An EEG may not be considered necessary to evaluate OSA, although it is required to evaluate UARS, REM sleep behavior disorder (RBD), narcolepsy or other sleep disturbances.
Split Night Polysomnography	A split night study utilizes the first two or three hours for evaluating the presence of sleep apnea and the second half to titrate and adjust CPAP. The same monitoring modalities used in full night PSG are used in split night study. In patients with severe obstructive sleep apnea, a reliable assessment of the respiratory disturbance index is possible with a partial night study. Half night study for CPAP titration is reliable in selected cases of obstructive sleep apnea.

Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing	
	Split night studies are appropriate in patients with severe sleep apnea syndrome. The decision to conduct a split night study depends on the technical skill and experience of the staff, the initial sleep latency period, the severity and frequency of respiratory events and patient compliance. Careful patient selection and education is required to conduct a successful split night study.
Home Sleep Apnea Testing Device (HSAT Device)	Per the 2017 American Academy of Sleep Medicine (AACM) Clinical Practice Guideline for diagnostic testing for adult obstructive sleep apnea, home sleep apnea testing with a technically adequate device may be used for the diagnosis of obstructive sleep apnea (OSA) in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA.[1] An uncomplicated patient is defined by the absence of: 1. Conditions that place the patient at increased risk of non-obstructive sleep-disordered breathing (e.g., central sleep apnea, hypoventilation and sleep related hypoxemia). Examples of these conditions include significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke and chronic opiate medication use. 2. Concern for significant non-respiratory sleep disorder(s) that require evaluation (e.g., disorders of central hypersomnolence, parasomnias, sleep related movement disorders) or interfere with accuracy of HSAT (e.g., severe insomnia). 3. Environmental or personal factors that preclude the adequate acquisition and interpretation of data from HSAT. An increased risk of moderate to severe OSA is indicated by the presence of excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring, witnessed apnea or gasping or choking, or diagnosed hypertension. HSAT is to be administered by an accredited sleep center under the supervision of a board-certified sleep medicine physician, or a board-eligible sleep medicine provider. A single HSAT recording is conducted over at least one night. A technically adequate HSAT device incorporates a minimum of the following sensors: nasal pressure, chest and abdominal respiratory inductance plethysmography, and oximetry; or else peripheral arterial tone (PAT) with oximetry and actigraphy. A technically adequate diagnostic test includes a minimum of 4 hours of technically adequate oximetry and flow data, obtained during a recording attempt that encompasses the habitual sleep period. If a single HSAT is negative, inconclusive, or technically inadequate, polysomnography should be performed for the diagnosis of OSA.
SNAP™ Testing	The SNAP testing system is a reflective acoustic device marketed as a screening and analysis system to locate the source of snoring and detect sleep apnea conditions.

Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing	
Multiple Sleep Latency Tests (MSLT)	The MSLT measures the speed of falling asleep under conditions that favor sleep, in a series of 20-minute trials during the patient's habitual periods of wakefulness. MSLT is the preferred method of establishing the presence of true physiological sleepiness but is accurate only if following strict protocols. MSLT is used in patients with complaints of irresistible daytime sleepiness suggestive of narcolepsy.
Maintenance of Wakefulness Test (MWT)	The patient is monitored during the usual periods of wakefulness but the patient is instructed not to fall asleep as a test of the patient's ability to stay awake. It may be used to evaluate the safety of drivers and their ability to stay alert.
Radiologic Studies	Radiologic images of the head and neck for anatomic abnormalities include MRI, CT scan, and cephalometry. Such studies are intended to assess for hypopharyngeal obstruction or other suspected pathology that might explain the symptoms associated with sleep disordered breathing.
Endoscopic Studies	Nasopharyngeal and laryngeal endoscopic measurements of structure and function of the upper airway are used in selected patients with suspected abnormal anatomy as an aid in the diagnosis of OSA or in the management of complications of treatment.
Epworth Sleepiness Scale	Excessive daytime sleepiness is predominantly a subjective symptom. The Epworth sleepiness scale is a self-administered questionnaire, performed as part of the clinical evaluation, that asks patients their likelihood of falling asleep in eight situations ranked from 0 (would never fall asleep) to 3 (high chance of dozing). The numbers are then added together to give a global score between 0 and 24. A value of 10 or below is considered normal. A decrease of 2 points is considered the minimum important difference (MID).[65]
Apnea-Hypopnea Index (AHI); Respiratory Disturbance Index (RDI)	Apnea is defined as the cessation of respiration for at least 10 seconds. Hypopnea is a reduction but not cessation of air exchange. Apneic and hypopneic events are combined into the apnea-hypopnea index (AHI). In turn the AHI is often referred to as the respiratory disturbance index (RDI), although more recently the RDI has been redefined by some physicians to include EEG arousals in addition to apneic and hypopneic events. An AHI of greater than or equal to 20 is typically considered moderate OSA, and AHI of greater than 50 is considered severe OSA. An increase in mortality is associated with an AHI of greater than 15.
Polysomnography (PSG)	Full night PSG consists of five to eight hours of monitoring, supervised by a sleep technician, while the patient sleeps. It is performed in a sleep lab and involves the following monitoring modalities: electroencephalogram (EEG) (to stage sleep and detect arousals), electro-oculogram (EOG) (to detect arousal and REM sleep) submental electromyogram, (EMG), electrocardiogram (EKG), two-leg EMG, respiratory airflow and effort (to detect apnea), snoring, oxygen saturation, time and position. In addition, a full night PSG may include additional monitoring modalities as indicated, such as esophageal pressure monitoring, blood pressure monitoring, carbon dioxide trends, and pulse transit time.

Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing	
	The first three elements listed above (EEG, submental electromyogram, and electro-oculogram) are required for sleep staging. By definition, a polysomnogram always includes sleep staging, while a “sleep study” does not include sleep staging. The actual components of the study will be dictated by the clinical situation. Typically, the evaluation of obstructive sleep apnea would include respiratory airflow and effort, electro-oculogram, and oxygen desaturation. An EEG may not be considered necessary to evaluate OSA, although it is required to evaluate UARS, REM sleep behavior disorder (RBD), narcolepsy or other sleep disturbances.
Split Night Polysomnography	A split night study utilizes the first two or three hours for evaluating the presence of sleep apnea and the second half to titrate and adjust CPAP. The same monitoring modalities used in full night PSG are used in split night study. In patients with severe obstructive sleep apnea, a reliable assessment of the respiratory disturbance index is possible with a partial night study. Half night study for CPAP titration is reliable in selected cases of obstructive sleep apnea. Split night studies are appropriate in patients with severe sleep apnea syndrome. The decision to conduct a split night study depends on the technical skill and experience of the staff, the initial sleep latency period, the severity and frequency of respiratory events and patient compliance. Careful patient selection and education is required to conduct a successful split night study.

Appendix 2: Nonsurgical Devices for Treatment of OSA or UARS	
CPAP	Nasal or oral continuous positive airway pressure (CPAP) or auto-titrating continuous positive airway pressure (APAP) is continuous positive airway pressure applied through the nose or via oral appliance. It is delivered by a flow generator through a mask to supply a pressure level sufficient to keep the upper airway patent. The pressure used is determined individually with a range of three to 15 centimeters of water.
BiPAP ®	Bi-level respiratory assist device delivers alternating levels of positive airway pressure instead of the continuous pressure applied by CPAP. A bi-level positive airway pressure device with back-up rate feature is a ventilation support system. These devices are in the FDA category of non-continuous ventilator, and as such, are primarily intended to augment patient ventilation. The term BiPAP® is a registered trademark of *Respironics Inc*., but is widely used to describe any bi-level positive airway pressure device as described above.
APAP	Auto-adjusting CPAP (APAP) is a more recent technology which alternates airway pressure between exhalation and inhalation on a breath-by-breath basis. With the C-Flex™ (Respironics, Inc) airway pressure is reduced during early exhalation in proportion to the patient’s expiratory flow rate. Pressure is then increased again toward the end of exhalation when airway collapse is most likely. Unlike BiPAP which delivers a static lower expiratory pressure, the C-Flex varies the pressure within the expiratory phase.

Appendix 2: Nonsurgical Devices for Treatment of OSA or UARS	
Oral Appliances (OA)	OA for the treatment of sleep disordered breathing are devices worn in the mouth during sleep to maintain a patent airway by raising the uvula, depressing the tongue, and/or advancing the mandible (in which case they are also known as mandibular advancement devices [MAD]). Commercially available devices are usually custom-molded or custom-fitted for the individual patient by a qualified dental health professional trained and experienced in the overall care of oral health, the temporomandibular joint, dental occlusion and associated oral structures. According to the American Academy of Sleep Medicine, dental management of patients with oral appliances should be overseen by practitioners who trained in sleep medicine and sleep related breathing disorders.[66, 67] Oral appliances can range from simple retaining devices, to adjustable, hinged, or two-piece designs. Some designs can be used in conjunction with a CPAP device (e.g., OPAP®).

Date of Origin: *March 2009*

Regence

Medical Policy Manual Surgery, Policy No. 174

Occipital Nerve Stimulation

Effective: April 1, 2024

Next Review: February 2025
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Occipital nerve stimulation (ONS) delivers a small electrical charge to the occipital nerve in an attempt to prevent migraines and other headaches in patients who have not responded to medications. The device consists of a subcutaneously implanted pulse generator (in the chest wall or abdomen) attached to extension leads that are tunneled to join electrodes placed across one or both occipital nerves at the base of the skull. Continuous or intermittent stimulation may be used.

MEDICAL POLICY CRITERIA

Occipital nerve stimulation is considered **investigational** for all indications, including but not limited to headaches.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Interferential Current Stimulation, Durable Medical Equipment, Policy No. 83.07
2. Sphenopalatine Ganglion Block for Headache and Pain, Medicine, Policy No. 160
3. Spinal Cord Stimulation, Surgery, Policy No. 45
4. Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin, Surgery, Policy No. 205

BACKGROUND

Implanted peripheral nerve stimulators have been used for treatment of refractory pain for many years but only recently proposed for management of craniofacial pain. Occipital, supraorbital, and infraorbital stimulation have been reported in the literature.

There are four types of headache: vascular, muscle contraction (tension), traction, and inflammatory. Primary (not the result of another condition) chronic headache is defined as headache occurring more than 15 days of the month for at least three months. An estimated 45 million Americans experience chronic headaches. For at least half of these people, the problem is severe and sometimes disabling.

Migraine is the most common type of vascular headache. Migraine headaches are usually characterized by severe pain on one or both sides of the head, an upset stomach, and, at times, disturbed vision. One- year prevalence of migraine ranges from 6% to15% in adult men and from 14% to35% in adult women. Migraine headaches may last a day or more and can strike as often as several times a week or as rarely as once every few years. Drug therapy for migraine is often combined with biofeedback and relaxation training. Sumatriptan is commonly used for relief of symptoms. Drugs used to prevent migraine include methysergide maleate, propranolol hydrochloride, ergotamine tartrate; amitriptyline, valproic acid, and verapamil.

Hemicrania continua, also a vascular headache, causes moderate pain with occasional severe pain on only one side of the head. At least one of the following symptoms must also occur; conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, or ptosis and/or miosis. Headache occurs daily and is continuous with no pain-free periods. Hemicrania continua occurs mainly in women, and its true prevalence is not known. Indomethacin usually provides rapid relief of symptoms. Other nonsteroidal anti-inflammatories (NSAIDs), including ibuprofen, celecoxib, and naproxen, can provide some relief from symptoms. Amitriptyline and other tricyclic antidepressants are effective in some patients.

Cluster headache is a vascular headache that occurs in cyclical patterns or clusters of severe or very severe unilateral orbital or supraorbital and/or temporal pain. The headache is accompanied by at least one of the following autonomic symptoms: ptosis (drooping eyelid), conjunctival injection, lacrimation, rhinorrhea, and, less commonly, facial blushing, swelling, or sweating. Bouts of one headache every other day to eight attacks per day may last from weeks to months, usually followed by remission periods when the headache attacks stop completely. The pattern varies from one person to another, but most people have one or two cluster periods a year. During remission, no headaches occur for months, and sometimes even years. The intense pain is caused by the dilation of blood vessels, which creates pressure on the trigeminal nerve. While this process is the immediate cause of the pain, the etiology is not fully understood. It is more common in men than in woman. One-year prevalence is estimated to be 0.5 to 1.0/1,000. Management of cluster headache consists of abortive and preventive treatment. Abortive treatments include subcutaneous injection of sumatriptan, topical anesthetics sprayed into the nasal cavity, and strong coffee. Some patients respond to rapidly inhaled pure oxygen. A variety of other pharmacologic and behavioral methods of aborting and preventing attacks have been reported with wide variation in patient response.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has not yet cleared any occipital nerve stimulation device for treatment of headache.

The Synergy™ IPG (implantable pulse generator) device from Medtronic received marketing clearance in 1999 for management of chronic, intractable pain of the trunk or limbs, and off-label use for headache is described in the literature.

The Genesis™ neuromodulation system (St. Jude Medical) is approved by the FDA for spinal cord stimulation and has received CE mark approval in Europe for the treatment of chronic migraines.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of headache are relief of pain, return to work, and improved functional level. Relief of pain can be a subjective outcome associated with a placebo effect. Therefore, data from adequately powered, blinded, randomized controlled trials (RCT) are required to control for the placebo effect and determine whether any treatment effect provides a significant advantage.

The technology must also be evaluated in general groups of patients against existing treatments. In patients with mild to moderate symptoms, occipital nerve stimulation may be compared to other forms of conservative therapy such as topical anesthetics, rest, or non-steroidal anti-inflammatory or migraine medications.

Therefore, the focus of the evidence summary is on RCTs comparing occipital nerve stimulation (ONS)-treated patients with those in a sham treatment or standard of care group.

SYSTEMATIC REVIEWS

Membrilla (2023) published a systematic review and meta-analysis to evaluate the effectiveness of pharmacologic and non-pharmacologic interventions in preventative treatment of chronic cluster headache (CCH) for people who do not respond to conventional therapy.[1] Studies were included if at least a portion of the participants met European Headache Federation diagnostic criteria for refractory CCH (rCCH), and if the reported outcome was reduced attack frequency. The review included a total of 45 studies, of which 12 were of ONS. Wilbrink (2021), as detailed below, was the only RCT on ONS. The meta-analysis also included the following studies that are cited below: Diaz-de-Teran (2021), Leplus (2021), and Magis (2011).[2-5] The pooled response rate from the 12 ONS studies was 57.3% (odds ratio [OR] 0.573, 95% confidence interval [CI] 0.481-0.665, I^2=68.45, p<0.001). Of the 45 studies included in the review only 7 were RCTs. While the authors concluded the available evidence supported the use of ONS, its harms were minimized (“these adverse events will likely be less prevalent because of technical advances”). The study noted that the overall analysis had high heterogeneity of interventions, study designs, and response measures, and most evidence was rated as having moderate to serious risk of bias.

As part of a consensus development process Barad (2022) published the results of a systematic review of studies on percutaneous strategies for migraine intervention.[6] This review included four randomized controlled trials (RCTs) on implantable ONS (Serra 2012, Slotty 2015, Silberstein 2012, and Saper 2011). An additional publication (Mekhail (2017) was excluded, as it was a subgroup analysis of the Silberstein cohort. The overall strength for the certainty of evidence for reduction of headache days was moderate with a moderate effect size. The strength of certainty of evidence for reduction in acute medication use was very low with a low, nonsignificant effect size. The strength of certainty of evidence for impairment as related to patient-related outcomes was moderate at 12 weeks with a moderate effect size.

Implantable ONS had significantly more adverse events that other interventional therapies examined. The recommendation was “weak” for the potential net benefit of implantable ONS for chronic migraine prevention.

Occipital nerve stimulation was addressed in the Comparative Effectiveness Review of Interventional Treatments for Acute and Chronic Pain that was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Pacific Northwest Evidence-Based Practice Center (2021).[7] The review assessed three studies, Saper (2011), Serra (2012), Silberstein (2012), and focused on the following outcomes: pain, function, number of days with headache, and mood state.[8-10] There was insufficient evidence to assess ONS compared to sham treatment for headache. While there was evidence of a reduction in headache pain, headache days, and disability at 3 months vs. usual care, the difference was not statistically significant ($p>0.05$). The review found evidence of harm from ONS, most often from lead migration that occurred in 14-24% of patients in the assessed studies, and one trial reported a 5.9% rate of device-related serious adverse events that required hospitalization.

Patel (2021) published a systematic review (SR) of data from RCTs on electrical nerve stimulation modalities, including occipital nerve stimulation (ONS), in the treatment of migraine.[11] Although 16 studies were included in the review, only three (Mekhail 2017, Dodick 2015, and Slotty 2015) were studies of ONS. Studies were rated low risk of bias in most domains, however, the authors note two of the ONS studies had “unknown” risk of bias due to open-label study design or high occurrence of adverse events. No pooled or quantitative comparisons for any outcomes were reported for any of the modalities.

A SR with meta-analysis of neuromodulation for acute and preventative migraine treatment was published by Moisset (2020).[12] This broad review included three studies of invasive ONS, all investigating its use for the treatment of chronic migraine. Only one of the identified studies was of high quality (Silbertstein 2012) which, as discussed below, did not identify a significant effect of the intervention on the primary outcome, although positive effects were found for secondary outcomes. The other two trials included in the review (Saper 2011 and Serra 2012) were low and moderate quality due to risk of biases in selective reporting, sample calculation, statistical methods, and/or blinding. Outcomes of the meta-analysis favored a positive effect of invasive ONS, with a large effect size (-1.090; 95%CI: -1.977 to -0.204) however high heterogeneity between studies ($I2 = 88\%$) was reported. Ultimately, the authors conclude that larger well-conducted studies are needed to confirm treatment efficacy and determine true effect sizes.

Cadalso (2017) published a systematic review (SR) evaluating the impact occipital nerve stimulation had on healthcare outcomes, for intractable primary headache disorders.[13] The SR included four RCTs, one follow-up study, and 19 case series. The authors stated that although the RCTs showed a decrease in headache frequency and improved migraine disability assessment scores, ONS did not improve pain intensity and there was heterogeneity of outcomes. In addition, the RCTs had small sample sizes and risk of bias.

Yang (2016) identified the same five RCTs as the 2015 SR by Chen, summarized below.[14] The Yang review only included studies conducted with patients with migraine of at least six months in duration who did not respond to oral medications. In addition to the RCTs, five case series met the inclusion criteria. Yang et al did not pool study findings. The definition of response rate varied across studies and could include frequency and/or severity of headaches. Response rates in three case series with self-reported efficacy were 100% each, and response

rates in the other two series were 50% and 89%, respectively. Complication rates in the series ranged from 40% to 100%. The authors noted that the case series were subject to biases (e.g., inability to control for the placebo effect), that RCT evidence was limited, and that complication rates were high.

Two SRs of the literature on occipital nerve stimulation (ONS) were published in 2015. Both included RCTs and observational studies. Chen identified five RCTs and seven case series with at least 10 patients.[15] Three of the RCTs were industry-sponsored, multicenter, parallel-group trials and two were single-center crossover trials. All five included a sham control group and one trial also included a medication management group. Risk of bias was judged to be high or unclear for all trials. Meta-analyses were performed on two outcomes. A pooled analysis of 2 studies did not find a significant difference in response rate between active and sham stimulation (risk ratio [RR], 2.07; 95% confidence interval [CI], 0.50 to 8.55; p=0.31) and a pooled analysis of three studies showed a significantly greater reduction in the number of days with prolonged moderate-to-severe headache (mean difference, 2.59; 95% CI, 0.91 to 4.27; p=0.003. Sweet (2015) published a SR that identified nine small case series (<15 patients each) assessing the efficacy of ONS for treating medically refractory occipital neuralgia.[16] The authors did not pool study findings. No conclusions can be drawn about the impact of ONS on occipital neuralgia due to the lack of RCTs or other controlled studies.

The National Institute for Health and Care Excellence (NICE, 2013) evaluated two RCTs and one case series to determine if ONS was effective in decreasing headache frequency, duration and severity.[17] Both RCTs compared ONS with sham stimulation at three months. Although the smaller RCT with 67 patients determined that the ONS group responded better than the sham group, the larger RCT with 157 patients showed no difference in responder rate. NICE concluded that ONS for intractable chronic migraines is efficacious in the short-term, but there is little evidence to indicate long-term outcome effects. NICE stated ONS should only be used for clinical governance, consent, and audit or research.

RANDOMIZED CONTROLLED TRIALS

Wilbrink (2021) published the safety and efficacy data from of a multicenter randomized controlled trial (RCT) of ONS for medically intractable chronic cluster headache (MICCH).[2] This trial is termed the ICON study (ClinicalTrials.gov NCT01151631). Patients were randomized (1:1) to 24 weeks of ONS at either 100% or 30% of the individually determined range between paraesthesia threshold and near-discomfort. Because ONS causes paraesthesia precluding masked comparison to placebo, high-intensity was compared to low-intensity stimulation, which is hypothesized to cause similar paraesthesia but with different efficacy. There were 150 patients enrolled and 131 were randomly assigned to treatment: 65 patients to 100% ONS and 66 to 30% ONS. In weeks 25-48, participants received individually optimized open-label ONS. The primary outcome was the weekly mean attack frequency in weeks 21-24 compared with baseline. In the 100% ONS stimulation group, attack frequency decreased from 17.58 (9.83 to 29.33) at baseline to 9.50 (3.00 to 21.25) at 21-24 weeks (median change from baseline -4.08, -11.92 to -0.25), and for the 30% ONS stimulation group, attack frequency decreased from 15.00 (9.25 to 22.33) to 6.75 (1.50 to 16.50; -6.50, -10.83 to -0.08). The difference in attack frequency between groups at the end of the masked phase in weeks 21-24 was -2.42 (95% CI -5.17 to 3.33). In the masked study phase, 129 adverse events occurred in the 100% ONS group and 95 occurred in the 30% ONS group. Of these, 17 and eight of the adverse events in the 100% and 30% groups, respectively, were considered serious, as they required hospital admission for minor hardware-related issues. The most

common adverse events were local pain, impaired wound healing, neck stiffness, and hardware damage.

Serra and Marchioretto (2012) conducted a crossover RCT in which 30 patients with chronic migraine (100% of patients) and medication overuse headache (85% of patients) were implanted with an ONS and randomized to “Stimulation On” or “Stimulation Off” arms.[9] After one month, or if headaches worsened during the off period, patients were crossed over to the other arm. The mean number of days when patients randomized to the off condition turned on the generators was 4.65 days (range, 1-12 days). Follow-up examinations were conducted at one, three, six, and 12 months after nerve stimulator implantation, during which time the stimulation parameters were adjusted in order to optimize the perception of paresthesia. In addition, the patients were provided with remote controls to modify the stimulation amplitude. At baseline, the average frequency of migraines was 5.8 days per week and the median headache severity was eight on an 11-point numerical rating scale. Headache intensity and/or frequency were significantly lower in the on arm compared to the off arm and decreased from baseline to each follow-up visit in all patients with Stimulation On. For example, the number of headaches decreased from a median of 6.3 days per week in the off phase to 2.1 days per week in the on phase. The median Migraine Disability Assessment (MIDAS) score decreased from 79 at baseline to 10 at 12-month follow-up. Quality of life measured by the SF-36 significantly improved from baseline throughout the follow-up period. Use of triptans decreased from a median of 20 to three doses/month and use of nonsteroidal anti-inflammatory drug (NSAIDs) use decreased from a median of 25.5 to two doses/month. There were two infections (6.7%) and three lead migrations (10%) during the study. This study is limited by the lack of a control group during follow-up and lack of blinding, although blinding of patients may be difficult due to paresthesia with this treatment.

Silberstein (2012) published a RCT of patients diagnosed with chronic migraine (CM), implanted with a neurostimulation device and randomized 2:1 to active (n=105) or sham (n=52) stimulation.[10] Authors defined the primary endpoint as the difference in the percentage of responders (defined as patients that achieved a ≥50% reduction in mean daily visual analog scale scores) in each group at 12 weeks. A significant difference was reported at a secondary endpoint of 30% reduction; however, no difference was reported between groups at the primary endpoint of 50% reduction. At a 30% reduction, significant difference in reduction of number of headaches, migraine-related disability, and direct reports of pain relief were reported compared to the sham group, but it is unknown if these results are clinically meaningful considering researchers did not meet their established primary endpoint of at least a 50% reduction in mean daily analog scores. In addition, the overall treatment effect was low, with only 17.1% of the active group and 13.5% of the control group classified as responders.

Results from the 52-week open-label extension of this study were published in 2014.[18] Results were reported for the intent-to-treat (ITT) population and for the 125 patients who met criteria for intractable chronic migraine. Twenty-four patients were excluded from analysis due to explantation of the system (n=18) or other loss to follow-up. Mean headache days at baseline were 21.6 for the ITT population and 24.2 for the intractable chronic migraine group. In the ITT population, headache days were reduced by 6.7 days, and a 50% or greater reduction in headache days and/or pain intensity was observed in 47.8% of patients. Sixty-eight percent of patients were satisfied with the headache relief provided by the device. Seventy percent experienced at least one of 183 device-related adverse events, of which 8.6% required hospitalization and 40.7% required surgical intervention. Eighteen percent of patients had persistent pain and/or numbness with the device.

A small industry-sponsored feasibility RCT reported preliminary safety and efficacy data on ONS for treatment of medically intractable chronic migraine (CM).[8] However, the findings from this small (n=110) and very short (follow-up=three months) study must be interpreted with caution due to the exploratory nature of the design:

- The sample size was chosen to gain experience with ONS and the study was not prospectively powered for efficacy evaluation.
- No primary end points were specified at the outset; at three months, a range of efficacy measures were evaluated in comparison to baseline.

Although the findings from this study may provide direction for future research, they do not provide reliable evidence on the clinical utility of ONS. Per the authors, “reliable conclusions regarding efficacy cannot be established on the basis of this study alone.”

NONRANDOMIZED STUDIES

Evidence from nonrandomized studies of occipital nerve stimulation (ONS) for treatment of headaches is considered insufficient due to methodological limitation such as nonrandom allocation of treatment, lack of adequate comparison groups, small sample size, and short-term follow-up, all of which limit conclusions regarding the safety and effectiveness of ONS treatment.[3, 19-21] Of note, several of these nonrandomized studies reported high rates of ONS revision (20-60%)[5, 22, 23] and/or complications (20-60%)[4, 5, 19, 24-26].

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PAIN MEDICINE

A 2022 evidence-based practice guideline from the American Academy of Pain Medicine on percutaneous interventional strategies for the prevention of migraine provides a “weak” recommendation of implantable stimulation (based on studies of occipital nerve stimulation) for chronic migraine prevention.[6] Implantable stimulation was noted to have significantly more adverse events than other percutaneous interventions, contributing to this “weak” recommendation.

AMERICAN SOCIETY OF PAIN AND NEUROSCIENCE

A 2022 consensus-based guideline on the use of implantable peripheral nerve stimulation for treatment of chronic pain states multiple randomized trials have demonstrated benefit of ONS for chronic migraine.[27] The guideline cites Dodick (2014), Mekhail (2017), Saper (2011), and Serra (2012).[8-10, 18]

- Stimulation of occipital nerves may be offered to patients with chronic migraine headache when conservative treatments have failed. The average size for relief of migraine symptoms is modest to moderate (Level I, Grade B).

- There is presently insufficient evidence to recommend stimulation of supraorbital or infraorbital nerves for neuropathic craniofacial pain (Level II-3, Grade C).

CONGRESS OF NEUROLOGICAL SURGEONS

A 2023 evidence-based guideline from the Congress of Neurological Surgeons states: “the use of occipital nerve stimulation is a treatment option for patients with medically refractory

occipital neuralgia." The guideline was jointly funded by Congress of Neurological Surgeons and the Joint Section on Pain of the American Association of Neurological Surgeons/Congress of Neurological Surgeon. The statement had a level III recommendation based on a systematic review of the literature that only included case series with methodological limitations.

SUMMARY

There is not enough research to show that occipital nerve stimulation (ONS) improves net health outcomes for patients with any condition. Clinical guidelines based on research list ONS as a treatment option but consideration of evidence of benefits vs. harm of ONS is inconsistent in the guidelines. Therefore, ONS is considered investigational for all indications, including but not limited to as a treatment of headache.

REFERENCES

1. Membrilla JA, Roa J, Díaz-de-Terán J. Preventive treatment of refractory chronic cluster headache: systematic review and meta-analysis. *J Neurol.* 2023;270(2):689-710. PMID: 36310189
2. Wilbrink LA, de Coo IF, Doesborg PGG, et al. Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): a randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial. *Lancet Neurol.* 2021;20(7):515-25. PMID: 34146510
3. Diaz-de-Teran J, Membrilla JA, Paz-Solis J, et al. Occipital Nerve Stimulation for Pain Modulation in Drug-Resistant Chronic Cluster Headache. *Brain Sci.* 2021;11(2). PMID: 33668570
4. Leplus A, Fontaine D, Donnet A, et al. Long-Term Efficacy of Occipital Nerve Stimulation for Medically Intractable Cluster Headache. *Neurosurgery.* 2021;88(2):375-83. PMID: 32985662
5. Magis D, Gerardy PY, Remacle JM, et al. Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. *Headache.* 2011;51(8):1191-201. PMID: 21848953
6. Barad M, Ailani J, Hakim SM, et al. Percutaneous Interventional Strategies for Migraine Prevention: A Systematic Review and Practice Guideline. *Pain Med.* 2022;23(1):164-88. PMID: 34382092
7. Chou R, Fu R, Dana T, et al. AHRQ Comparative Effectiveness Reviews. Interventional Treatments for Acute and Chronic Pain: Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US), 2021.
8. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia.* 2011;31(3):271-85. PMID: 20861241
9. Serra G, Marchioretto F. Occipital nerve stimulation for chronic migraine: a randomized trial. *Pain physician.* 2012;15(3):245-53. PMID: 22622909
10. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia.* 2012;32(16):1165-79. PMID: 23034698

11. Patel K, Batchu S, Wang R, et al. The Use of Electrical Nerve Stimulation to Treat Migraines: A Systematic Review. *Cureus.* 2021;13(8):e17554. PMID: 34646611
12. Moisset X, Pereira B, Ciampi de Andrade D, et al. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. *J Headache Pain.* 2020;21(1):142. PMID: 33302882
13. Cadalso RT, Jr., Daugherty J, Holmes C, et al. Efficacy of Electrical Stimulation of the Occipital Nerve in Intractable Primary Headache Disorders: A Systematic Review with Meta-Analyses. *Journal of oral & facial pain and headache.* 2017. PMID: 29161336
14. Yang Y, Song M, Fan Y, et al. Occipital Nerve Stimulation for Migraine: A Systematic Review. *Pain practice : the official journal of World Institute of Pain.* 2016;16(4):509-17. PMID: 25865962
15. Chen YF, Bramley G, Unwin G, et al. Occipital nerve stimulation for chronic migraine--a systematic review and meta-analysis. *PloS one.* 2015;10:e0116786. PMID: 25793740
16. Sweet JA, Mitchell LS, Narouze S, et al. Occipital Nerve Stimulation for the Treatment of Patients With Medically Refractory Occipital Neuralgia: Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline. *Neurosurgery.* 2015;77(3):332-41. PMID: 26125672
17. NICE. IPG452 Occipital nerve stimulation for intractable chronic migraine: National Institue of Health and Care Excellence, 2013.
18. Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia.* 2014. PMID: 25078718
19. Trentman TL, Rosenfeld DM, Vargas BB, et al. Greater occipital nerve stimulation via the Bion microstimulator: implantation technique and stimulation parameters. Clinical trial: NCT00205894. *Pain physician.* 2009;12(3):621-8. PMID: 19461827
20. Lagrata S, Cheema S, Watkins L, et al. Long-Term Outcomes of Occipital Nerve Stimulation for New Daily Persistent Headache With Migrainous Features. *Neuromodulation.* 2021;24(6):1093-99. PMID: 32996695
21. Magown P, Becker WJ, Kiss ZH. Outcomes of Occipital Nerve Stimulation for Craniofacial Pain Syndromes. *Can J Neurol Sci.* 2021;48(5):690-97. PMID: 33234176
22. Schwedt TJ, Dodick DW, Hentz J, et al. Occipital nerve stimulation for chronic headache--long-term safety and efficacy. *Cephalalgia.* 2007;27(2):153-7. PMID: 17257236
23. Vadivelu S, Bolognese P, Milhorat TH, et al. Occipital nerve stimulation for refractory headache in the Chiari malformation population. *Neurosurgery.* 2012;70(6):1430-6; discussion 36-7. PMID: 22418582
24. Hansrani V, Abbas A, Bhandari S, et al. Trans-venous occlusion of incompetent pelvic veins for chronic pelvic pain in women: a systematic review. *European journal of obstetrics, gynecology, and reproductive biology.* 2015;185:156-63. PMID: 25590499
25. Ashkan K, Sokratous G, Gobel H, et al. Peripheral nerve stimulation registry for intractable migraine headache (RELIEF): a real-life perspective on the utility of occipital nerve stimulation for chronic migraine. *Acta Neurochir (Wien).* 2020;162(12):3201-11. PMID: 32377948
26. Raoul S, Nguyen JM, Kuhn E, et al. Efficacy of Occipital Nerve Stimulation to Treat Refractory Occipital Headaches: A Single-Institution Study of 60 Patients. *Neuromodulation.* 2020;23(6):789-95. PMID: 32725745
27. Strand N, D'Souza RS, Hagedorn JM, et al. Evidence-Based Clinical Guidelines from the American Society of Pain and Neuroscience for the Use of Implantable Peripheral

Nerve Stimulation in the Treatment of Chronic Pain. *J Pain Res.* 2022;15:2483-504. PMID: 36039168

CODES

Codes	Number	Description
CPT	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64568	Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64575	Open implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64585	Revision or removal of peripheral neurostimulator electrode array
	64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver
	64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array
	64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)
	64598	
	64999	Unlisted procedure, nervous system
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system

Codes	Number	Description
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non- rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Date of Origin: *June 2010*

Regence

Medical Policy Manual Surgery, Policy No. 182

Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast

Effective: January 1, 2024

Next Review: October 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Autologous fat grafting to the breast has been used as an adjunct to reconstructive breast surgery to address issues such as post-mastectomy pain and irradiated skin. Adipose-derived stem cells have been proposed as a supplement to the fat graft in an attempt to improve graft survival.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address the use of autologous fat grafting without adipose stem cell enrichment for breast reconstruction, which may be considered medically necessary.
- This policy does not address free flap autologous fat grafting with micro vascularization.
- This policy does not address the use of autologous fat tissue in aesthetic breast augmentation (i.e., cosmesis).

The use of autologous fat grafting to the breast with supplemented adipose-derived stem cells is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Gender Affirming Interventions for Gender Dysphoria, Medicine, Policy No. 153
2. Endometrial Ablation, Surgery, Policy No. 01
3. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
4. Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants, Surgery, Policy No. 40
5. Reduction Mammaplasty, Surgery, Policy No. 60

BACKGROUND

AUTOLOGOUS FAT GRAFTING TO THE BREAST

Autologous fat grafting to the breast has been proposed for indications which include breast augmentation and following oncologic surgery. Proposed indications following oncologic surgery include as an adjunct to reconstruction post mastectomy or lumpectomy for contour deformities and improved shape and volume of the breast, for post mastectomy pain syndrome (neuropathic pain), and for irradiated skin to soften the skin and restore it to non-irradiated appearance and consistency.

ADIPOSE-DERIVED STEM CELLS (ADSCS)

Stem cell biology, and the related field of regenerative medicine, involves multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. Studies have shown that 1 gram of adipose tissue yields approximately 5 x 10^3 stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow.[1] Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. Adipose tissue in particular represents an abundant and easily accessible source of adipose-derived stem cells (ADSCs), which can differentiate along multiple mesodermal lineages.[1] ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site.

This identification of several potentially beneficial therapeutic properties of ADSC has led to proposed novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting, including the differentiation of ADSC into adipocytes as a reservoir for adipose tissue turnover, the differentiation of ADSC into endothelial cells and the subsequent increase in blood supply to the grafted fat tissue, thereby decreasing the rate of graft resorption, the release of angiogenic growth factors by ADSC and the induction of angiogenesis, protection of the graft from ischemic reperfusion injury by ADSC, and acceleration of wound healing at the recipient site.[1]

Current methods for isolating ADSCs can involve various processes, which may include centrifugation and enzymatic techniques that rely on collagenase digestion followed by centrifugal separation to isolate the stem cells from primary adipocytes. Isolated ADSCs can be expanded in monolayer on standard tissue culture plastic with a basal medium containing 10% fetal bovine serum,[2] and newly developed culture conditions provide an environment

within which the study of ADSCs can be done without the interference of animal serum. They also allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

Yoshimura (2008), in an effort to address the problems of unpredictability and low rates of fat graft survival, developed a technique known as cell-assisted lipotransfer (CAL), which produces autogenous fat rich in ADSCs.[3] In CAL, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs, while the other half is washed, enzymatically digested, filtered, and spun down to an ADSC-rich pellet. The latter is then mixed with the former, converting a relatively ADSC-poor aspirated fat to ADSC-enriched fat.

REGULATORY STATUS

A point-of care system is available for concentrating ADSCs from mature fat. The Celution™ system (Cytori Therapeutics, Inc.) is designed to transfer a patient's own adipose tissue from one part of the body to another in the same surgical procedure. The system received 510(k) marketing clearance from the U.S. Food and Drug Administration as a cell saver device. The system is cleared for the collection, concentration, washing and re-infusion of a patient's own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urological surgeries and procedures.

In 2017, the Revolve Envi 600 Advanced Adipose System (LifeCell Corporation, Branchburg, NJ) was cleared for marketing by the FDA through the 510(k) process. The system harvests, filters, and transfers autologous adipose tissue for fat grafting. Uses include reconstructive surgery. In May of 2020, the Revolve Envi 600 System underwent various design modifications (K163647). FDA product code: MUU.

EVIDENCE SUMMARY

The literature on the use of fat grafting to the breast with the use of adipose-derived stem cell (ADSC) enrichment consists of retrospective cohort studies, case series, and case reports. The following is a summary of the key literature to date, including all identified case series using fat grafting to the breast with the supportive use of ADSCs.

Systematic Reviews

A 2021 SR published by Li and Chen compared the efficacy of CAL and conventional lipotransfer in breast augmentation.[4] Six studies including 353 patients met inclusion criteria. Of these, one was a randomized trial, four were retrospective observational case-series, and one was a prospective controlled trial. No evaluation of study quality was reported. The fat survival rate was significantly higher in the CAL group than in the control group (standard mean difference [SMD]=1.79, 95% CI 0.28 to 3.31; p=0.02). No statistically significant differences in complication rates between groups (SMD=1.79, 95% CI 0.28 to 3.31; p=0.02). There were also no statistically significant differences identified in the subgroup analyses between the groups in fat survival rate (SMD=1.52, 95% CI -0.21 to 3.24; p=0.08).

In 2017, Lazole conducted a SR to evaluate the safety and efficacy of CAL. Twenty-five studies addressing fat grafting to the breast and face were included in the systematic review and 16 in the meta-analysis.[5] The fat survival rate was significantly higher with CAL than non-CAL fat graft, only for injection volumes < 100 mL. There was no significant difference between groups in frequency of multiple procedures after fat grafting. The incidence of complications

was significantly higher in the CAL group.

In 2016, Zhou conducted a SR with the same purpose as the above systematic review, and included seventeen articles (n=387) for all indications, including breast.[6] For all indications combined, the pooled fat survival rate was significantly higher in the CAL group than in the nonlipotransfer group (60% vs. 45%, p=0.0096). Complication incidence was similar in the two groups. In breast fat grafting fat survival was improved by only 9% in the CAL group, which was not statistically significant. In addition, lipotransfer in breast cases was associated with a higher complication incidence compared with other indications (p<0.001).

Randomized Control Trial

Vester-Glowinski (2022) published a randomized control trial (RCT) trial aimed to investigate whether ADSCs improve fat graft volume retention in patients undergoing breast augmentation with lipofilling.[7] This was a double-blind, randomized controlled trial of breast augmentation with ADSC-enriched fat grafting. Healthy women aged 30 to 45 years were enrolled. First, the participants underwent liposuction to obtain fat for culture expansion of ASCs. Then, the participants were randomly assigned to undergo a 300- to 350-mL breast augmentation with ADSC-enriched fat grafting (10 × 106 ASCs/mL fat graft) to 1 of their breasts and placebo-enriched fat grafting of identical volume to the contralateral breast. Fat graft volume retention after one year was 54.0% (95% CI, 30.4%-77.6%) in the breasts treated with ASC-enriched fat grafting (n = 10) and 55.9% (95% CI, 28.9%-82.9%) in the contralateral breasts treated with placebo-enriched fat grafting (n = 10) (p=0.566). The authors concluded that the findings of this trial do not support that ASC-enriched fat grafting is superior to standard fat grafting for breast augmentation.

Nonrandomized Studies

Jørgensen (2021) performed a phase I trial aimed to assess whether ADSCs can alleviate lymphedema in clinical reality with long-term follow-up in patients with breast cancer-related lymphedema (BCRL).[8] They treated 10 patients with BCRL using ADSCs and a scar-releasing lipotransfer to the axillary region, and all patients were followed one, three, six, twelve, and forty-eight months after treatment. There was no significant decrease in BCRL volume after treatment. However, self-reported upper extremity disability and arm heaviness and tension improved. The authors reported that in this phase I study with four years of follow-up, axillary delivered ADRCs and lipotransfer were safe and feasible and improved BCRL symptoms and upper extremity function. The authors also recommended more RCTs to confirm the results of this study.

Jeon et al (2020) evaluated the efficacy of CAL on the fat graft retention rate in patients with volume deficit after undergoing autologous breast reconstruction following total mastectomy.[9] This 12-month prospective study included 20 patients (20 breasts) between 2017 and 2019. Patients were divided into two groups: autologous fat graft without stromal-vascular fraction (i.e., without ADSC) or autologous fat graft with stromal-vascular fraction of ADSC. The retention rate of the fat graft was higher in the group with ADSC than in the group without at both postoperative 6 months (73.8% vs 62.2%; p=0.03) and 12 months (65.4% vs 48.4%; p=0.03). Based on a modified BREAST-Q questionnaire at 12 months, the group who received fat graft with ADSC reported higher patient satisfaction (49.4 points out of 55 compared to 44.2 points out of 55), although this was not statistically significant. Fat necrosis occurred in one patient each in both groups, however, locoregional recurrence was not observed in any patient during follow-up. The authors concluded that CAL with stromal-vascular fraction provided

better outcomes in terms of volume retention compared to CAL without ADSC.

Mazur (2018) evaluated the risk of cancer recurrence in 56 patients having the breast reconstructed with autologous ASC (transplanted as the subpopulation present in the stromal vascular fraction [SVF]).[10] Tumor recurrence in these patients was compared with tumor recurrence in 252 matched patients that did not receive breast reconstruction. Cancer recurrence in the ASC and control groups was 3.7% and 4.13%, respectively, which was not significantly different (p=1.0).

In 2016, Jung conducted a small single-arm, prospective study to evaluate the impact of ADSCs, using CAL, on graft survival, including five patients.[11] One year after CAL, breast volume had decreased to 47% of the initial postoperative volume. The ratio of ADSC cell count to grafted fat volume showed no correlation with graft survival. The addition of SVF cells did not appear to improve the retention of grafted fat in these patients. Skin tension may be an important factor influencing the absorption pattern of grafted fat.

In 2013, Peltoniemi conducted a prospective comparative study to evaluate if stem cell enrichment is important for success in lipofilling for cosmetic breast augmentation.[12] A total of 18 women underwent breast augmentation, with 10 of the cases including transferred lipoaspirate enriched with ADSCs using the Cytori Celution(®) system MRI-based volumetric analysis was done preoperatively and six months post-procedure. MRI analysis revealed mean graft survival was not significantly different between groups (54% in nonADSC group vs. 50% in the ADSC-enrichment patients). After centrifugation survival was not significantly different between groups (79% in nonADSC group vs. 74% in the ADSC-enrichment patients. The investigators concluded that they did not see any advantage in stem cell enrichment by the Celution(®) system in cosmetic fat transplantation to the breast.

In 2012, Pérez-Cano conducted a single-arm, prospective, multicenter clinical trial of 71 women who underwent breast conserving surgery for breast cancer and autologous adipose-derived regenerative cell (ADRC)-enriched fat grafting for reconstruction of defects ≤150 mL (the RESTORE-2 trial).[13] Trial endpoints included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months post-procedure. Female patients (18 to 75 years of age) presenting with partial mastectomy defects and without breast prosthesis were eligible. The RESTORE-2 protocol allowed for up to two treatment sessions and 24 patients elected to undergo a second procedure following the six-month follow-up visit. Of the 67 patients treated, 50 reported satisfaction with treatment results through 12 months. Sixty-one patients underwent radiation therapy as part of their treatment; two patients did not receive radiation and the status of radiation treatment was not known for the other four patients. Using the same metric, investigators reported satisfaction with 57 out of 67 patients. There were no serious adverse events associated with the ADRC-enriched fat graft injection procedure. There were no reported local cancer recurrences. The LENT-SOMA scale included investigator and patient assessment of post-radiation signs and symptoms. The investigators of the trial found that LENT-SOMA was insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA III and IV scores (most severe symptoms) were excluded during screening, which may have contributed to the subtle LENT-SOMA score changes observed in the trial. The investigators reported improvement from baseline through 12 months in the degree of retraction or atrophy in 29 out of 67 patients, while 34 patients had no change and four patients reported worse symptoms. Post-radiation fibrosis at 12 months was reported as improved in 29 patients, while 35 patients had no change and three patients had worse symptoms. Management of atrophy

was reported as improved in 17 patients, with 48 patients having no change and two patients reporting worse symptoms. Improvement in these measures reached statistical significance. The authors concluded that future comparative studies are needed to determine the incremental benefit of ADRC-enriched fat grafting as compared to traditional fat grafting in various clinical circumstances.

In 2011, Kamakura and Ito reported on the use of ADSC enriched fat grafting for breast augmentation in a prospective, nonrandomized open-label study of 20 Japanese women.[14] After the adipose tissue was harvested by liposuction, it was processed in the Celution 800 System® to wash and isolate the adipose-derived regenerative cells and produce a fat graft enriched with the regenerative cells. Clinical outcomes measured included improvement in circumferential breast measurement from baseline state. There was improvement in circumferential breast measurement in all patients, and breast measurements were stable by three months after grafting. At nine months, the mean breast measurement had increased 3.3 cm from preoperative measurements. The procedure was well-tolerated without any serious adverse events. Postoperative cyst formation was seen in two patients.

In 2008, Yoshimura and colleagues reported on the development of CAL, in which autologous ADSCs are used in combination with lipoinjection.[3] From 2003 to 2007, the group performed CAL in 70 patients: in the breast in 60 patients (including eight who had breast reconstruction after mastectomy). They reported outcomes for 40 patients with healthy thoraxes and breasts who underwent CAL for purely cosmetic breast augmentation; patients undergoing breast reconstruction for an inborn anomaly or after mastectomy were not included. Nineteen of the 40 patients had been followed for more than six months, with a maximum follow-up of 42 months. The authors observed that the transplanted adipose tissue was gradually absorbed during the first two postoperative months, and the breast volume showed a minimal change thereafter. Final breast volume showed augmentation by 100 to 200 mL after a mean fat amount of 270 mL was injected. The difference in breast circumference (defined as the chest circumference at the nipple minus the chest circumference at the inframammary fold) had increased in all cases by 4 to 8 cm at six months. Cyst formation or microcalcification was detected in four patients. The authors concluded that their preliminary results suggest that CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection but that additional study is necessary to further evaluate the efficacy of this technique.

In 2007, Rigotti reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (LENT-SOMA scale grade 3 and 4). LENT-SOMA is one of the most common systems to assess the late effects of radiotherapy.[15] The mean patient age was 51 years (range, 37 to 71 years). The rationale behind the study was that the ADSCs, which have been shown to secrete angiogenic and antiapoptotic factors and to differentiate into endothelial cells, could promote neovascularization in ischemic tissue such as irradiated tissue. Targeted areas included the supraclavicular region, the anterior chest wall after mastectomy with or without breast prosthesis, and breast after quadrantectomy. A lipoaspirate purification procedure was performed by centrifugation to remove a large part of the triglyceride portion of the tissue and disrupt the cytoplasm of the mature adipocytes to favor their rapid clearance after injection. A stromal-vascular fraction was isolated by enzymatic digestion of extracellular matrix, centrifugation and filtration, and the fractions were cultured for two to three weeks to obtain a homogenous cell population. To assess the presence of mesenchymal stem cells, the stromal-vascular fraction derived from the adipose tissue was

cultured and characterized by flow cytometry. The number of procedures was one in five patients, two in eight patients, three in six patients, and six in one patient. Clinical follow-up varied between 18 and 33 months (mean, 30 months). Clinical results after treatment with lipoaspirates were assessed by LENT-SOMA scoring. The 11 patients initially classified as LENT-SOMA grade 4 (irreversible functional damage) progressed to grade 0 (no symptoms), grade 1 and grade 2 in four, five, and one cases, respectively. In one case, no improvements were observed. In the four patients who had undergone mastectomy and had breast prostheses and areas of skin necrosis, the necrosis showed complete remission. In the group of nine patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and 1 in five and four cases, respectively.

PRACTICE GUIDELINE SUMMARY

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)

In 2012 NICE published an evidence-based clinical practice guideline addressing breast reconstruction using lipomodelling after breast cancer treatment. Regarding the use of stem cell enrichment, it states, “Further information about the outcomes of this and other adaptations of the technique of lipomodelling is desirable for guiding their future use in clinical management.”[16]

AMERICAN SOCIETY OF AESTHETIC PLASTIC SURGERY AND AMERICAN SOCIETY OF PLASTIC SURGEONS[17]

A joint task force of the American Society for Aesthetic Plastic Surgery (ASAPS) and the American Society of Plastic Surgeons released a position statement on the use of stem cells in aesthetic surgery during the 2011 annual meeting of ASAPS.[17] Based on a systematic review of the peer-reviewed literature, the task force concluded that while there is potential for the future use of stem cells in aesthetic surgical procedures, the scientific evidence and other data are very limited in terms of assessing the safety or efficacy of stem cell therapies in aesthetic medicine.

SUMMARY

The current research on the use of supplemented adipose-derived stem cells in combination with fat grafting to the breast has many limitations. In addition, the research is starting to show that the use of these cells does not increase graft survival or decrease resorption rates. More research is needed on the long-term effectiveness and safety of enrichment of adipose-derived stem cells in fat grafting to the breast. In addition, no evidence-based clinical practice guidelines recommend the use of adipose-derived stem cell enrichment in fat grafting to the breast. Therefore, the use of adipose-derived stem cell enrichment in conjunction with fat grafting to the breast is considered investigational.

REFERENCES

1. Mizuno H, Hyakusoku H. Fat grafting to the breast and adipose-derived stem cells: recent scientific consensus and controversy. *Aesthet Surg J.* 2010;30(3):381-7. PMID: 20601560

2. Sterodimas A, de Faria J, Nicaretta B, et al. Tissue engineering with adipose-derived stem cells (ADSCs): current and future applications. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2010;63(11):1886-92. PMID: 19969517
3. Yoshimura K, Sato K, Aoi N, et al. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg.* 2008;32(1):48-55; discussion 56-7. PMID: 17763894
4. Li M, Chen C. The Efficacy of Cell-Assisted Lipotransfer Versus Conventional Lipotransfer in Breast Augmentation: A Systematic Review and Meta-Analysis. *Aesthetic Plast Surg.* 2021;45(4):1478-86. PMID: 33452543
5. Laloze J, Varin A, Gilhodes J, et al. Cell-assisted lipotransfer: friend or foe in fat grafting? Systematic review and meta-analysis. *Journal of tissue engineering and regenerative medicine.* 2017. PMID: 28719946
6. Zhou Y, Wang J, Li H, et al. Efficacy and Safety of Cell-Assisted Lipotransfer: A Systematic Review and Meta-Analysis. *Plastic and reconstructive surgery.* 2016;137:44e-57e. PMID: 26710060
7. Vester-Glowinski PV, Herly M, Orholt M, et al. Fat Grafting With Expanded Adipose-Derived Stromal Cells for Breast Augmentation: A Randomized Controlled Trial. *Aesthet Surg J.* 2022;42(11):1279-89. PMID: 35704475
8. Jorgensen MG, Toyserkani NM, Jensen CH, et al. Adipose-derived regenerative cells and lipotransfer in alleviating breast cancer-related lymphedema: An open-label phase I trial with 4 years of follow-up. *Stem Cells Transl Med.* 2021;10(6):844-54. PMID: 33594819
9. Jeon HJ, Choi DH, Lee JH, et al. A Prospective Study of the Efficacy of Cell-Assisted Lipotransfer with Stromal Vascular Fraction to Correct Contour Deformities of the Autologous Reconstructed Breast. *Aesthetic Plast Surg.* 2021;45(3):853-63. PMID: 32995982
10. Mazur S, Zolocinska A, Siennicka K, et al. Safety of adipose-derived cell (stromal vascular fraction - SVF) augmentation for surgical breast reconstruction in cancer patients. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University.* 2018;27(8):1085-90. PMID: 29989681
11. Jung HK, Kim CH, Song SY. Prospective 1-Year Follow-Up Study of Breast Augmentation by Cell-Assisted Lipotransfer. *Aesthet Surg J.* 2016;36:179-90. PMID: 26342099
12. Peltoniemi HH, Salmi A, Miettinen S, et al. Stem cell enrichment does not warrant a higher graft survival in lipofilling of the breast: a prospective comparative study. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2013;66(11):1494-503. PMID: 23845909
13. Perez-Cano R, Vranckx JJ, Lasso JM, et al. Prospective trial of adipose-derived regenerative cell (ADRC)-enriched fat grafting for partial mastectomy defects: the RESTORE-2 trial. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2012;38(5):382-9. PMID: 22425137
14. Kamakura T, Ito K. Autologous Cell-Enriched Fat Grafting for Breast Augmentation. *Aesthetic Plast Surg.* 2011. PMID: 21533662
15. Rigotti G, Marchi A, Galie M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plastic and reconstructive surgery.* 2007;119(5):1409-22; discussion 23-4. PMID: 17415234

16. (NICE) NIfHaCE. Breast reconstruction using lipomodelling after breast cancer treatment. Interventional procedures guidance [IPG417]. [cited 11/09/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg417.
17. American Society for Aesthetic Plastic Surgery and American Society of Plastic Surgeons. ASAPS and ASPS Issue Joint Position Statement on Stem Cells and Fat Grafting. [cited 11/09/2023]. 'Available from:' https://academic.oup.com/asj/article/31/6/716/210262.

CODES

NOTE: There is no specific code to report the use of the additional adipose-derived stem cell enrichment in autologous fat grafting.

Codes	Number	Description
CPT	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	19380	Revision of reconstructed breast (eg, significant removal of tissue, re-advancement and/or re-inset of flaps in autologous reconstruction or significant capsular revision combined with soft tissue excision in implant-based reconstruction)
	19499	Unlisted procedure, breast
HCPCS	None	

Date of Origin: *November 2011*

Regence

Medical Policy Manual Surgery, Policy No. 184

Bronchial Valves

Effective: July 1, 2023

Next Review: March 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Bronchial (endobronchial, intrabronchial) valves are synthetic devices that are deployed with bronchoscopy into ventilatory airways of the lung for the purpose of controlling airflow.

MEDICAL POLICY CRITERIA

I. The use of a bronchial valve may be considered **medically necessary** for the treatment of *severe emphysema* when all of the following Criteria (A.- O.) are met:

A. The valve has been approved by the FDA (Zephyr® Endobronchial Valve System or Spiration® Valve System); and

B. Patient is age 40 years or older; and

C. Body mass index (BMI) less than 35kg/m^2; and

D. Patient has completed a pulmonary rehabilitation program prior to valve placement; and

E. The patient is not a cigarette smoker OR there is clinical documentation that the patient has been abstinent from cigarette smoking for at least four consecutive months prior to and throughout evaluation for the procedure; and

F. Little or no collateral ventilation as determined using the Chartis (Zephyr) or

SeleCT (Spiration) systems (see Policy Guidelines) is present; and

G. Total lung capacity (TLC) is greater than 100% predicted; and

H. Six-minute walking distance (6MWD) ≥100m and <500m; and

I. Patient has not had any of the following: prior lung transplant, lung volume reduction surgery (LVRS), ipsilateral bullectomy, or lobectomy; and

J. Residual volume (RV) is greater than or equal to 175% predicted; and

K. High resolution computed tomography (HRCT) obtained within 90 days of screening demonstrates all of the following (1.- 3.):

1. *Absence* of large bullae encompassing greater than 30% of either lung; and
2. Target lobe has greater than or equal to 40% emphysema destruction; and
3. Greater than or equal to 10% disease severity difference (heterogenous emphysema) between the targeted lobe and the ipsilateral lobe; and

L. Post-bronchodilator forced expiratory volume (FEV1) is between 15% and 45% of predicted value; and

M. PaCO2 <60mmHg and PaO2 >45mm Hg on room air; and

N. Stable with less than 20 mg daily of prednisone (or equivalent); and

O. Patient has *no record of any of the following contraindications* as documented by an echocardiogram, right heart catheterization, and/or electrocardiogram completed within 90 days from screening:

1. Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure greater than 45 mm Hg); and
2. Left ventricular ejection fraction (LVEF) less than 45%; and
3. Evidence or history of cor pulmonale; and
4. Congestive heart failure; and
5. Resting bradycardia (less than 50 beats/min).

II. Removal, replacement, or revision of a U.S. Food and Drug Administration (FDA) approved bronchial valve (Zephyr® Endobronchial Valve System or Spiration® Valve System) may be considered **medically necessary** once the valve has been placed for the treatment of emphysema.

III. The use of a bronchial valve is considered **investigational** for all other indications, including but not limited to the following:

A. For the treatment of emphysema when Criterion I. is not met; or

B. For the treatment of air leaks.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

The goal of bronchial valve treatment is to achieve a lobar volume reduction or atelectasis

(collapse). In many patients, atelectasis cannot be achieved due to interlobar collateral ventilation (CV) generated through incomplete lobar fissures. There are several methods to assess the presence of CV, with endobronchial pulmonary assessment (e.g., the Chartis System) and CT-fissure analysis (e.g., SeleCT or StratX) being the most common.

CT-fissure analysis can be used to assess the completeness of the fissure. Typically, the analysis is done by experienced radiologists or pulmonologists. The target lobe and ipsilateral lobe must be separated with an intact fissure and an intact fissure is estimated visually to be ≥90% complete with no segmental vessels crossing from one lobe to the adjacent lobe after viewing the high-resolution CT in three dimensions (sagittal, axial, and coronal). Automated methods (SeleCT) to provide exact quantifications and support visual readings are recommended.

The Chartis system is used for bronchoscopic assessment of collateral ventilation and consists of a catheter with a balloon component at the distal tip. The Chartis system was originally validated in spontaneous breathing patients under conscious sedation, however the measurement has been performed under general anesthesia with positive pressure support or high frequency jet ventilation. The airway is blocked when the balloon is inflated and air from the targeted segment or lobe can flow only through the catheter. This air is directed to the Chartis console, which can assess both expiratory air flow, pressure, and resistance. Presence of collateral airflow is observed if expiratory airflow persists after occlusion of a lobe, and if there is no flow, this indicates no collateral airflow.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Medical records, including history and physical/chart notes related to documenting that all of the requirements in Criteria I. are met, including but not limited to:
  - results of high-resolution CT obtained within 90 days of screening documenting the sub-criteria in Criterion I. are met
  - results of echocardiogram, right heart catheterization, and/or electrocardiogram documenting sub-criteria in Criterion I. are met
  - the type of valve system to be used.

CROSS REFERENCES

None

BACKGROUND

Proper lung functioning is dependent upon a separation between the air-containing parts of the lung and the small vacuum-containing space around the lung called the pleural space. When air leaks into the pleural space, the lung is unable to inflate resulting in hypoventilation and hypoxemia; this condition is known as a pneumothorax. A pneumothorax can result from a variety of processes including trauma, high airway pressures induced during mechanical ventilation, lung surgery, and rupture of lung blebs or bullae, which may be congenital or a result of chronic obstructive pulmonary disease (COPD).

Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. They have been investigated for use in patients who have prolonged bronchopleural air leaks and as an alternative to lung volume reduction surgery in patients with hyperinflation from severe or advanced emphysema.

Emphysema, a form of COPD, is a progressive, debilitating disease characterized by irreversible destruction of alveolar tissue. This destruction results in reduced elastic recoil, progressive hyperinflation and gas trapping with patients experiencing chronic dyspnea, limited exercise tolerance and poor health related quality of life. In emphysematous COPD, diseased portions of the lung ventilate poorly, cause air trapping, and hyperinflate, compressing relatively normal lung tissue. The patterns and degree of emphysema heterogeneity (i.e., the extent and distribution of air space enlargements) can be measured using computed tomography (CT) density as an indicator for tissue destruction. The most diseased portions of lung can then potentially be targeted for lung volume reduction procedures. In homogeneous emphysema, there is minor or no regional difference in disease within or between lobes of the lung. Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. During inhalation, the valve is closed, preventing air flow into the diseased area of the lung. The valve can open during exhalation to allow air to escape from the diseased area of the lung. They have been investigated for use in patients who have prolonged bronchopleural air leaks and in patients with hyperinflation from severe or advanced emphysema.

When used to treat persistent air leaks from the lung into the pleural space, the bronchial valve theoretically permits less air flow across the diseased portion of the lung during inhalation, aiding in air leak closure. The valve may be placed, and subsequently removed by bronchoscopy. The use of bronchial valves to treat emphysema is based on the improvement observed in patients who have undergone lung volume reduction surgery. Lung volume reduction surgery involves excision of peripheral emphysematous lung tissue, generally from the upper lobes. The precise mechanism of clinical improvement for patients undergoing lung volume reduction has not been firmly established. However, it is believed that elastic recoil and diaphragmatic function are improved by reducing the volume of the diseased lung. Currently, and at the time the clinical trials were designed, very few lung volume reduction procedures were performed. The procedure is designed to relieve dyspnea and improve functional lung capacity and quality of life; it is not curative. Medical management remains the most common treatment for a majority of patients with severe emphysema.

In early trials of bronchial valves for treatment of emphysema, absence of collateral ventilation (pathways that bypass the normal bronchial airways) was associated with better outcomes, presumably because patients with collateral ventilation did not develop lobar volume reduction or atelectasis (collapse). In subsequent trials, patients were selected for absence of collateral ventilation, and it is current practice for patients to be assessed for the presence of collateral ventilation prior to undergoing the procedure. Collateral ventilation is measured by the Chartis system, which requires bronchoscopy, or as a surrogate, CT scanning to assess the completeness of fissures, SeleCT or StratX systems. After 45 days post-procedure, residual volume can provide information on whether lung volume reduction has been achieved successfully.

REGULATORY STATUS

Currently, two endobronchial valve systems are FDA-approved for treatment of patients with

severe emphysema (FDA product code: NJK). Both are one-way valves which work to prevent air flow to the diseased area of the lung during inhalation. The valves allow air to escape from the treated lobe(s) during exhalation. In June 2018, the FDA granted the Zephyr® Endobronchial Valve (formerly Emphasys, now Pulmonx) system breakthrough device status with expedited approval for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.[1] The Zephyr Endobronchial Valve (EBV) is a one-way, removable, silicone, duckbill valve mounted in a nitinol, self-expanding retainer that is covered with a thin silicone membrane. The valve is available in three sizes and implanted during bronchoscopy in bronchial lumens ranging from 4.0 to 8.5 mm in diameter. In December 2018, the FDA approved the Spiration® Valve System.[2] The Spiration® Valves are one-way endobronchial valves intended for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have low collateral ventilation. The Spiration® Valve System is deployed into the bronchial tree using the deployment catheter passed through the working channel of a flexible bronchoscope with working channel 2.6 mm or greater. The Spiration valves are provided in four sizes to accommodate airway diameters ranging from 4.75 to 8.75 mm. Both valves may require repeat procedures to reposition or restore functioning. Although more than one valve may be needed to achieve the desired clinical outcome, FDA safety testing assumed no more than 10 valves will be placed in a clinical procedure for the treatment of severe emphysema.

The intrabronchial IBV® Valve System (Spiration, Inc) was approved by the U.S. Food and Drug Administration (FDA) under the Humanitarian Device Exemption (HDE) number H060002. It is intended for use in controlling prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks following lobectomy, segmentectomy, or lung volume reduction surgery (LVRS), for a duration up to 6 weeks.[3]

EVIDENCE SUMMARY

PROLONGED OR SIGNIFICANT AIR LEAKS

The principal outcome associated with treatment of prolonged or significant air leaks include resolution of the leak. In order to understand the impact of bronchial valves for treatment of prolonged or significant air leaks, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as chest tube placement, performing a thoracotomy with mechanical or chemical pleurodesis, or additional operations, are needed.[3]

Systematic Review

No systematic reviews (SRs) were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

Randomized Controlled Trials

No randomized controlled trials (RCTs) were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

Nonrandomized studies

No comparative observational studies were identified. Nonrandomized studies have reported on the use of either intrabronchial[4], endobronchial valves[5, 6], or both types[7]. Conclusions

cannot be reached from of these studies, as the data are limited by a variety of factors, including but not limited to:

- Small study populations, less than 100 patients total, which limit the ability to rule out the role of chance as an explanation of study findings;[4, 5, 7] and
- Retrospectively abstracted records, leading to potential study bias in sample selection, including selection criteria.[5, 7]
- Follow-up of study subjects was over a short period of time, less than 6 months, so medium and long-term effects of endobronchial valves treatment are unknown.[4, 5, 7]

ADVANCED EMPHYSEMA

In patients with advanced emphysema, valves may be compared to other forms of medical treatment, such as bronchodilators, short courses of systemic corticosteroids, noninvasive positive pressure ventilation (NIPPV) and/or oxygen therapy. In patients who have exhausted conservative therapy, valves must be compared to more invasive treatment, such as lung volume reduction surgery. RCTs are needed in order to isolate the contribution of these implants from other components of therapy. Further, for treatment of chronic conditions, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits to understand the net treatment effect.

Systematic Reviews

Patel (2022) published a systematic review and meta-analysis of RCTs using EBVs to provide bronchoscopic lung volume reduction (BLVR) for emphysema. Nine studies that included 1383 randomized patients were analyzed. Of the 1383 patients, 888 received EBV and 495 received standard medications. The primary outcome measures were FEV_1, percent predicted FEV_1 ($\%FEV_1$), six-minute walk distance (6MWD), RV, and St. George's respiratory questionnaire (SGRQ) after EBV placement. Secondary outcomes were mortality and adverse event rates. All physiologic outcome measures showed significant improvement with EBV. FEV_1 (weighted mean difference [WMD] = 102.61 mL; 95% confidence interval [CI]: 82.80-122.43; p<0.05; I^2 = 42.61%, p=0.08) and %FEV1 (WMD=11.71; 95% CI: 9-14.42; p<0.05; I^2 = 71.13, p<0.05) were increased for the EBV group. EBV was associated with a reduction in RV (WMD= -533.48mL; 95% CI: -653.01 -- -413.94; p<0.05; I^2=26.90%, p=0.22). Quality of life and activity measures also showed significant improvement with EBV. SGRQ scores in the EBV arm compared with standard care were improved (WMD = -7.44; 95% CI: -9.01 -- -5.86; p<0.05; I^2 = 50.89%; p=0.03). 6MWD in patients who had EBV were also superior to those who were not treated with EBV (WMD = 37.45; 95% CI: 27.68-47.21, p<0.05; I^2 =72.98%; p<0.05). Other adverse events included pneumothorax, which was more likely in the EBV group (odds ratio [OR] = 10.50, 95% CI=5.31-20.79, p<0.05, I^2 = 32.55%, p=0.10). The difference in the incidence of respiratory failure was not significant between the two groups (OR = 0.93,95% CI = 0.49-1.76, p=0.82, I^2=0.00%, p=0.96). Pneumonia, acute exacerbation of COPD (AECOPD), and hemoptysis were increased in short-term (OR = 3.12, 95% CI=1.47-6.64, p<0.05; (OR-1.48, 95% CI = 1.02-2.13, p<0.05; OR = 3.56, 95% CI = 1.41-8.96 respectively), but not long-term follow-up (OR=1.66, 95% CI=0.90-3.06; OR=0.83, 95% CI: 0.57-1.19; OR=1.65, 95% CI=0.80-3.39). Patients without collateral ventilation (CV) who received EBV had more improvement in FEV_1 (p=0.01), %FEV1 (p<0.05) and RV (-619.87 vs. -370mL, p=0.18) than patients with unknown CV status. EBV was associated with improvement in most physiologic outcomes as well as quality of life measures; however, mortality rates were not significantly different between the EBV and control group (OR = 1.08, CU: 0.57-2.05, p=0.82; I^2=0.0%, p=0.95).

A 2020 systematic review (SR) with network meta-analysis by Iftikhar evaluated the effect of bronchial valves in patients with heterogeneous emphysema without lobar collateral ventilation (CV).[8] The review included 10 RCTs studying adult COPD patients with severe emphysema on optimal medical management and undergoing intervention with Zephyr or Spiration valves or coils for the intervention and standard of care as the comparator. A total of 912 total study participants (544 in intervention arms and 368 in control arms) were included in the meta-analysis. No statistical evidence of funnel plot asymmetry (or publication bias) was found. In patients with heterogeneous emphysema without CV, both Spiration and Zephyr valves showed significant increases in forced expiratory volume in 1 second (FEV1) (0.11 L [95% confidence interval (CI), 0.05 to 0.16] and 0.14 L [0.08 to 0.19], respectively) and in reducing St. Georges Respiratory Questionnaire (SGRQ) scores (-9.32 [-14.18 to -4.45] and -8.14 [-11.94 to -4.35], respectively) as compared with control, with no significant differences between interventions. Significant improvement (52.3 m [95% CI, 26.53 to 77.93]) in six-minute walk distance (6MWD) also was found for Zephyr valves, specifically. Both Spiration and Zephyr valves were associated with more frequent pneumothorax as compared with control (odds ratio, 10.32 [1.35 to 79.13] and 11.47 [2.91 to 45.27], respectively). No statistically significant association for COPD exacerbations was found for any of the interventions.

Majid (2020) published a systematic review (SR) with meta-analysis of four RCTs (N= 629) evaluating the Spiration® Valve System (SVS) in patients with severe emphysema and hyperinflation.[9] The RCTs included were published by Ninane (2012),[10] Wood (2014),[11] Li (2019),[12] and Criner (2019).[13] Outcomes evaluated were changes in: forced expiratory volume in 1s (FEV1), 6-min walking test (6MWT), residual volume, modified medical research council (mMRC) and Saint George respiratory questionnaire (SGRQ), as well as all-cause mortality, risk of pneumothorax, and risk of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). An overall change of 0.03 L (-0.07 to 0.13, I^2 = 90%) in FEV1 and 2.03% (-2.50 to 6.57, I^2 = 96%) in the predicted FEV1 compared to baseline was found with SVS but no benefit in 6MWT (mean difference = 4.56 m [95% CI -21.88 to 31.00, I^2 = 73%]). Relative risk of mortality was 2.54 (95% CI 0.81-7.96, I^2 = 0%), for pneumothorax 3.3 (95% CI 0.61-18.12, I2 = 0%) and AECOPD 1.68 (95% CI 1.04-2.70, I^2 = 0%). In patients with severe heterogeneous emphysema and hyperinflation without collateral ventilation, treatment with SVS improved pulmonary function, quality of life, and dyspnea score. However, the significantly increased relative risk of adverse events, including mortality, warrants additional RCTs addressing the safety and long-term benefit of this treatment.

In a SR with network meta-analysis by Xu (2020), bronchoscopic lung volume reduction treatments for emphysema, including intrabronchial valve (IBV) and endobronchial valve (EBV) treatments, were evaluated.[14] Thirteen trials were included (N=1993), seven of which were on IBV or EBV, including some studies reported in previous SRs.[15-19] The quality of evidence was rated as moderate in most comparisons using the GRADE framework. Medical care (MC) was associated with the fewer adverse events than IBV (-2.5, [-4.70 to -0.29]) and EBV (-1.73, [-2.37 to -1.09]) treatments. Less of an improvement in FEV1 and 6MWT was found in MC compared with EBV (-0.45, [-0.69 to -0.20] and -0.39, [-0.71 to -0.07], respectively) and significantly more positive change in SGRQ was found in EBV compared with MC (0.44, [0.11 to 0.78]). This analysis provides important comparisons of bronchial valve treatments to medical care alone for emphysema. Although clinical and quality of life variables improved with valve treatment, more adverse events occurred with both IBV and EBV treatment compared to MC alone, which is consistent with other systematic reviews evaluating safety of these devices.

A SR with meta-analysis published by Low (2019) evaluated RCTs comparing EBV implantation versus standard medical treatment or sham bronchoscopy for advanced emphysema.[20] This SR included five RCTs (N= 703) published by Valipour (2016)[21], Sciruba (2010)[22], Klooster (2015),[23] Herth (2012),[19] and Davey (2015).[15] Across these studies, the percentage change of FEV1 was significantly improved in the EBV group compared with the control group [weighted mean difference (WMD)=11.43; 95% confidence interval (CI), 6.05-16.80; P<0.0001] as was the SGRQ score (WMD=-5.69; 95% CI, -8.67 to -2.70; P=0.0002). No group difference was found in the 6MWT (WMD=14.12; 95% CI, -4.71 to 32.95; P=0.14). There was an increased rate of pneumothorax [relative risk (RR)=8.16; 95% CI, 2.21-30.11; P=0.002), any hemoptysis (RR=5.01; 95% CI, 1.12-22.49; P=0.04)] and valve migration (RR=8.64; 95% CI, 2.01-37.13; P=0.004) in the EBV group. Although there were short-term improvements in lung function and quality of life observed with the EBV, the significant increases in complication rates demonstrate the need for additional studies to determine the long-term safety and effectiveness of the treatment.

La Barca (2019) published a SR with meta-analysis of RCTs evaluating the efficacy and safety of the Zephyr® valve.[24] Seven RCTs reported on Zephyr® valves and five RCTs included only patients without collateral ventilation. Outcomes evaluated were change in: FEV1, 6MWT, SGRQ, and in residual volume (RV). Safety analysis included relative risk (RR) of pneumothorax. Treatment with the Zephyr® valve improved FEV1 with a mean difference (MD) of 20.74% (CI, 15.68, 25.79, I^2 = 25%). Subgroup analysis showed significant FEV1 improvement following Zephyr® placement in patients with heterogeneous emphysema distribution: MD = 25.98%% (CI, 17.72, 34.24, I^2 = 58%) and 16.27% (CI, 8.78-23.76, I^2 = 0%) in patients with homogeneous emphysema. Follow-up of 6-12 months showed a consistent improvement of FEV1 MD = 17.90% (CI, 11.47-24.33, I2 = 0%). Despite these positive clinical outcomes, the relative risk of pneumothorax was 6.32 (CI, 3.74-10.67, I2 = 0%). While this SR found clinically meaningful improvements with Zephyr® valve, there also was a significant increase in adverse events with the device. These conclusions are consistent with a comprehensive review of lung volume reducing surgical and endoscopic interventions for emphysema published by van Geffen (2019) that also included seven RCTs of the Zephyr® valve.[25] Five of the studies are included in Table 1 under Endobronchial Valve Studies, and the additional two are LIBERATE[26, 27] and TRANSFORM[28]. Participants in the included studies were those with emphysema, older than 35 years, post-bronchodilator FEV1 < 60% of predicted, and residual volume >150% of predicted (N = 620 total, range per study varied 50-190). Studies lasted from 3-12 months in duration. Meta analyses found adverse events including mortality to be greater in those who received valves: OR 9.58 (5.56 to 16.50), p=<0.00001.

A 2017 SR with meta-analysis by Wang evaluated bronchoscopic lung volume reduction therapy in patients with severe emphysema which included six RCTs for EBVs and two RCTs for IBVs.[29] Better response in minimal clinically important difference (MCID) was found in EBV trials for FEV1 (RR = 2.96, 95% CI = 1.49 – 5.87, p = 0.002, I2 = 58%), for 6MWT (RR = 2.90, 95% CI = 1.24 – 6.79, p = 0.01, I2 = 80%), for SGRQ (RR = 1.53, 95% CI = 1.22 – 1.92, p = 0.0002, I2 = 0%), as well as for mMRC (RR = 2.53, 95% CI = 1.71 – 3.76, p <0.00001, I2 = 0%). Similarly, EBV therapy was associated with significant improvement in ΔFEV_1 (WMD = 11.44%, 95% CI = 6.11 – 16.77, p < 0.0001, I^2 = 57%), in Δ6WMT (WMD = 33.86m, 95% CI = 11.54 – 56.19, p = 0.003, I^2 = 76%), and in ΔSGRQ (WMD = -7.06 points, 95% CI = -10.71 – -3.41, p = 0.0001, I^2 = 63%), in ΔmMRC (WMD = -0.35 point, 95% CI = -0.56 – -0.14, p = 0.0008, I^2 = 30%). The IBV group was not found to be superior to the conventional group. No sub-analysis was provided for emphysema type (homogenous vs. heterogenous).

In 2017, a Cochrane Systematic Review evaluating bronchoscopic lung volume procedures for COPD was published by van Agteren.[30] Authors conducted in-depth analyses aimed at assessing the effects of bronchoscopic lung volume reduction procedures on the short- and long-term health outcomes in participants with moderate to severe COPD and determining the effectiveness of each technique. Endobronchial and intrabronchial valves were among the six techniques analyzed; only individually and cluster randomized controlled trials were included. See Table 1 for endobronchial and intrabronchial valve studies included for analyses. Studies including participants with giant or bullous emphysema were excluded. Primary outcomes included: lung capacity as measured by FEV1; survival as measured by perioperative and postoperative mortality; and health-related quality of life, measured by questionnaire (e.g., St Georges Respiratory Questionnaire [SGRQ]). Given the heterogeneity in treatment approaches, outcomes were meta-analyzed only per treatment type. Outcomes for continuous or dichotomous data were analyzed using a fixed-effect model up to the end of follow-up. Continuous outcomes were calculated using mean differences, and dichotomous outcomes with odds ratios, both with 95% confidence intervals. Heterogeneity was calculated using the I^2 statistic, and subgroup analysis was performed as appropriate. Studies were graded for bias as high, low, or unclear, with rationale reported. Quality of evidence was rated using the GRADE scale. EBV and IBV studies included both heterogenous and homogeneous disease status patients, though majority of the EBV studies included participants with only a heterogenous disease distribution. The average of participants ranged between 58 and 65 years of age; the STELVIO 2015 trial having the youngest average age (58 to 59 years of age); the IBV Valve Trial 2014 and the VENT US 2010 studies having the highest average age ranging between 64.7 and 64.8, and 64.9 and 65.3, respectively. Majority of the trials recruited more males than females.

Table 1. RCTs included in 2017 Cochrane Review

Endobronchial Valve Studies (Year)	Intrabronchial Valve Studies (Year)
BeLieVeR HIFi (2015)[15, 31]	Eberhardt (2012)[32]
IMPACT (2016)[21]	IBV Valve Trial (2014)[11]
STELVIO (2015)[23, 33]	Ninane (2012)[10]
VENT EU (2012)[19]	
VENT US (2010)[22, 34-39]	

Endobronchial Valves

The conclusions from the EBV studies were drawn from five studies totalling 703 participants, which used standard medical care as the comparator. The results from the Cochrane SR by van Agteren are consistent with the subsequent SRs noted above. The number of adverse events experienced by patients with endobronchial valves was higher than those who received standard medical treatment (OR [95% confidence interval], 5.85 [2.16, 15.84], high quality of evidence), though no significant difference in mortality was found. From baseline to follow-up, between-group differences in the EBV group compared to control, change in lung function (FEV1, standardized mean difference [SMD], of 0.48 [95% CI: 0.32 to 0.64], low-quality evidence), quality of life (mean difference [MD], -6.20 units [95% CI: -8.19 to -4.20]; low quality of evidence), and exercise capacity (38.40 meters [95% CI: 24.69 to 52.12]; low quality of evidence) were significantly improved. While positive results may have been found, due to high confidence intervals and standard deviations, the authors urged caution in interpreting the means reported for outcomes of their systematic review. Earlier trials found better outcomes in patients with intact fissures which affected selection criteria in future trails, and thus improvement in functional outcomes.

Intrabronchial Valves

Two RCTs comparing intrabronchial valves to standard medical treatment were included for review,[10, 11] as well as one trial comparing unilateral versus partial bilateral valve placement with intrabronchial valves[32]. Adverse events experienced by patients with intrabronchial valves was higher than those who received standard medical treatment (OR, 3.41 [1.48, 7.84]), and no significant risk in mortality. Between group difference in exercise capacity was found to favor controls (MD -19.54 meters; [95% CI -37.11 to -1.98], moderate-quality evidence), as did lung function. Lack of difference in the IBV Valve trials by Wood (2014) and Ninane (2012) may be explained by the Eberhardt (2012) trial, as the latter found those treated with unilateral valve placement as opposed to partial bilateral treatment showed significantly better results in lung function, quality of life, and exercise capacity. The other two trials did not specifically address collateral ventilation, nor did they aim to achieve lobar occlusion; this is supported by the EBV trials which all aimed to achieve lobar occlusion and found better functional results when achieved.

Overall, findings in the Cochrane meta-analyses are limited by the lack of long-term follow-up data, significant heterogeneity in results, presence of skew and high CIs, and the open-label character of a number of the studies.

Choi (2015) published a systematic review evaluating bronchoscopic lung volume reduction using a one-way endobronchial valve.[40] The systematic review included 15 studies and meta-analyzed RCTs. Forced expiratory volume in one second (FEV1) improved compared to control groups in favor of the valve group (mean difference of 6.71, 95% CI: 3.31-10.11). The six-minute walking distance and cycle workload were also improved. A subgroup analysis of patients with complete fissure, reported that the FEV1 change was higher in the valve group at six and 12-months compared to the control group. No deaths were reported for the bronchial valve group although the pneumothorax incidence and respiratory failure rates were higher in the EBV group.

Randomized Controlled Trials

RCTs not included in the above-described systematic reviews are summarized here.

Gompelmann (2019) published long-term follow-up data on patients with severe emphysema with no collateral ventilation treated with endobronchial or intrabronchial valves.[41] Of the 256 patients, 220, 200, 187, 100 and 66 patients completed the three-month, six-month, one-year, two-year and three-year follow-up visit, respectively. Lung function parameters [FEV1, vital capacity (VC), residual volume (RV), total lung capacity (TLC)] and exercise capacity [6-minute walk test (6-MWT)] were outcomes evaluated. Response rates were calculated as the number of patients who met the minimal important difference (MID) of >100 ml improvement in FEV1, >430 ml reduction in RV and >26 m improvement in 6-MWT. Patients who underwent further interventional strategies (LVRS, coil therapy, polymeric lung volume reduction, lung transplantation) within the observation timeframe were excluded after the additional therapeutic intervention. At six-month follow-up, 37% of the patients met the efficacy threshold of greater than 100 ml improvement in FEV1, 78% of the patients developed a greater than 430 ml reduction in RV and 58% of the patients experienced a greater than 26 m improvement on the 6-MWT. At one-year follow-up, significant improvement from baseline ($p<0.05$ in paired t-tests, uncontrolled for repeated observations) was found for lung function parameters including FEV1 and RV and exercise capacity (6-MWT). At three-year follow-up (n=66), the proportion of patients achieving the MID from baseline in RV and 6-MWT was 71% and 46%,

respectively. Radiological follow up was assessed in 251 of the patients, and of these, 22% (56/251) developed a pneumothorax. Management of pneumothorax was via chest tube insertion in 86% (48/56) of these patients, and in 41% (23/56), valve removal was necessary for pneumothorax management. Over the three-year observation, all valves were permanently removed in 24.6% (63/256) of the patients. Permanent valve removal was conducted due to the following reasons: missing clinical benefit in 55.6% (35/63), pneumothorax in 11.1% (7/63), definitive LVRS in 19% (12/63), poststenotic pneumonia in 6.3% (4/63), lung cancer in 3.2% (2/63), respiratory insufficiency in 3.2% (2/63) and recurrent pulmonary infections in 1.6% (1/63). No analyses specific to endobronchial versus intrabronchial valve use was provided. This trial is limited by the lack of a comparative group such as medical management alone and by the retrospective design, as well as considerable loss to follow-up. Despite these limitations, this study provides important data regarding longer-term outcomes for highly-selected patients undergoing endobronchial valve treatment for severe emphysema and indicate clinically meaningful improvement can be achieved in these selected patients.

In 2017, Klooster reported one-year follow-up data from the STELVIO study not included in the SRs above.[42] An intention-to-treat analysis showed greater improvements in all primary outcomes in the EBV group compared to the controls. However, of the 64 patients with follow-up data available, 47 serious adverse events were reported from 0-6 mos, and 11 from 6 mos to one year. Two patients in the valve group died.

Nonrandomized Studies

Everaerts (2023) published a retrospective review of 53 patients with emphysema due to alpha-1 antitrypsin deficiency (AATD) who were treated with EBV. AATD is a rare hereditary cause of COPD.[43] The authors note that people with AATD were largely excluded from clinical trials that led to the current clinical indications for EBV, but treatment for emphysema due to AATD is generally similar to treatment for COPD that is not AATD-induced. The study divided patients into two groups: 30 patients with serum alpha-1 antitrypsin levels (AAT) of less than 0.6g/L or a confirmed AATD diagnosis, and 23 patients with possible or mild AATD, and serum AAT levels of between 0.6 and 1g/L. The group with confirmed AATD was significantly younger ($p<0.01$) and had fewer pack-years of smoking ($p<0.001$). The AATD group also had less pronounced hyperinflation at baseline ($p<0.05$). The groups had similar baseline FEV_1, RV, diffuse capacity for carbon monoxide ($DL_{CO)}$, 6MWD, and SGRQ measures. Six weeks after EBV, more than 90% of patients in both groups experienced target lobe volume reduction (TLVR) at levels higher than 563ml, which was the minimally important clinical difference (MCID) cutoff. After EBV, both groups had significant improvement compared to baseline in FEV_1 increase, RV, 6MWD, and SGRQ ($p<0.01$ for all measures). Adverse events were similar in both groups, with 10% of the AATD group and 13% of the AAT group experiencing pneumothorax. Three patients (10%) in the AATD group and two (9%) in the AAT group required revision bronchoscopy. The authors concluded that while further study on larger groups is indicated, the evidence supports EBV as a therapy for people with AATD.

Hartman (2022) published a retrospective review of 1471 patients who had consultation and pulmonary function testing for BLVR treatment evaluation to compare survival rates between patients treated with BVLR and those that were not. The patients had evaluation at a centralized referral center in The Netherlands between June 2006 and July 2019.[44] Of the 1471 patients, 483 had BLVR treatment, 353 with EBV and 130 with coils; and 988 did not have BVLR treatment. At baseline, patients treated with BLVR had fewer COPD exacerbations in the previous year ($p<0.001$) but had worse pulmonary function (FEV_1 % of predicted; p

<0.001) lower body mass index (BMI) (p=0.10), and more cat scan (CT)-detected emphysema (p<0.001) and air-trapping (:<0.001). The BLVR treatment group was also more likely to be female (p=0.008), and more likely to have had either myocardial infarction, percutaneous coronary intervention, or stroke (p=0.007). Patients who were treated with BLVR had a significantly longer median survival time compared to patients who did not (3133 days; 95% CI 2777-3489 vs. 2503 days; 95% CI 2281-2725, p < 0.001), which equates to a difference between the groups of 630 days, or approximately 1.7 years. Multivariant analysis found that BLVR treatment was an independent predictor of survival when adjusted for age, gender, packyears, BMI, and multiple factors related to disease severity (p< 0.001). The authors note that the reason patients did not have BLVR treatment was largely due to ineligibility for the treatment, not personal preference. Therefore, even though BLVR was found to be an independent predictor of survival, it is not possible to know if the deaths in the non-BLVR group would have been altered with BLVR in people who do not meet criteria for the treatment.

Hartman (2021) conducted a prospective cohort study to investigate patient satisfaction and patient-specific treatment goals among individuals who received bronchial valves for treatment of severe emphysema at a single hospital in The Netherlands.[45] Patient satisfaction was measured by a questionnaire administered one year after valve placement. Patient-specific goals were measured using the Dutch patient-specific complaint (PSC) questionnaire. In this questionnaire, patients reported their three most personally desired post-treatment goals and used a numeric rating scale (0-10) to score the level of disability per goal before and one year after treatment. Lung function, exercise capacity, dyspnea severity, and quality of life were also measured before treatment and at one-year follow-up. Of 134 patients who underwent bronchial valve placement prior to January 1, 2019, 109 (81.3%) completed the patient-satisfaction questionnaire, 88 (65.7%) completed the PSC questionnaire at baseline and follow-up, and 94 (70.1%) returned to the hospital for a follow-up visit at one year. Reasons for loss to follow-up in 40 patients were bronchial valve removed (16 patients), died (n=5), comorbidity (n=5), revision at that time (n=3) lung volume reduction surgery (LVRS) or lung transplant (n=2), and other (n=9). The PSC-questionnaire score significantly improved one year after bronchial valve treatment, from 23.7 to 17.1 points (mean decrease of 6.5 points; p =0.001) and an improvement in the PSC-questionnaire sum score was significantly associated with a larger improvement in FEV1, residual volume, exercise capacity, dyspnea severity, and quality of life. Seventy-five percent of the patients who completed the questionnaire were satisfied or very satisfied with the treatment and 11% were unsatisfied or very unsatisfied. Just over half of the questionnaire respondents (52.6%) were satisfied or very satisfied with the reduction in their symptoms after treatment, and 24.9% were unsatisfied or very unsatisfied. For the question of whether the treatment satisfied their expectations (range 1 to 5), the mean score was 3.29 (standard deviation 1.43). Most of those who completed the questionnaire (91.4%) would recommend the treatment to other patients. This study was limited by its uncontrolled design and relatively high loss to follow-up (29.9%), but it provides information on outcomes important to patients.

A retrospective review of 1500 patients with severe COPD referred for bronchoscopic lung volume reduction (BLVR) treatment was conducted by Welling (2020) to investigate the differences between patients selected for BLVR and patients that were not.[46] Of those reviewed, 282 (19%) patients were selected for BLVR treatment, and of these, 175 patients (62%) were selected for EBV, 93 patients (33%) for lung volume reduction coil (LVRC), three patients (0.2%) for airway bypass stents, nine patients (3%) for polymeric lung volume reduction and two patients (0.1%) for a pneumostoma. Although the authors found that patients who were selected for any BLVR option lived significantly longer than those who were

not selected for BLVR (median 3060 versus 2079 days, p<0.001), these patients also were significantly younger (59 versus 63 years), had a lower FEV1 (28% versus 34% of predicted) and a higher residual volume (237% versus 215% of predicted) compared to the group of patients not selected for BLVR (all p<0.001). No significant survival difference was observed between patients who were selected for EBV treatment and those who were selected for LVRC (p=0.45).

Skowasch (2016) reported six month follow-up results from the VENT trial, a retrospective analysis of registry data for patients who have received endobronchial valves also described below.[47] Although lung function (FEV1 and residual volume), and COPD Assessment Test scores improved, 66 serious adverse events were reported in 55 patients. In the subsequent six months of follow-up, a total of 170 serious adverse events were reported in 125 patients.

Liberator (2016) published a retrospective analysis of the VENT trial.[37] The analysis evaluated outcomes and response based on lobe selection in patients receiving EBV therapy. The authors concluded that lobe selection does have a major role in EBV therapy. There was no difference in FEV1 outcomes between upper and lower lobe treatment groups. The authors further conclude that complete fissure status preprocedure has the greatest influence on FEV1 outcome improvement.

Several other small case series (n<100) have been published on the use of the Zephyr or IBV valves for severe emphysema.[18, 33, 48-52] The ability to draw conclusions based on these data is limited by a variety of factors, including small sample sizes, limited long-term follow-up data, and heterogeneity in study design including patient inclusion criteria and varying numbers of valves placed per patient. For example, a mean of four (SD: 1.6) and range of 1-8 in one study[53] and a mean of 6.7 and range of 3-11 in the other[48], and unreported mean and range in the third[50, 51], limiting comparisons of treatment effectiveness.

Section Summary: Advanced Emphysema

In patients with severe emphysema and low collateral ventilation, RCTs provide consistent evidence of clinically meaningful benefit for endobronchial valves compared to standard medical management on measures of lung function and quality of life. Systematic review of the available evidence also finds significant improvement in clinical and functional outcomes in select patients treated with endobronchial valves compared to standard medical management. Systematic review of the current evidence also indicates there is a greater risk of serious adverse events compared to usual care, including mortality and pneumothorax.

PRACTICE GUIDELINE SUMMARY

The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report on the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease makes the following statements on lung volume reduction interventions:[54]

- In selected patients with heterogeneous or homogeneous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils, or thermal ablation) may be considered.
- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment (Evidence Level A for endobronchial valves: well-

designed RCTs with consistent findings in the intended population without any important limitations).

SUMMARY

There is enough research to show that bronchial valves improve net health outcomes (balance of benefit and harm) compared to current standard of care for highly selected patients with advanced emphysema. Clinical guidelines based on research recommend endobronchial valves in the treatment of advanced emphysema for select patients. Therefore, US Food and Drug Administration (FDA) – approved endobronchial valve placement may be considered medically necessary for the treatment of advanced emphysema when policy criteria are met.

Removal, replacement, or revision of bronchial valves placed for the treatment of severe emphysema may be required after the device has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device or removal may be appropriate when the condition of the patient has changed. Therefore, revision, replacement, or removal of an existing US Food and Drug Administration (FDA) – approved endobronchial valve may be considered medically necessary after the device has been placed.

There is not enough research to show that bronchial valves improve net health outcomes (balance of benefit and harm) compared to current standard of care for any indication other than for the treatment of severe emphysema when criteria are met. Clinical guidelines based on research recommend bronchial valves only in select patients. Therefore, bronchial valve placement is considered investigational for all indications other than for the treatment of severe emphysema when policy criteria are met, including for the treatment of air leaks and for the treatment of emphysema when policy criteria are not met.

REFERENCES

1. U.S. Food and Drug Administration. Zephyr® Endobronchial Valve. Approval order. [cited 04/24/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180002a.pdf.
2. U.S. Food and Drug Administration. Spiration® Valve System. Approval order. [cited 04/24/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180007A.pdf.
3. U.S. Food and Drug Administration. IBV® Valve System. Summary of safety and probable benefit. [cited 04/24/2023]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf6/H060002b.pdf.
4. Gillespie CT, Sterman DH, Cerfolio RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. *Ann Thorac Surg.* 2011;91(1):270-3. PMID: 21172529
5. Travaline JM, McKenna RJ, Jr., De Giacomo T, et al. Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest.* 2009;136(2):355-60. PMID: 19349382
6. Bakhos C, Doelken P, Pupovac S, et al. Management of Prolonged Pulmonary Air Leaks With Endobronchial Valve Placement. *JSLS : Journal of the Society of Laparoendoscopic Surgeons.* 2016;20(3). PMID: 27647978

7. Firlinger I, Stubenberger E, Muller MR, et al. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. *Ann Thorac Surg.* 2013;95(4):1243-9. PMID: 23434254
8. Iftikhar IH, Schimmel M, Sardi A, et al. Bronchoscopic Lung Volume Reduction with Valves and Coils. A Network Meta-analysis. *Ann Am Thorac Soc.* 2020;17(11):1468-75. PMID: 32574516
9. Majid A, Labarca G, Uribe JP, et al. Efficacy of the Spiration Valve System in Patients with Severe Heterogeneous Emphysema: A Systematic Review and Meta-Analysis. *Respiration.* 2020;99:62-72. PMID: 31760389
10. Ninane V, Geltner C, Bezzi M, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. *Eur Respir J.* 2012;39(6):1319-25. PMID: 22654006
11. Wood DE, Nader DA, Springmeyer SC, et al. The IBV Valve trial: a multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema. *Journal of bronchology & interventional pulmonology.* 2014;21:288-97. PMID: 25321447
12. Li S, Wang G, Wang C, et al. The REACH Trial: A Randomized Controlled Trial Assessing the Safety and Effectiveness of the Spiration(R) Valve System in the Treatment of Severe Emphysema. *Respiration.* 2019;97:416-27. PMID: 30554211
13. Criner GJ, Delage A, Voelker K, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE). A Multicenter, Open-Label Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med.* 2019;200(11):1354-62. PMID: 31365298
14. Xu W, Wang J, He X, et al. Bronchoscopic lung volume reduction procedures for emphysema: A network meta-analysis. *Medicine (Baltimore).* 2020;99:e18936. PMID: 32000409
15. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. *Lancet.* 2015;386(9998):1066-73. PMID: 26116485
16. Gaspard D, Bartter T, Boujaoude Z, et al. Endobronchial valves for bronchopleural fistula: pitfalls and principles. *Therapeutic advances in respiratory disease.* 2017;11(1):3-8. PMID: 27742781
17. Zoumot Z, Davey C, Jordan S, et al. Endobronchial valves for patients with heterogeneous emphysema and without interlobar collateral ventilation: open label treatment following the BeLieVeR-HIFi study. *Thorax.* 2017;72(3):277-79. PMID: 27999170
18. Pizarro C, Ahmadzadehfar H, Essler M, et al. Effect of endobronchial valve therapy on pulmonary perfusion and ventilation distribution. *PLoS One.* 2015;10:e0118976. PMID: 25822624
19. Herth FJ, Noppen M, Valipour A, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J.* 2012;39(6):1334-42. PMID: 22282552
20. Low SW, Lee JZ, Desai H, et al. Endobronchial Valves Therapy for Advanced Emphysema: A Meta-Analysis of Randomized Trials. *Journal of bronchology & interventional pulmonology.* 2019;26(2):81-89. PMID: 29901536
21. Valipour A, Slebos DJ, Herth F, et al. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med.* 2016;194(9):1073-82. PMID: 27580428

22. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med.* 2010;363(13):1233-44. PMID: 20860505
23. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med.* 2015;373(24):2325-35. PMID: 26650153
24. Labarca G, Uribe JP, Pacheco C, et al. Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis. *Respiration.* 2019;98:268-78. PMID: 31117102
25. van Geffen WH, Slebos DJ, Herth FJ, et al. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. *The Lancet Respiratory medicine.* 2019;7(4):313-24. PMID: 30744937
26. Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med.* 2018;198(9):1151-64. PMID: 29787288
27. Dransfield MT, Garner JL, Bhatt SP, et al. Effect of Zephyr Endobronchial Valves on Dyspnea, Activity Levels, and Quality of Life at One Year. Results from a Randomized Clinical Trial. *Ann Am Thorac Soc.* 2020;17(7):829-38. PMID: 32223724
28. Kemp SV, Slebos DJ, Kirk A, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). *Am J Respir Crit Care Med.* 2017;196(12):1535-43. PMID: 28885054
29. Wang Y, Lai TW, Xu F, et al. Efficacy and safety of bronchoscopic lung volume reduction therapy in patients with severe emphysema: a meta-analysis of randomized controlled trials. *Oncotarget.* 2017;8(44):78031-43. PMID: 29100445
30. van Agteren JE, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2017;2:CD012158. PMID: 28230230
31. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi trial): study design and rationale. *Thorax.* 2015;70(3):288-90. PMID: 24664535
32. Eberhardt R, Gompelmann D, Schuhmann M, et al. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. *Chest.* 2012;142(4):900-8. PMID: 22459779
33. Hartman JE, Klooster K, Slebos DJ, et al. Improvement of physical activity after endobronchial valve treatment in emphysema patients. *Respir Med.* 2016;117:116-21. PMID: 27492521
34. Argula RG, Strange C, Ramakrishnan V, et al. Baseline regional perfusion impacts exercise response to endobronchial valve therapy in advanced pulmonary emphysema. *Chest.* 2013;144(5):1578-86. PMID: 23828481
35. Brown MS, Kim HJ, Abtin FG, et al. Emphysema lung lobe volume reduction: effects on the ipsilateral and contralateral lobes. *European radiology.* 2012;22(7):1547-55. PMID: 22466511
36. Eberhardt R, Herth FJ, Radhakrishnan S, et al. Comparing Clinical Outcomes in Upper versus Lower Lobe Endobronchial Valve Treatment in Severe Emphysema. *Respiration.* 2015;90(4):314-20. PMID: 26340540
37. Liberator C, Shenoy K, Marchetti N, et al. The Role of Lobe Selection on FEV1 Response in Endobronchial Valve Therapy. *Copd.* 2016:1-6. PMID: 26789984

38. Pietzsch JB, Garner A, Herth FJ. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. *Respiration.* 2014;88(5):389-98. PMID: 25277549
39. Strange C, Herth FJ, Kovitz KL, et al. Design of the Endobronchial Valve for Emphysema Palliation Trial (VENT): a non-surgical method of lung volume reduction. *BMC pulmonary medicine.* 2007;7:10. PMID: 17711594
40. Choi M, Lee WS, Lee M, et al. Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:703-10. PMID: 25848246
41. Gompelmann D, Heinhold T, Rotting M, et al. Long-term follow up after endoscopic valve therapy in patients with severe emphysema. *Therapeutic advances in respiratory disease.* 2019;13:1753466619866101. PMID: 31373259
42. Klooster K, Hartman JE, Ten Hacken NH, et al. One-Year Follow-Up after Endobronchial Valve Treatment in Patients with Emphysema without Collateral Ventilation Treated in the STELVIO Trial. *Respiration.* 2017;93(2):112-21. PMID: 27974713
43. Everaerts S, Hartman JE, Van Dijk M, et al. Bronchoscopic Lung Volume Reduction in Patients with Emphysema due to Alpha-1 Antitrypsin Deficiency. *Respiration.* 2023;102(2):134-42. PMID: 36549279
44. Hartman JE, Welling JBA, Klooster K, et al. Survival in COPD patients treated with bronchoscopic lung volume reduction. *Respir Med.* 2022;196:106825. PMID: 35325741
45. Hartman JE, Klooster K, Ten Hacken NHT, et al. Patient Satisfaction and Attainment of Patient-Specific Goals after Endobronchial Valve Treatment. *Ann Am Thorac Soc.* 2021;18(1):68-74. PMID: 32881586
46. Welling JBA, Hartman JE, Augustijn SWS, et al. Patient Selection for Bronchoscopic Lung Volume Reduction. *Int J Chron Obstruct Pulmon Dis.* 2020;15:871-81. PMID: 32368033
47. Skowasch D, Fertl A, Schwick B, et al. A Long-Term Follow-Up Investigation of Endobronchial Valves in Emphysema (the LIVE Study): Study Protocol and Six-Month Interim Analysis Results of a Prospective Five-Year Observational Study. *Respiration.* 2016;92(2):118-26. PMID: 27562904
48. Wan IY, Toma TP, Geddes DM, et al. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. *Chest.* 2006;129(3):518-26. PMID: 16537847
49. Sterman DH, Mehta AC, Wood DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration.* 2010;79(3):222-33. PMID: 19923790
50. Hopkinson NS, Toma TP, Hansell DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med.* 2005;171(5):453-60. PMID: 15579725
51. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J.* 2011;37(6):1346-51. PMID: 20947683
52. Park TS, Hong Y, Lee JS, et al. Bronchoscopic lung volume reduction by endobronchial valve in advanced emphysema: the first Asian report. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1501-11. PMID: 26251590
53. Anzueto A. Endobronchial valves to reduce lung hyperinflation. *N Engl J Med.* 2010;363(13):1280-1. PMID: 20860512
54. Global Initiative for Chronic Obstructive Lung Disease: 2023 Report. [cited 04/24/2023]. 'Available from:' https://goldcopd.org/.

CODES

Codes	Number	Description
CPT	31647	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe
	31648	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe
	31649	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure)
	31651	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure[s])
HCPCS	None	

Date of Origin: *February 2012*

Regence

Medical Policy Manual Surgery, Policy No. 186

Gastroesophageal Reflux Surgery

Effective: April 1, 2024

Next Review: December 2024
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Surgical fundoplication involves wrapping the fundus of the stomach around the lower esophagus in order to create a high-pressure zone that reduces gastroesophageal reflux.

MEDICAL POLICY CRITERIA

I. Esophagogastric fundoplication may be considered **medically necessary** for one or more of the following:

   A. In children and adolescents age 17 years and younger; or

   B. In patients with pulmonary fibrosis with symptomatic or asymptomatic gastroesophageal reflux disease; or

   C. When the procedure is performed with a paraesophageal hiatal hernia (Types II-IV as defined in List of Information Needed for Review), and the paraesophageal hiatal hernia is confirmed by imaging; or

   D. When the procedure is performed with esophageal myotomy in patients with achalasia; or

E. Initial esophagogastric fundoplication to treat symptomatic gastroesophageal reflux disease (e.g., heartburn, regurgitation) when all of the following criteria (1.-4.) are met:

1. A paraesophageal hiatal hernia repair (Types II-IV as defined in List of Information Needed for Review) is not requested or documented.
2. Symptoms are unresponsive to lifestyle modifications as appropriate to the individual patient (e.g., weight loss for overweight or obese patients, avoidance of late meals, elevation of the head of the bed); and
3. Medication therapy that meets one or more of the following:
    i. A 4-month total trial of proton pump inhibitors (PPIs) is ineffective, contraindicated, or not tolerated; or
    ii. PPIs are used for 12 or more consecutive months within the past 18 months, and surgery is considered an alternative to long-term medication use.
4. There is objective diagnostic confirmation by either of the following:
    i. Reflux and/or esophagitis is confirmed via endoscopy; or
    ii. If endoscopy is normal, objective evidence of reflux should include one or more of the following:
        a.) 24-hour ambulatory esophageal pH monitoring; or
        b.) Barium swallow.

F. Repeat esophagogastric fundoplication for a failed previous antireflux procedure when one or more of the following criteria are met:

1. Criteria I.E.1.-4. for initial esophagogastric fundoplication above are met; or
2. Repeat surgery is for a documented mechanical failure of previous antireflux procedure (e.g., obstruction).

II. Esophagogastric fundoplication is considered **not medically necessary** for the treatment of symptomatic gastroesophageal reflux disease (e.g., heartburn, regurgitation) when Criterion I. is not met.

III. The following surgical procedures are considered **investigational** for the treatment of gastroesophageal reflux:

A. Distal or partial gastrectomy performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction.

B. Hiatal hernia repair without current or prior fundoplication, including repair of sliding or paraesophageal hernia.

C. Hiatal hernia repair without fundoplication of greater than 180 degree wrap (e.g., Nissen, Toupet) due to prior bariatric surgery, including repair of sliding or paraesophageal hernia.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could our impact review and decision outcome.

- The specific surgical procedure and treatment plan;
- Medical records must document the following:
    - symptomatic gastroesophageal reflux disease (GERD; e.g., heartburn, regurgitation, etc);
    - any lifestyle modifications attempted and the outcomes (e.g., weight loss if appropriate, avoidance of late meals or foods that cause heartburn, avoidance of activities that cause heartburn, elevation of the head, etc.);
    - medication therapies, including PPIs, that have been attempted, and their outcomes;
    - diagnostic confirmation of reflux and/or esophagitis via endoscopy, 24-hour ambulatory esophageal pH monitoring, or barium swallow.
    - A paraesophageal hernia (**Types II-IV)** must be clearly documented by imaging for coverage of paraesophageal hernia repair. For example, esophagram, upper GI study, and CT scan are acceptable forms of documentation.
        - Hernia Classifications-

            - Type I – A hiatal hernia, commonly known as a sliding hernia, (type I), occurs when there is protrusion of the upper part of the stomach and esophagus (gastroesophageal junction) into the chest. This is the most common type (about 95%) of all hiatal hernias. This is also called a sliding hiatal hernia. A hiatal hernia of this type may also contain the upper segment of a sleeve gastrectomy or the pouch of a gastric band or gastric bypass. Additionally, if less than 50% of the stomach is located above the diaphragm, this is still considered a type I hiatal hernia and is not considered a paraesophageal hiatal hernia.
            - Type II - A paraesophageal hernia (type II) occurs when the esophagus and the gastroesophageal junction remain in their normal location but a part of the stomach, typically the fundus, protrudes through the hiatus next to the esophagus into the chest. These ‘pure' type II paraesophageal hiatal hernias seldom occur.
            - Type III – A paraesophageal hiatal hernia (type III) occurs when there is a combination of both type I and II hiatal hernias, when the stomach and esophagus protrude into the chest AND the fundus of the stomach lies above the gastroesophageal junction and rotates along its long axis in a rolling or twisting fashion, referred to as an organo-axial torsion. A "giant" hiatal hernia is a subset of type III hiatal hernias and defined when greater than 50% of the stomach has protruded into the chest. The majority of paraesophageal hernias are type III. However, all types of paraesophageal hiatal hernias make up about 5% of hiatal

hernias but account for most of the hiatal hernia complications. The complications are primarily due to interference with the blood flow from the left gastric artery to the twisted fundus.
    - Type IV – A paraesophageal hiatal hernia (type IV) occurs when a structure other than the stomach, such as the large intestine, small intestine, or omentum protrude through the hiatus into the chest.
  - Repair of the typical Type I hiatal hernia (e.g. sliding hernias) cannot be coded by a paraesophageal hernia (Types II-IV) repair code per CPT code definitions. The paraesophageal hiatal hernia repair codes cannot be reported unless a paraesophageal hiatal hernia is clearly documented.

- Indicate if request is for an initial treatment or a repeat esophagogastric fundoplication and reason for the need to repeat the procedure (e.g., continued symptoms, mechanical failure, etc.)
- Presence of other conditions, such as pulmonary fibrosis, hiatal hernia, achalasia, etc.

CROSS REFERENCES

1. Bariatric Surgery, Surgery, Policy No. 58
2. Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD), Surgery, Policy No. 110
3. Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease (GERD), Surgery, Policy No. 190
4. Peroral Endoscopic Myotomy for Treatment of Esophageal Achalasia, Surgery, Policy No. 196
5. Hiatal Hernia Repair / Gastropexy When Performed With Major Surgical Procedures, Reimbursement Policy, Surgery, Policy No. 104

BACKGROUND

Gastroesophageal reflux disease (GERD) is a chronic medical condition, defined as “troublesome symptoms and/or complications” caused by reflux or regurgitation of stomach acid.[1] GERD is a common disorder; the proportion of North American adults with GERD (those who report experiencing symptoms such as heartburn or acid reflux at least once a week, or those with a physician diagnosis of GERD) is estimated to be around 19.8-20%.[2] GERD has also been associated with extraesophageal symptoms or conditions, such as cough, laryngitis, asthma and pulmonary fibrosis, although a direct causal relationship with GERD has not been established.

Standard treatment of GERD may address lifestyle modifications as appropriate to individual patients such as weight loss, smoking cessation, avoidance of specific foods that may precipitate reflux or heartburn, elevating the head of the bed, and avoiding recumbent positions until 2-3 hours after a meal.[1] When these actions are not successful, treatment generally consists of a daily regimen of proton pump inhibitors (PPIs). However, some patients with chronic GERD are unable or unwilling to continue ongoing medical treatment. For these patients, surgical treatment may be considered.

Surgical fundoplication involves wrapping the fundus of the stomach around the lower esophagus in order to create a high pressure zone that reduces gastroesophageal reflux. The fundal wrap can be either total (360 degrees) or partial (<360 degrees). Fundoplication may be performed as an open procedure but is more commonly performed laparoscopically.

ESOPHAGOGASTRIC FUNDOPLICATION WITH PARAESOPHAGEAL HIATAL HERNIA REPAIR

Paraesophageal hiatal hernias, also known as Type II or III hiatal hernias, occur when the stomach, and in some cases the gastroesophageal junction (GEJ), herniates through the diaphragmatic esophageal hiatus into the mediastinum. These cases are rare compared to the more common Type I or “sliding” type hiatal hernia. Diagnosis of a “true” paraesophageal hiatal hernia is confirmed through endoscopy or imaging studies. Prophylactic surgical treatment of paraesophageal hiatal hernias is usually required as they account for most of the complications associated with hiatal hernias, including but not limited to obstruction, perforation and strangulation.[3] In some cases, patients may exhibit a paraesophageal hiatal hernia with additional symptoms of GERD, requiring not only a hiatal hernia repair, but additionally a fundoplication.[4]

Hiatal hernia classification

The hiatus is an opening in the diaphragm where the distal esophagus passes through to enter the abdomen. A hiatal hernia occurs when intrabdominal contents, such as the stomach, bulge up into the chest through the hiatus. There are four types of hiatal hernias:[5]

- Type I – A hiatal hernia, commonly known as a sliding hernia, (type I), occurs when there is protrusion of the upper part of the stomach and esophagus (gastroesophageal junction) into the chest. This is the most common type (about 95%) of all hiatal hernias. This is also called a sliding hiatal hernia. A hiatal hernia of this type may also contain the upper segment of a sleeve gastrectomy or the pouch of a gastric band or gastric bypass. Additionally, if less than 50% of the stomach is located above the diaphragm, this is still considered a type I hiatal hernia and is not considered a paraesophageal hiatal hernia.

- Type II - A paraesophageal hernia (type II) occurs when the esophagus and the gastroesophageal junction remain in their normal location but a part of the stomach, typically the fundus, protrudes through the hiatus next to the esophagus into the chest. These ‘pure' type II paraesophageal hiatal hernias seldom occur.

- Type III – A paraesophageal hiatal hernia (type III) occurs when there is a combination of both type I and II hiatal hernias, when the stomach and esophagus protrude into the chest AND the fundus of the stomach lies above the gastroesophageal junction and rotates along its long axis in a rolling or twisting fashion, referred to as an organo-axial torsion. A "giant" hiatal hernia is a subset of type III hiatal hernias and defined when greater than 50% of the stomach has protruded into the chest. The majority of paraesophageal hernias are type III. However, all types of paraesophageal hiatal hernias make up about 5% of hiatal hernias but account for most of the hiatal hernia complications. The complications are primarily due to interference with the blood flow from the left gastric artery to the twisted fundus.

- Type IV – A paraesophageal hiatal hernia (type IV) occurs when a structure other than the stomach, such as the large intestine, small intestine, or omentum protrude through the hiatus into the chest.

ESOPHAGOGASTRIC FUNDOPLICATION IN PATIENTS WITH PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease which is often associated with additional comorbidities (e.g., pulmonary hypertension and gastroesophageal reflux) and symptoms (e.g., dyspnea, exercise limitation, fatigue, anxiety, mood disturbance, sleep disorders) that negatively affect patients' lives. GERD is highly prevalent in patients with IPF with up to 50% of patients with asymptomatic disease. Although the pathological significance of GERD in IPF remains uncertain, studies indicate that medical or surgical treatment of GERD may stabilize lung function and increase oxygenation.[6-9] It is hypothesized that fundoplication surgery may offer increased benefit over medication treatment by reducing acid as well as microaspirations of the gastric contents in to the lungs.[6]

Due to the complexities of IPF, treatment protocols are not rigid or standardized and often require a management approach which is tailored to the patients' specific conditions and symptoms. Nissen fundoplication surgery is one option which may be considered for treating patients with pulmonary fibrosis with symptomatic or asymptomatic GERD.

Note: This policy does not address transesophageal endoscopic therapies for GERD, which are addressed separately in Surgery Policy No. 110 (see Cross References).

EVIDENCE SUMMARY

In order to determine whether the benefits of surgical fundoplication in patients with chronic GERD outweigh the risks, well-designed randomized controlled trials (RCTs) are necessary, comparing medical therapy (proton pump inhibitors) with surgical fundoplication and reporting on relevant clinical outcomes.

The focus of the following literature review is on systematic reviews, randomized trials published after the systematic reviews, and clinical practice guidelines.

FUNDOPLICATION

Systematic Reviews

A systematic review published by Li (2023) compared laparascopic Nissen and Toupet fundoplications in patients with GERD from eight clinical trials.[10] Primary outcomes included postoperative reflux recurrence, postoperative heartburn, dysphagia and postoperative chest pain, patient satisfaction, and several other clinically important measures. The results of the review showed no significant difference between the Nissen and Toupet surgery types for the majority of outcomes. Those receiving the Toupet procedure had lower lower esophageal sphincter pressure, fewer postoperative dysphagia and inability to belch in the short and long term as well as less gas bloating in the short term when compared to the Nissen procedures. Both procedure types were shown to be effective in treating GERD.

In 2018, Richter reported results from a systematic review with network meta-analysis or randomized controlled trials comparing efficacy of laparoscopic Nissen fundoplication (LNF) to proton pump inhibitors in patients with GERD.[11] The authors also compared the Nissen procedure to transoral incisionless fundoplication, which is not within the scope of this policy, but is summarized elsewhere (see Cross References). Overall, 7 trials were included, totalling 1128 patients. Network meta-analysis using Bayesian methods under random-effects multiple treatment comparisons were implemented for analysis, as well as ranking probability by surface under the cumulative ranking curve. Patients who underwent LNF had a higher probability of persistent esophagitis (0.38) than those on PPI therapy (0.19). Out of all the

interventions studied, LNF had the highest probability of increasing percent time at pH <4 (0.99), followed by PPIs (0.64), and LNF also had a higher probability of increasing patients' health-related quality of life (0.66) than those on PPI therapy (0.05).

In 2010, The Cochrane Collaboration published a systematic review on medical versus surgical management for GERD in adults.[12] Included in the review were all randomized or quasi-randomized controlled trials comparing laparoscopic fundoplication with medical management; nonrandomized studies were excluded. Four trials with a total of 1232 patients were included.[13-16] All reported outcomes at one year, with only one reporting outcomes up to three years. There were no studies that followed patients longer than three years. Overall, the authors concluded that in the short- to medium-term there is evidence that laparoscopic fundoplication is more effective than medical management.

A 2015 update concluded that there is considerable uncertainty in the balance of benefits versus harms of laparoscopic fundoplication compared to long-term medical treatment with proton pump inhibitors.[17] Four randomized controlled trials were included for meta-analysis, consisting of three studies previously reported in the 2010 review, and longer term follow-up for the Anvari study.[18] The available evidence was rated low or very low, and further high-quality studies are needed.

Randomized Controlled Trials

In 2017, Emken reported results of a secondary analysis of an industry sponsored multicenter randomized controlled trial comparing anti-reflux surgery (open fundoplication) to proton pump inhibitor (omeprazole) therapy.[19] From the same study, 3-year trial results were described by Lundell in 2000,[20] followed by 12-year outcomes in 2009[21]. Several of the authors were former employees of the industry sponsor.

> Study design: Three hundred and ten patients across 16 centers in 4 Nordic countries were originally enrolled in the trial, randomized in a 1:1 design (N=155 in each arm). Overall study duration was 14 years, from 1991-2005. In a pre-entry study period, all patients were treated with omeprazole 20mg twice daily with the option of increasing to 40mg if needed to achieve healing of esophageal lesions and control of symptoms. Of the 155 patients randomized to open fundoplication, 144 went on to have surgery; 129 had data available at 3-years follow-up. Of the 154 patients in the omeprazole therapy group (one dropped out prior to starting therapy), 139 had 3-year data available. The secondary analysis report (2017) included 1- and 10-year outcomes from patients who underwent surgery (N=137) and long-term treatment with omeprazole 20–60mg daily (N=108).
>
> Outcomes from 1-, 3-, 10-, and 12-years are summarized here:
>
> - At 3-years follow-up, the authors concluded efficacy from both approaches when omeprazole dose was adjusted over time.
> - In 2009, 12-year results were available for 71 who were given omeprazole (46%) and 53 treated with surgery (37%).
>   - There was no difference in percent of patients in continuous remission between treatment groups (including those who had a dose adjustment and those who did not).

    - Of the patients who underwent surgery, 38% required a change in therapeutic strategy (e.g., to medical therapy or additional surgeries), compared to 15% of those on omeprazole.
    - Adverse events: Therapies were generally well-tolerated in both groups, though heartburn and regurgitation were significantly more common in patients given omeprazole; whereas dysphagia, rectal flatulence, and the inability to belch or vomit were significantly more common in surgical patients. Over the entire follow-up period, fatal outcomes and those of heart-related cause were more common in the omeprazole group than the surgery group. Mean hemoglobin values did not change over time in either group, though mean ferritin levels increased after ten years in the medication treated group. Procedural complications were listed as more common serious adverse events in the surgery group as compared to the omeprazole group, as expected. Authors reported no surgery-related deaths in the original study; two of the surgery patients died of heart-related causes, and two experienced non-fatal heart attacks. In the omeprazole treated group, 8 patients died of heart-related causes, and 9 experienced non-fatal heart attacks. The authors reported that an Food and Drug Administration analysis of these events concluded that baseline differences between groups may have biased the safety outcomes. For example, the median age was four years greater in the medication group, and more patients had experienced a previous heart attack in the medication group as compared to the surgery group (six and zero, respectively).
- At 1- and 10-years follow-up, data were available for 108 patients in the omeprazole group, and 137 patients in the surgery group. One hundred fourteen patients had complete data for both timepoints, and 79 had only 1-year data. There were no statistically significant differences in demographics, manometry measurements, or 24-hour pH-monitoring measurements between those with complete data versus those with only 1-year of data.
    - In those who underwent surgery, measurement of lower esophageal sphincter (LOS) function (via manometry) showed statistically significant increase in median resting pressure at 1-year, which was sustained at 10-years. There were no significant changes in resting pressure in the omeprazole group.
    - Those in the surgery group had statistically significant increases in median total and intra-abdominal length of LOS at 1- and 10-years. In the omeprazole group, the median total and intra-abdominal length of LOS did not change from baseline to the 1-year manometry, however, at 10-years the results were comparable to the surgery group.

Included in the publication of the 2015 Cochrane review, Anvari reported 3-year outcomes from a prospective RCT (one-year results were included in the 2010 Cochrane review).[18] Of note, *a priori*, a sample size of 216 was calculated for this study at a statistical significance level of $\alpha = 0.05$; however only 104 participants were ultimately randomized which may have impacted the ability of the study to detect significant changes.

Of the original 104 subjects, 93 were available for the 3-year follow-up assessment. The authors reported the following outcomes:

- Improvement from baseline in GERD symptoms was significant in both the medical treatment and surgical groups. Differences between the two groups were not significant. (Primary outcome)
- Surgical patients experienced a mean of 1.35 more heartburn-free days per week compared with the medical group, a significant difference. (Primary outcome)
- Both groups demonstrated improvements in acid reflux and did not differ significantly in change from baseline. (Secondary outcome)
- The surgical group had significantly better lower esophageal sphincter pressure than the medical group. (Secondary outcome)
- With respect to global symptom control compared with baseline measurements, medically treated patients maintained their control, but the surgical patients demonstrated a statistically significant improvement from baseline. (Secondary outcome)
- Significant improvements in quality of life scores were also seen in the surgical group compared with the medical group. (Secondary outcome)
- 6 (11.8%) patients in the surgical group and 8 (16%) patients in the medical group failed their primary treatment.
- No adverse events were reported in the medical treatment group. In the surgical group:
    - There were no intraoperative complications, major morbidities, or mortality
    - 7 patients experienced minor postoperative complications
    - 4 patients reported dysphagia; 7 reported postprandial bloating at 3 months
    - 2 patients required dilation of the wrap

SURGICAL TREATMENT OF GERD PATIENTS WITH PULMONARY FIBROSIS

Current evidence regarding fundoplication in patients with pulmonary fibrosis (PF) mainly consist of case series[22-24] and review articles, which indicated that silent reflux, or asymptomatic GERD, occurs in about one third of PF patients.[7, 9] Only a single case series was identified regarding the efficacy of reflux surgery in patients with idiopathic PF (IPF) and GERD symptoms who were awaiting lung transplant:

In 2006, Linden and colleagues evaluated Laparoscopic fundoplication in patients with GERD symptoms and end-stage lung disease awaiting transplantation.[8] Of 149 patients on the transplant wait list, 19 were identified as having a history of reflux and of those, 14 were diagnosed with IPF. All 14 IPF patients underwent a Nissen fundoplication and were compared to 31 patients with IPF on the transplant list who did not have fundoplication surgery. No perioperative complications or decreases in lung function were reported over a mean 15-month follow-up period. Authors reported that, "patients with idiopathic pulmonary fibrosis treated with fundoplication had stable oxygen requirements, whereas control patients with idiopathic pulmonary fibrosis on the waiting list had a statistically significant deterioration in oxygen requirement."

Overall, the evidence regarding Nissen fundoplication as a treatment of gastrointestinal reflux disease (GERD) in patients with pulmonary fibrosis (PF) is limited; however, treatment of PF is often tailored to treat a patients' specific condition and symptoms. Potential benefits of fundoplication surgery in PF patients include improved oxygenation and reduction of acid and microaspiration into the lungs. Considering no standardized treatment protocol for patients with PF if available, Nissen fundoplication surgery may be considered in patients with symptomatic or asymptomatic GERD to reduce acid reflux and microaspirations to the lungs.

GASTRECTOMY

Gastrectomy involves a partial or full surgical removal of the stomach and is most often performed to treat cancer, non-cancerous tumors, perforation, polyps, ulcers, or obesity. In order to determine whether the benefits of surgical gastrectomy in patients with chronic GERD outweigh the risks, well-designed RCTs are necessary, comparing gastrectomy to medical therapy and accepted surgical interventions (fundoplication).

Systematic Reviews and Randomized Controlled Trials

In 2016, Oor published results of a systematic review and meta-analysis of 33 studies examining the impact of laparoscopic sleeve gastrectomy on prevalence of GERD.[25] Pooled data from seven studies using validated symptom questionnaires for new-onset of GERD symptoms resulted in a 20% incidence following LSG (follow-up time ranging from one- to 60-months). There was heterogeneity amongst these studies (I^2=68%). For difference in prevalence of GERD before and after LSG, as reported by questionnaire, the pooled risk difference was found to be 4.3%; with heterogeneity present (I^2=89%). Of the 24 studies reviewed, the authors found new-onset GERD symptom incidence to range from zero to 34.9%. Data for new-onset esophagitis, changes in the use of antireflux medication, 24-hour pH monitoring, manometry, and combined pH-impedance results could not be pooled. The authors therefore concluded that LSG could induce serious GERD symptoms in patients with no preoperative GERD complaints. The heterogeneity found in analyses may be due to a lack of a standardized approach to LSG, as well has the variability in follow-up length. The authors also noted that range in prevalence of GERD symptoms may be in part due to the variability in reported preoperative BMI, as the LSG will be a more technically challenging procedure in those with a BMI of 60 kg/m^2 versus those with a BMI of 40 kg/m^2.

Nonrandomized Studies

Current evidence regarding the use of distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction as a treatment of gastric reflux disease consists of small case series.[26-28] These studies do not permit conclusions due to the small sample size, lack of a control group, differences in patient characteristics and surgical techniques, and other methodological limitations. In addition, several studies[28-32] were identified which reported on GERD reduction after sleeve gastrectomy in obese patients; however, the primary focus of these studies was on weight reduction and the reduction of GERD symptoms was a secondary outcome. In order to isolate the direct effects of gastrectomy upon chronic GERD symptoms, well-designed RCTs are required which compare health outcomes of patients treated with gastrectomy versus medication or fundoplication.

HIATAL HERNIA REPAIR WITHOUT FUNDOPLICATION

Several studies were identified which reported an improvement in GERD symptoms associated with sliding type hernia repair; however, no studies were identified which evaluated the use of hiatal hernia repair as an independent treatment of gastric reflux disease.

PRACTICE GUIDELINE SUMMARY

Three evidence-based clinical practice guidelines address surgical treatment of GERD. These guidelines offer differing recommendations concerning indications for surgery. No evidence-

based clinical practice guidelines were identified which recommend fundoplication surgery as a treatment of GERD in patients with pulmonary fibrosis. In addition, no evidence-based clinical practice guidelines were identified which address the use of gastrectomy or hiatal hernia repair as a treatment of GERD.

SOCIETY OF AMERICAN GASTROINTESTINAL AND ENDOSCOPIC SURGEONS

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines recommend surgical therapy when the diagnosis of reflux is objectively confirmed, in individuals who:[33]

1) have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side effects)
   OR
2) opt for surgery despite successful medical management (due to quality of life considerations, lifelong need for medication intake, expense of medications, etc.)
   OR
3) have complications of GERD (e.g., Barrett's esophagus, peptic stricture)
   OR
4) have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration)

"Surgical therapy for GERD is an equally effective alternative to medical therapy and should be offered to appropriately selected patients by appropriately skilled surgeons (Grade A*). Surgical therapy effectively addresses the mechanical issues associated with the disease and results in long-term patient satisfaction (Grade A). For surgery to compete with medical treatment, it has to be associated with minimal morbidity and cost."

**Definitions*

- Grade A: "Based on high level (Level I or II), well-performed studies with uniform interpretation and conclusions by the expert panels"
- Level I Evidence: "Evidence from properly conducted randomized, controlled trials
- Level II Evidence: "Evidence from controlled trials without randomization; cohort or case-control studies; multiple time series; dramatic uncontrolled experiments

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2008, the American Gastroenterological Association (AGA) published a guideline regarding the management of gastroesophageal reflux disease which made the following recommendations:[1]

- "When antireflux surgery and PPI therapy are judged to offer similar efficacy in a patient with an esophageal GERD syndrome, PPI therapy should be recommended as initial therapy because of superior safety." (Grade A**)
- "When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative." (Grade A)
- Antireflux surgery is recommended "for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits of antireflux surgery should be weighed against the

deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms." (Grade B**)
- "Patients with an extraesophageal GERD syndrome with persistent troublesome symptoms despite PPI therapy should be considered for antireflux surgery. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms." (Grade C**)
- The AGA recommends against antireflux surgery (Grade D**):
    - "for patients with an esophageal syndrome with or without tissue damage who are symptomatically well controlled on medical therapy."
    - "as an antineoplastic measure in patients with Barrett's metaplasia."

***Definitions*

- Grade A: "strongly recommended based on good evidence that it improves important health outcomes."
- Grade B: "recommended with fair evidence that it improves important outcomes"
- Grade C: "balance of benefits and harms is too close to justify a general recommendation"
- Grade D: "recommend against, fair evidence that it is ineffective or harms outweigh benefits"

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2013, the American College of Gastroenterology (ACG) issued a guideline for the diagnosis and management of gastroesophageal reflux disease and made numerous recommendations regarding the management and surgical options for GERD.[34] The following are some of the major recommendations regarding PPI use and fundoplication:

- In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence)
- Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)
- Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)
- Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)

***Definitions*

- The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-offs.
- The level of evidence could range from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect) to "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect) or "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate).

SUMMARY

ESOPHAGOGASTRIC FUNDOPLICATION

There is enough research to show that initial or repeat esophagogastric fundoplication improves symptomatic gastroesophageal reflux disease (GERD) for most patients with chronic GERD who have tried lifestyle changes and long-term use of proton pump inhibitors (PPIs), or in those with a documented mechanical failure from a previous antireflux procedure. It appears that initial or repeat esophagogastric fundoplication may also improve symptoms in patients with pulmonary fibrosis. When esophagogastric fundoplication is performed with a paraesophageal hiatal hernia repair, patients with a paraesophageal type of hiatal hernia may also benefit. Patients with achalasia may also have improved health outcomes when esophagogastric fundoplication is performed with an esophageal myotomy. Clinical guidelines based on research recommend fundoplication for select patients. Therefore, initial or repeat esophagogastric fundoplication may be considered medically necessary when policy criteria are met.

There is not enough research to show that initial or repeat esophagogastric fundoplication for GERD improves health outcomes when policy criteria are not met. Therefore, initial or repeat esophagogastric fundoplication for GERD when policy criteria are not met is considered not medically necessary.

GASTRECTOMY

There is not enough research to show that distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction improves health outcomes for people with gastrointestinal reflux disease (GERD). No clinical practice guidelines based on research recommend gastrectomy for people with GERD. Therefore, distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction is considered investigational as a treatment of GERD.

HIATAL HERNIA REPAIR WITHOUT FUNDOPLICATION

There is not enough research to show that hiatal hernia repair without fundoplication, including repair of sliding or paraesophageal hernia, improves health outcomes for people with gastrointestinal reflux disease (GERD). No clinical practice guidelines based on research recommend independent hiatal hernia repair as a treatment for GERD. Therefore hiatal hernia repair without fundoplication is considered investigational as an independent treatment of GERD.

There is not enough research to show that hiatal hernia repair without fundoplication of greater than 180 degree wrap (e.g., Nissen, Toupet) due to prior bariatric surgery, including repair of sliding or paraesophageal hernia, improves health outcomes for people with gastrointestinal reflux disease (GERD). No clinical practice guidelines based on research recommend hiatal hernia repair without fundoplication of greater than 180 degree wrap (e.g., Nissen, Toupet) due to prior bariatric surgery, including repair of sliding or paraesophageal hernia as a treatment for GERD. Therefore, hiatal hernia repair without fundoplication of greater than 180 degree wrap (e.g., Nissen, Toupet) due to prior bariatric surgery, including

repair of sliding or paraesophageal hernia is considered investigational as a treatment of GERD.

REFERENCES

1. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008;135(4):1383-91, 91 e1-5. PMID: 18789939
2. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut.* 2005;54(5):710-7. PMID: 15831922
3. Mori T, Nagao G, Sugiyama M. Paraesophageal hernia repair. *Ann Thorac Cardiovasc Surg.* 2012;18:297-305. PMID: 22850094
4. Muller-Stich BP, Achtstatter V, Diener MK, et al. Repair of Paraesophageal Hiatal Hernias-Is a Fundoplication Needed? A Randomized Controlled Pilot Trial. *Journal of the American College of Surgeons.* 2015;221(2):602-10. PMID: 25868406
5. Kohn GP, Price RR, DeMeester SR, et al. Guidelines for the management of hiatal hernia. *Surgical endoscopy.* 2013;27(12):4409-28. PMID: 24018762
6. Lee JS, Ryu JH, Elicker BM, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine.* 2011;184(12):1390-4. PMID: 21700909
7. Morehead RS. Gastro-oesophageal reflux disease and non-asthma lung disease. *Eur Respir Rev.* 2009;18:233-43. PMID: 20956148
8. Linden PA, Gilbert RJ, Yeap BY, et al. Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *J Thorac Cardiovasc Surg.* 2006;131:438-46. PMID: 16434276
9. Pashinsky YY, Jaffin BW, Litle VR. Gastroesophageal reflux disease and idiopathic pulmonary fibrosis. *The Mount Sinai journal of medicine, New York.* 2009;76(1):24-9. PMID: 19170215
10. Li G, Jiang N, Chendaer N, et al. Laparoscopic Nissen Versus Toupet Fundoplication for Short- and Long-Term Treatment of Gastroesophageal Reflux Disease: A Meta-Analysis and Systematic Review. *Surgical innovation.* 2023;30(6):745-57. PMID: 36998190
11. Richter JE, Kumar A, Lipka S, et al. Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. *Gastroenterology.* 2018. PMID: 29305934
12. Wileman SM, McCann S, Grant AM, et al. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev.* 2010(3):CD003243. PMID: 20238321
13. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: One-year follow-up. *Surgical innovation.* 2006;13(4):238-49. PMID: 17227922
14. Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut.* 2008;57(9):1207-13. PMID: 18469091

15. Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *The British journal of surgery.* 2005;92(6):695-9. PMID: 15898130
16. Grant A, Wileman S, Ramsay C, et al. The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease - a UK collaborative study. The REFLUX trial. *Health Technol Assess.* 2008;12(31):1-181, iii-iv. PMID: 18796263
17. Garg Sushil K, Gurusamy Kurinchi S. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd, 2015.
18. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surgical endoscopy.* 2011;25(8):2547-54. PMID: 21512887
19. Emken BG, Lundell LR, Wallin L, et al. Effects of omeprazole or anti-reflux surgery on lower oesophageal sphincter characteristics and oesophageal acid exposure over 10 years. *Scandinavian journal of gastroenterology.* 2017;52(1):11-17. PMID: 27593706
20. Lundell L, Miettinen P, Myrvold HE, et al. Long-term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. The Nordic GORD Study Group. *European journal of gastroenterology & hepatology.* 2000;12(8):879-87. PMID: 10958215
21. Lundell L, Miettinen P, Myrvold HE, et al. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2009;7(12):1292-8; quiz 60. PMID: 19490952
22. Raghu G, Yang ST, Spada C, et al. Sole treatment of acid gastroesophageal reflux in idiopathic pulmonary fibrosis: a case series. *Chest.* 2006;129:794-800. PMID: 16537884
23. Patti MG, Tedesco P, Golden J, et al. Idiopathic pulmonary fibrosis: how often is it really idiopathic? *J Gastrointest Surg.* 2005;9:1053-6; discussion 56-8. PMID: 16269375
24. Allaix ME, Fisichella PM, Noth I, et al. Idiopathic pulmonary fibrosis and gastroesophageal reflux. Implications for treatment. *J Gastrointest Surg.* 2014;18(1):100-4; discussion 04-5. PMID: 24002768
25. Oor JE, Roks DJ, Unlu C, et al. Laparoscopic sleeve gastrectomy and gastroesophageal reflux disease: a systematic review and meta-analysis. *American journal of surgery.* 2016;211(1):250-67. PMID: 26341463
26. Galvez-Valdovinos R, Cruz-Vigo JL, Marin-Santillan E, et al. Cardiopexy with Ligamentum Teres in Patients with Hiatal Hernia and Previous Sleeve Gastrectomy: An Alternative Treatment for Gastroesophageal Reflux Disease. *Obesity surgery.* 2015;25(8):1539-43. PMID: 25990381
27. Lacy A, Ibarzabal A, Pando E, et al. Revisional surgery after sleeve gastrectomy. *Surg Laparosc Endosc Percutan Tech.* 2010;20:351-6. PMID: 20975509
28. Langer FB, Bohdjalian A, Shakeri-Leidenmuhler S, et al. Conversion from sleeve gastrectomy to Roux-en-Y gastric bypass--indications and outcome. *Obesity surgery.* 2010;20(7):835-40. PMID: 20393810
29. Afaneh C, Costa R, Pomp A, et al. A prospective randomized controlled trial assessing the efficacy of omentopexy during laparoscopic sleeve gastrectomy in reducing postoperative gastrointestinal symptoms. *Surgical endoscopy.* 2015;29(1):41-7. PMID: 24962864

30. Page MP, Kastenmeier A, Goldblatt M, et al. Medically refractory gastroesophageal reflux disease in the obese: what is the best surgical approach? *Surgical endoscopy.* 2014;28(5):1500-4. PMID: 24310740
31. Chiu S, Birch DW, Shi X, et al. Effect of sleeve gastrectomy on gastroesophageal reflux disease: a systematic review. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* 2011;7:510-5. PMID: 21130052
32. Pallati PK, Shaligram A, Shostrom VK, et al. Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: review of the Bariatric Outcomes Longitudinal Database. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* 2014;10(3):502-7. PMID: 24238733
33. Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surgical endoscopy.* 2010;24(11):2647-69. PMID: 20725747
34. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108:308-28; quiz 29. PMID: 23419381

CODES

NOTES:

- Repair of the typical Type I hiatal hernia cannot be coded by a paraesophageal hernia repair code per CPT code definitions.
- The paraesophageal hiatal hernia repair codes (i.e., 43281) cannot be reported unless a paraesophageal hiatal hernia is clearly documented.
- CPT 43280 cannot be reported unless a fundoplication is performed.
- There are related procedures without specific CPT codes, including sliding (type I) hiatal hernia repair and the Hill procedure, and these are reported by unlisted codes.

Codes	Number	Description
CPT	43279	Laparoscopy, surgical, esophagomyotomy (Heller type), with fundoplasty, when performed
	43280	Laparoscopy, surgical, esophagogastric fundoplasty (eg, Nissen, Toupet procedures)
	43281	Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplasty, when performed; without implantation of mesh
	43282	; with implantation of mesh
	43325	Esophagogastric fundoplasty; with fundic patch (Thal-Nissen procedure)
	43327	Esophagogastric fundoplasty partial or complete; laparotomy
	43328	;thoracotomy
	43332	Repair, paraesophageal hiatal hernia (including fundoplication), via laparotomy, except neonatal; without implantation of mesh or other prosthesis
	43333	; with implantation of mesh or other prosthesis
	43334	Repair, paraesophageal hiatal hernia (including fundoplication), via thoracotomy, except neonatal; without implantation of mesh or other prosthesis
	43335	; with implantation of mesh or other prosthesis
	43336	Repair, paraesophageal hiatal hernia (including fundoplication), via thoracoabdominal incision, except neonatal; without implantation of mesh or other prosthesis
	43337	; with implantation of mesh or other prosthesis
	43338	Esophageal lengthening procedure (eg, Collis gastroplasty or wedge gastroplasty) (List separately in addition to code for primary procedure)

Codes	Number	Description
	43631	Gastrectomy, partial, distal; with gastroduodenostomy
	43632	;with gastrojejunostomy
	43633	;with roux-en-Y reconstruction
	43634	;with formation of intestinal pouch
HCPCS	None	

Date of Origin: *November 2012*

Regence

Medical Policy Manual Surgery, Policy No. 189

Microwave Tumor Ablation

Effective: January 1, 2024

Next Review: November 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Microwave ablation (MWA) uses microwave thermal energy to create thermal coagulation and localized tissue necrosis. MWA is proposed for treating tumors, controlling local tumor growth and palliating symptoms.

MEDICAL POLICY CRITERIA

Note: This policy does not address liver tumors (primary or metastatic). See Cross References.

I. Microwave ablation may be considered **medically necessary** to treat tumors when one or more of the following criteria are met:

A. Isolated peripheral non-small cell lung cancer (NSCLC) lesion that is no more than 3 cm in size when both of the following criteria are met:

1. Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; and

2. Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

B. Malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when all of the following criteria (1. – 3.) are met:

1. In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status, or the patient is not considered a surgical candidate; and
2. There is no evidence of extrapulmonary metastases; and
3. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

II. Microwave ablation is considered **investigational** as a technique for ablating all other benign or malignant tumors other than liver tumors that do not meet the policy criteria above.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE), Medicine, Policy No. 140
2. Radiofrequency Ablation (RFA) of Tumors Other than Liver, Surgery, Policy No. 92
3. Cryosurgical Ablation of Miscellaneous Solid Organ and Breast Tumors. Surgery, Policy No. 132
4. Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation, Surgery, Policy No. 139
5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204

BACKGROUND

MICROWAVE ABLATION

MWA is a technique in which the use of microwave energy induces an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field which causes water molecule rotation and the creation of heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, approximately 2 to 3 cm elliptical area (5 x 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2 to 3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within one minute after a pulse of energy, and multiple pulses may be delivered within a treatment session depending on the size of the tumor. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edges. Treatment may be repeated as needed. MWA may be used to: 1) control local tumor growth and prevent recurrence; 2) palliate symptoms; and 3) extend survival duration.

Complications from MWA are usually considered mild and may include pain and fever. Other potential complications associated with MWA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of

procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant patients since potential risks to the patient and/or fetus have not been established and in patients with implanted electronic devices such as implantable pacemakers that may be adversely affected by microwave power output.

MWA is an ablative technique similar to radiofrequency or cryosurgical ablation; however, MWA may have some advantages. In MWA, the heating process is active, which produces higher temperatures than the passive heating of radiofrequency ablation and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (over 100° C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating, and therefore, does not have electrical current flow through patients and does not require grounding pads be used during the procedure to prevent skin burns. Unlike radiofrequency ablation, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference. Finally, MWA can be completed in less time than radiofrequency ablation since multiple antennas can be used simultaneously.

APPLICATIONS

MWA was first used percutaneously in 1986 as an adjunct to liver biopsy. Since then, MWA has been used to ablate tumors and tissue to treat many conditions including hepatocellular carcinoma, breast cancer, colorectal cancer metastatic to the liver, renal cell carcinoma, renal hamartoma, adrenal malignant carcinoma, non-small-cell lung cancer, intrahepatic primary cholangiocarcinoma, secondary splenomegaly and hypersplenism, abdominal tumors, and other tumors not amenable to resection. Well-established local or systemic treatment alternatives are available for each of these malignancies. The potential advantages of MWA for these cancers include improved local control and other advantages common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, shortening length of hospitalization). MWA also has been investigated as a treatment for unresectable hepatic tumors (see Cross References).

REGULATORY STATUS

There are several devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (a subsidiary of Tyco Healthcare) Evident Microwave Ablation System has 510(k) clearance for soft tissue ablation, including partial or complete ablation of non-resectable liver tumors. The following are selected microwave ablation devices that have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical Corporation’s MicroThermX® Microwave Ablation System (MTX-180);
- Microsulis Holdings Ltd’s Acculis Accu2i;
- MedWaves Microwave Coagulation/Ablation System;
- Covidien’s Emprint™ Ablation System and Emprint™ SX Ablation Platform with Thermosphere™ Technology;
- Angiodynamics’ Solero Microwave Tissue Ablation System;
- Surgnova Healthcare Technologies’ Microwave Ablation System; and
- Johnson & Johnson’s NEUWAVE Microwave Ablation System

FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

EVIDENCE SUMMARY

The principal health outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment.

In order to understand the impact of microwave ablation (MWA) on these outcomes, well-designed randomized controlled trials (RCTs) are needed that compare this therapy with standard medical and/or surgical treatment of primary and metastatic tumors.

BREAST

SYSTEMATIC REVIEWS

A 2017 systematic review of imaging-guided breast cancer treatments by Mauri compared technical success, efficacy, and complications.[1] 1,156 patients and 1,168 lesions were included in the analysis. The results showed that the microwave technique had the lowest technical success (93%) amongst the techniques that were analyzed including laser (98%), HIFU (96%), radiofrequency (96%), and cryoablation (75%). Additionally, there were significant differences and heterogeneity in the technical efficacy of the methods used.

A 2010 review of ablation techniques by Zhao for breast cancer found only 0 to 8% of breast tumors were completely ablated with microwave ablation (MWA).[2] The authors noted that studies identified for the review were mostly feasibility and pilot studies conducted in research settings.

NONRANDOMIZED STUDIES

Yang (2020) published a prospective multicenter study of MWA for the treatment of benign breast lesions.[3] A total of 440 patients with clinicopathologically confirmed benign breast lesions were treated with MWA and evaluated for technical success, complications, volume reduction ratio (VRR), palpability, and cosmetic satisfaction. In the 755 treated lesions (mean maximum diameter 1.7 ± 0.6 cm), complete ablation was achieved in 100%. The median follow-up was 13.7 months. The 12-month VRR was 97.9% for all lesions, 98.6% for 1.0- to 2.0-cm lesions, and 96.9% for ≥ 2.0-cm lesions. The percent of palpable lesions went from 85.7% pre-treatment to 55.9% post-treatment. Patients rated the cosmetic and minimally invasive satisfaction rates as good or excellent in 98.4% and 94.5% of cases, respectively.

Yu (2020) reported a small cohort study comparing MWA with nipple-sparing mastectomy for invasive ductal carcinoma of the breast.[4] A total of 21 MWA-treated and 43 nipple sparing mastectomy-treated patients were retrospectively enrolled. The mean age of the MWA-treated patients was 24 years older than that of the nipple sparing mastectomy patients. Median follow-up was 26.7 months (range, 14.6 to 62.5 months). Technical effectiveness was 100%. No significant differences between groups in tumor progression were identified (p=0.16).

In 2012, Zhou reported on 41 patients treated with MWA directly followed by mastectomy for single breast tumors with a mean volume of 5.26 cm + 3.8 (range, 0.09 to 14.14 cm).[5]

Complete tumor ablation was found by microscopic evaluation in 37 of the 41 tumors ablated (90%; 95% CI 76.9 to 97.3%). Reversible thermal injuries to the skin and pectoralis major muscle occurred in three patients. Results from this study should be met with caution due to its small sample size and lack of comparison group. The MWA group had significantly lower hospitalization time ($p<0.001$) and better cosmetic results ($p<0.001$). No major complications occurred.

LUNG

SYSTEMATIC REVIEWS

Laeseke (2023) conducted a systematic review and meta-analysis that compared the efficacy of image guided thermal ablation, including MWA, to stereotactic body radiation therapy (SBRT) in patients with stage IA NSCLC among studies with at least 40 patients.[6] Comparative and single-arm studies, as well as single treatments from comparative studies were included in the meta-analysis. Studies that enrolled patients with recurrent NSCLC, or that used interventions as salvage treatments, were excluded. Key outcomes of interest were local tumor progression, overall survival, and disease-free survival. 40 image-guided thermal ablation study-arms (n=2,691 patients) and 215 SBRT study-arms (n=54,789 patients) were identified. Local tumor progression was lowest after SBRT at years one and two in single-arm pooled analyses (4% and 9% versus 11% and 18%) and at one year in meta–regressions when compared to ablative therapies (odds ratio [OR]=0.2, 95% CI = 0.07 to 0.63). Microwave ablation patients had the highest disease-free survival of all treatments in single-arm pooled analyses. In meta–regressions at two and three years, disease-free survival was significantly lower for radiofrequency ablation compared to MWA (OR=0.26, 95% CI = 0.12 to 0.58; OR=0.33, 95% CI = 0.16 to 0.66, respectively). Overall survival was similar across treatment types and time points. Older age, male patients, larger tumors, retrospective studies, and non-Asian study region were predictors of worse clinical outcomes. Among high quality studies, stage IA microwave ablation patients had lower local tumor progression, higher overall survival, and generally lower disease-free survival, compared to the main analysis of all NSCLC patients.

Chan (2021) reported a systematic review and meta-analysis comparing survival outcomes for surgical resection versus CT-guided percutaneous ablation (RFA and MWA) for stage 1 non-small cell lung cancer (NSCLC).[7] A total of eight studies with 792 patients met inclusion criteria. The difference between groups for one- to five-year overall survival (OS) and cancer-specific survival (CSS) and three- and five-year disease-free survival (DFS) were not statistically significant. However, differences between groups in one- and two-year DFS were statistically significant, favoring sublobar resection (OR 2.22, 95% CI 1.14 to 4.34; OR 2.60, 95% CI 1.21 to 5.57 respectively). According to a subgroup analysis, there was no significant difference in OS between lobectomy and MWA, but one- and two-year OS were significantly better in those treated with sublobar resection (wedge resection or segmentectomy) versus RFA (OR 2.85, 95% CI 1.33 to 6.10; OR 4.54, 95% CI 2.51 to 8.21, respectively).

Nelson (2019) included 12 retrospective observational studies of MWA in patients with primary or metastatic lung tumors.[8] The reviewers did not pool results due to clinical and methodological heterogeneity across the studies. The studies varied with regard to patient characteristics (tumor size, histology, number of treated nodules), outcome measures, and technical experience of surgeons performing the procedures. The primary outcome was local recurrence, and survival outcomes were not assessed. Overall, local recurrence rates ranged

from 9% to 37% across the studies. Newer reports and those that targeted smaller tumors showed more favorable efficacy rates. Results in patients with multiple tumors were not reported separately. Four studies reported results by tumor size; the local recurrence rate for large tumors (> 3 or 4cm depending on the study) were 50%, 75%, 36%, and 26%. In the same four studies, for small tumors (<3 or 3.5 cm depending on the study), local recurrence rates were 19%, 18%, 18%, and 5%, respectively. The most frequent adverse event with MWA was a pneumothorax requiring a chest tube. The reviewers concluded that MWA may be a useful tool in selected patients who are not ideal surgical candidates.

In a meta-analysis of observational studies, Yuan (2019) found higher overall survival for patients who received RFA compared to those who received MWA.[9] However, these estimates were not directly comparable because they came from different sets of studies, and the reviewers concluded that percutaneous RFA and MWA were both effective with a high safety profile. The studies used different patient eligibility criteria (e.g., tumor size, lesion number, age, follow-up). Subgroup analyses by tumor size or tumor number were not possible from the data reported.

Jiang (2018) conducted a network meta-analysis to determine the effectiveness of different ablation techniques in patients with lung tumors.[10] Tumor size, stage of disease, and primary versus metastatic disease were not accounted for in the analysis. For MWA, weighted average overall survival rates were 82.5%, 54.6%, 35.7% 29.6%, and 16.6% at one, two, three, four, and five years, respectively. According to the meta-analysis, RFA and MWA were more effective in decreasing the progression rate of lung malignancies than cryoablation (OR 0.04, 95% CI 0.002 to 0.38, p=0.005 and OR 0.02, 95% CI 0.002 to 0.24, p=0.001, respectively). Major complications were not significantly different between RFA, MWA, and cryoablation (p>0.05).

RANDOMIZED CONTROLLED TRIAL

In a 2017 RCT published by Macchi, 52 patients were randomized into a radiofrequency ablation group or a microwave ablation group.[11] Within each group, the technical and clinical success were measured along with survival and complication rates. The radiofrequency ablation group saw significant reduction in tumor size between 6 and 12 months and the microwave ablation group saw a significant reduction in tumor size from pre-therapy to 12 months including from 6 to 12 months. There was no significant difference in survival between the groups. The authors reported that the microwave ablation group experienced less pain than the radiofrequency ablation group (p=0.0043).

NONRANDOMIZED STUDIES

Hu (2020) reported a retrospective comparison of wedge resection and microwave ablation as a first-line treatment of stage I NSCLC.[12] A total of 223 consecutive patients with T1N0 NSCLC received first-line treatment either using wedge resection (n=155) or MWA (n=68). A propensity matched analysis, which yielded 56 pairs of patients, identified no significant differences in three- or five-year PFS (MWA 54.0% and 36.0%, respectively; wedge resection 66.0% and 56.0%, respectively; p=0.029) or OS (MWA 60.0% and 55.0%; wedge resection 81.0% and 72.0%, respectively; p=0.031). According to a subgroup analysis, local recurrence and PFS for NSCLCs that were contiguous to the pericardium were better in the wedge resection group than in the MWA group (p<0.05).

Das (2020) performed a retrospective analysis to compare the safety and efficacy of cryoablation and MWA for the treatment of NSCLC.[13] Patients who were treated with microwave ablation (n=56) or cryoablation (n=45) for stage IIIB or IV NSCLC were included. The primary endpoint was PFS, which was not significantly different between groups (10 months for cryoablation versus 11 months for MWA; p=0.36). The secondary endpoints were OS (27.5 months for cryoablation versus 18 months for MWA; p=0.07) and adverse events (p>0.05). Dividing the group by tumor size showed that for large tumors (>3 cm; p=0.04), but not for small tumors (≤3 cm; p0.79), the microwave ablation group had significantly longer median PFS.

Aufranc (2019) reported the efficacy and complication rate of cryoablation and MWA for the treatment of primary and secondary lung tumors.[14] The authors performed a retrospective analysis of 115 patients with primary (n=41) or secondary (n=119) lung tumors. Mean overall follow-up was 488 days. Ablation volumes, local recurrence, and mean length of hospital stay were not significantly different between groups at one month (24.1±21.7 cm^3 for RFA and 30.2±35.9 cm^3 for MWA; p=0.195; 6/79 in the radiofrequency group and 3/81 in the MWA group; p=0.049; 4.5±3.7 days for RFA and 4.7±4.6 days for MWA; p=0.76). However, the difference in pneumothoraces between groups was statistically significant (32/79 for radiofrequency and 20/81 for MWA; p=0.049).

In 2016, Vogl evaluated local tumor control, time to tumor progression, and survival rates among patients with lung metastatic colorectal cancer who underwent ablation therapy (N=109) performed using laser-induced thermotherapy (LITT), radiofrequency ablation (RFA), or microwave ablation (MWA).[15] Twenty-one patients underwent LITT (31 ablations), 41 patients underwent RFA (75 ablations), and 47 patients underwent MWA (125 ablations). Local tumor control was achieved in 17 of 25 lesions (68.0%) treated with LITT, 45 of 65 lesions (69.2%) treated with RFA, and 91 of 103 lesions (88.3%) treated with MWA. The progression-free survival rate at one, two, three, and four years was 96.8%, 52.7%, 24.0%, and 19.1%, respectively, for patients who underwent LITT; 77.3%, 50.2%, 30.8%, and 16.4%, respectively, for patients who underwent RFA; and 54.6%, 29.1%, 10.0%, and 1.0%, respectively, for patients who underwent MWA, with no statistically significant difference noted among the three ablation methods.

Other evidence regarding MWA for lung tumors is limited to nonrandomized retrospective studies.[16-32] These studies are all have limitations, including lack of comparison group, small sample size, short-term follow-up. Larger studies with a randomized design are needed to isolate the effect of MWA upon PFS and OS in patients with lung cancer.

PRIMARY RENAL TUMORS

SYSTEMATIC REVIEWS

Wu (2023) published a systematic review and meta-analysis of MWA for the treatment of renal cell carcinoma and larger (T1b) tumors.[33] Among 27 studies and 1584 patients with malignant renal tumors, pooled technical success and efficacy rates were 99.6% (95% confidence interval [CI], 98.0% to 100%) and 96.2% (95% CI, 93.8% to 98.2%), respectively. Local recurrence rate was 3.2% (95% CI, 1.9%-4.7%). At one, three, and five years, overall survival rates were 99.0% (95% CI, 97.5% to 99.9%), 96.0% (95% CI, 93.1% to 98.3%), and 88.1% (95% CI, 80.3% to 94.2%). In 204 patients with T1b tumors, pooled technical success and efficacy rates were 100% (95% CI, 96.6% to 100%) and 85.2% (95% CI, 71.0% to 95.8%). Local recurrence rate was 4.2% (95% CI, 0.9% to 8.9%). At one and three years, overall

survival rates were 94.3% (95% CI, 85.7% to 99.6%) and 89.3% (95% CI, 68.7% to 100%). Review authors concluded that MWA yielded favorable short- to intermediate-term oncologic outcomes with low complication rates.

Uhlig (2019) published a systematic review with meta-analyses to compare partial nephrectomy, radiofrequency ablation, cryoablation and microwave ablation and the effect on oncologic, perioperative and functional outcomes in studies published from 2005 to 2017.[34] Microwave ablation was a treatment in 344 of 24,077 patients and represented in 6 of 47 studies. The review included the single RCT (Guan 2012, described below) which is the only study with results for all three outcomes of interest. No new data was included but the review utilized a network meta-analyses technique. Microwave ablation when compared to partial nephrectomy, the comparator of interest, was reported to have a lower procedural complication rate but higher local recurrence and cancer-specific mortality rates.

In a 2014 systematic review and meta-analysis, Katsanos compared thermal ablation (MWA and RFA) with surgical nephrectomy for small renal tumors (mean size 2.5 cm).[35] Included in the analysis were one randomized study[36] on MWA and five cohort studies on RFA with a total of 587 patients. In the ablation group, the complication rates and renal function decline were significantly lower than in the nephrectomy group (p=0.04 and p=0.03, respectively). The local recurrence rate was 3.6% in both groups (risk ratio=0.92, 95% CI 0.4 to 2.14, p=0.79) and disease-free survival up to five years was not significantly different between groups (hazard ratio=1.04, 95% CI 0.48 to 2.24, p=0.92). The authors indicated additional RCTs were needed to compare MWA to nephrectomy and other ablative techniques.

Martin (2013) reported on a meta-analysis of MWA versus cryoablation for small renal tumors in 2013.[37] Included in the analysis were seven MWA studies (n=164) and 44 cryoablation studies (n=2989). The studies were prospective or retrospective, nonrandomized, noncomparative studies. The mean follow-up duration was shorter for MWA than cryoablation (17.86 months vs 30.22 months, p=0.07). While the mean tumor size was significantly larger in the MWA studies than the cryoablation studies (2.58 cm vs 3.13 cm, respectively, p=0.04), local tumor progression (4.07% vs 2.53%, respectively; p=0.46), and progression to metastatic disease (0.8% vs 0%, respectively; p=0.12) were not significantly different.

RANDOMIZED CONTROLLED TRIALS

In 2012, Guan reported on a prospective randomized study to compare the use of MWA to partial nephrectomy (the gold standard of nephron-sparing surgical resection) for solitary renal tumors less than 4 cm.[36] Forty-eight patients received MWA and 54 had partial nephrectomy. Patients in the MWA group had significantly fewer postoperative complications than the partial nephrectomy group (6 [23.5%] vs. 18 [33.3%]; p=0.0187). MWA patients also had significantly less postoperative renal function declines (p=0.0092) and estimated perioperative blood loss (p=0.0002) than partial nephrectomy patients. At last follow-up, estimated glomerular filtration rate declines in both groups were similar (p=1.0000). Disease-specific deaths did not occur and overall local recurrence-free survival by Kaplan-Meier estimates at three years were 91.3% for MWA and 96.0% for partial nephrectomy (p=0.5414). Studies with longer follow-up are needed in order to assess the benefits of MWA compared to nephrectomy.

NONRANDOMIZED STUDIES

Yu (2022) reported long-term follow-up of 323 consecutive patients with T1N0M0 renal cell carcinoma who underwent MWA.[38] Patients were analyzed by stage. A total of 275 cT1a

patients were followed for a median of 66.0 months (interquartile range [IQR] 58.4 to 73.6). In these patients, 10-year local neoplastic processes, cancer-specific survival, disease-free survival, and overall survival rates were 1.9%, 87.4%, 71.8, and 67.5%, respectively. A total of 48 cT1b patients were followed for a median of 30.4 months (IQR, 17.7 to 44.8). In these patients, five-year local tumor progression, cancer-specific survival, disease-free survival, and overall survival rates were 11.3%, 91.4%, 69.1, and 89.2%, respectively. Major complications were 3.5% in cT1a patients and 6.9% in cT1b patients.

Vanden Berg (2021) reported a case series of 101 patients with renal tumors treated with MWA.[39] All ablation procedures were performed by a single board-certified urologist/interventional radiologist. Median tumor size was 2.0 cm (IQR 1.5 to 2.6). All patients achieved technical success. All patients but one were discharged on the day of the procedure. Two Clavien-Dindo type-I complications, one type-II complication, and one type-III complication were reported. At a median radiographic follow-up of 376.5 days, two tumors had recurred.

John (2020) published a prospective case series of 113 patients treated with MWA for renal cell carcinoma.[40] The median tumor diameter was 25 mm (IQR 20 to 32 mm) and median follow-up was 12 months. One patient (0.9%) had local recurrence, which was treated with re-ablation. Two patients developed metastatic progression, one had a lung nodule at follow-up, and one had a possible local recurrence. Associations were identified between post-procedure complications and total ablation time (OR 1.152/min, 95% CI 1.040 to 1.277) and total ablation energy (OR 1.017/kJ, 95% CI 1.001 to 1.033).

An (2020) published a retrospective review of 114 patients with renal cell carcinoma who were treated with MWA.[41] Patients were divided by tumor location, either central (n=44) or peripheral (n=70). No significant differences were found between locations (17.7% vs. 11.7%, p=0.34) for overall adverse event rate or Grade II or higher adverse event rate (7.8% vs. 2.6%, p = 0.17). There was a statistically significant difference in rate of adjunctive maneuvers of hydrodissection and/or pyeloperfusion (53% for central tumors vs. 29% for peripheral tumors, p=0.006).

Acosta Ruiz (2020) reported the results of another retrospective review of MWA for renal tumors.[42] Ninety-three patients with 105 tumors were treated with CT-guided MWA. The median tumor size was 25 mm. The primary efficacy rate was 92.2%. Periprocedural complications occurred in 5.2% of sessions (four Clavien-Dindo I and one Clavien-Dindo IIIa) and one postprocedural Clavien-Dindo II complication was reported.

Guo (2021) reported a retrospective review of 106 patients with 119 T1a renal cell carcinoma tumors treated with MWA.[43] Complete response was achieved in 95.3% of patients (mean tumor diameter, 2.4 cm; range, 1 to 4 cm). Local tumor progression was observed in six patients at a mean of 20 months post-procedure. Local progression-free survival rates were 100%, 92.8%, and 90.6% at one, two, and three years, respectively. OS rates were 99%, 97.7%, and 94.6% at one, two, and three years respectively. Complications were reported in six patients (5.7%) within 30 days of the procedure, but none of these required intervention.

Aarts (2020) conducted another retrospective review of 100 patients with 108 T1 renal cell carcinomas treated with MWA.[44] The median tumor size in this study was 3.2 cm (interquartile range, 2.4 to 4 cm). Primary efficacy was achieved for 81% (88/108) of lesions overall, but primary efficacy rates were lower among patients with T1b tumors (52%) versus T1a tumors

(89%; p<0.001). Secondary efficacy was achieved for 97% (101/103). Over a median follow-up time of 19 months, local tumor recurrence was observed for 4 (4%) tumors.

Shapiro (2020) compared outcomes in patients with clinical T1b renal cell carcinoma treated with MWA, partial nephrectomy, or radical nephrectomy.[45] A retrospective analysis was completed of 40 MWA, 74 partial nephrectomy, and 211 radical nephrectomy patients. Median follow-up was 34, 35, and 49 months for MWA, partial nephrectomy, and radical nephrectomy, respectively. The decrease in post-treatment estimated glomerular filtration rate was significantly greater in radical nephrectomy patients (29%, p<0.001) than partial nephrectomy (3.2%) or microwave ablation (4.5%). The local recurrence rates were 5%, 1.4%, and 0.5% in the MWA, partial nephrectomy, and radical nephrectomy treatment groups, respectively. The estimated five-year local recurrence-free survival rates were 94.5%, 97.9%, and 99.2% for the MWA, partial nephrectomy, and radical nephrectomy treatment groups, respectively. Although the estimated five-year local recurrence-free survival rate was significantly lower for the MWA group, after a univariable Cox regression, local recurrence was not associated with microwave ablation treatment.

De Cobelli (2019) performed a retrospective evaluation of the comparative safety and effectiveness of cryoablation and MWA for the treatment of T1a renal tumors.[46] T1a renal cancer patients with either a contraindication to surgery or a refusal of surgery were treated at a single center for with either cryoablation (n=44) or MWA (n=28). Median follow-up was 20 and 22 months, for cryoablation and MWA, respectively. Technical success, defined as the absence of arterial enhancement in the ablation zone at the one-month cross-sectional imaging, was not significantly different between groups (92% vs. 94% for cryoablation and MWA, respectively; p=0.8), nor was the occurrence of complications (cryoablation 5/51, MWA 2/32; p=0.57), or disease recurrence (cryoablation 3/47, MWA 1/30; p=0.06). The median procedure time was significantly lower in the MWA group (110 min. and 40 min. for cryoablation and MWA, respectively; p=0.003).

Zhou (2019) compared the outcomes following three ablation techniques for the treatment of T1a biopsy-proven renal cell carcinoma.[47] A total of 297 patients were treated with radiofrequency ablation (n=244), cryoablation (n=26), and MWA (n=27). They were retrospectively assessed for adverse events, treatment efficacy, and therapeutic outcomes. Technical success rates were not significantly different between groups (p=0.33). The authors reported that primary efficacy one month following ablation was more likely following RF ablation and MW ablation than cryoablation. At the two-year follow-up, there were no reports of local recurrence, metastatic progression, or renal cell carcinoma-related deaths in any treatment group. Also at two years, there was also no significant change in estimated glomerular filtration rate compared with baseline (p=0.71).

Additional evidence regarding MWA treatment in patients with primary renal tumors primarily consists of several nonrandomized case studies, all of which are limited by lack of comparison and small sample size.[48-55] In addition, one study was also limited by short-term follow-up.[49]

OTHER TUMORS OR CONDITIONS

Wu (2022) conducted a systematic review and meta-analysis comparing MWA versus conventional surgery for the treatment of papillary thyroid microcarcinoma.[56] There were 13 included studies which were all non-randomized. There was no differences between the 2 groups in recurrence rate or lymph node metastasis; however, the MWA group did have a

shorter operation time, less intra-operative blood loss, shorter postoperative hospital stay, and few complications.

Nonrandomized studies of MWA for other indications are limited by lack of comparison group. Cui (2019) conducted a non-comparative systematic review and meta-analysis of five retrospective studies and two prospective studies in patients with benign thyroid nodules or papillary thyroid microcarcinoma and found that MWA improved nodule volume and symptom scores in these patients.[57] More recent studies also lack control groups or do not compare to standard of care.[58-61]

Examples of other indications include adrenal carcinoma,[62, 63] oligometastases,[64] bone tumors,[65-68] thyroid carcinoma,[69, 70] pancreatic cancer,[71] sinus mucoceles,[72] and other non-oncologic conditions (e.g., bleeding peptic ulcers, esophageal varices, secondary hypersplenism, myomas).

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

National comprehensive cancer network (NCCN) guidelines for non-small cell lung cancer (v4.2023) recommend “image-guided thermal ablation (e.g., cryotherapy, microwave, radiofrequency [as] an option for select patients.”[73] image-guided thermal ablation therapy is considered an option for the management of NSCLC lesions <3 cm as ablation for NSCLC lesions >3 cm has been associated with higher rates of local recurrence and complications.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians (ACCP) 2013 evidence-based guidelines on the treatment of non-small cell lung cancer note the role of ablative therapies in the treatment of high-risk patients with stage I non-small cell lung cancer (NSCLC) is evolving. However, the ACCP does not recommend MWA for patients with NSCLC.[74]

SUMMARY

Surgical resection is the treatment of choice for primary non-small cell lung cancer (NSCLC) or metastatic tumors in the lung. For those patients who are unable to tolerate surgery, microwave ablation (MWA) may be a treatment option in certain cases. While available studies are limited by study design, accumulating evidence suggests that MWA may be similar to surgery in survival rates, and rates of procedure-related complications and mortality. Therefore, in patients with NSCLC or metastatic tumors in the lung who are ineligible for surgical treatment, MWA may be considered medically necessary when the policy criteria are met.

For patients with tumors that do not meet policy criteria, it appears that microwave ablation (MWA) may improve health outcomes, though more research is needed to know for sure. Therefore, MWA is considered investigational as a treatment of these tumors.

REFERENCES

1. Mauri G, Sconfienza LM, Pescatori LC, et al. Technical success, technique efficacy and complications of minimally-invasive imaging-guided percutaneous ablation procedures of breast cancer: A systematic review and meta-analysis. *European radiology.* 2017;27(8):3199-210. PMID: 28050693
2. Zhao Z, Wu F. Minimally-invasive thermal ablation of early-stage breast cancer: a systemic review. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2010;36(12):1149-55. PMID: 20889281
3. Yang Q, Li H, Chen BH, et al. Ultrasound-guided percutaneous microwave ablation for 755 benign breast lesions: a prospective multicenter study. *European radiology.* 2020;30(9):5029-38. PMID: 32356159
4. Yu J, Han ZY, Li T, et al. Microwave Ablation Versus Nipple Sparing Mastectomy for Breast Cancer ≤5 cm: A Pilot Cohort Study. *Front Oncol.* 2020;10:546883. PMID: 33117685
5. Zhou W, Zha X, Liu X, et al. US-guided percutaneous microwave coagulation of small breast cancers: a clinical study. *Radiology.* 2012;263(2):364-73. PMID: 22438362
6. Laeseke P, Ng C, Ferko N, et al. Stereotactic body radiation therapy and thermal ablation for treatment of NSCLC: A systematic literature review and meta-analysis. *Lung Cancer.* 2023;182:107259. PMID: 37321074
7. Chan MV, Huo YR, Cao C, et al. Survival outcomes for surgical resection versus CT-guided percutaneous ablation for stage I non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. *European radiology.* 2021;31(7):5421-33. PMID: 33449192
8. Nelson DB, Tam AL, Mitchell KG, et al. Local Recurrence After Microwave Ablation of Lung Malignancies: A Systematic Review. *Ann Thorac Surg.* 2019;107(6):1876-83. PMID: 30508527
9. Yuan Z, Wang Y, Zhang J, et al. A Meta-Analysis of Clinical Outcomes After Radiofrequency Ablation and Microwave Ablation for Lung Cancer and Pulmonary Metastases. *J Am Coll Radiol.* 2019;16(3):302-14. PMID: 30642784
10. Jiang B, McClure MA, Chen T, et al. Efficacy and safety of thermal ablation of lung malignancies: A Network meta-analysis. *Ann Thorac Med.* 2018;13(4):243-50. PMID: 30416597
11. Macchi M, Belfiore MP, Floridi C, et al. Radiofrequency versus microwave ablation for treatment of the lung tumours: LUMIRA (lung microwave radiofrequency) randomized trial. *Med Oncol.* 2017;34(5):96. PMID: 28417355
12. Hu H, Zhai B, Liu R, et al. Microwave Ablation Versus Wedge Resection for Stage I Non-small Cell Lung Cancer Adjacent to the Pericardium: Propensity Score Analyses of Long-term Outcomes. *Cardiovascular and interventional radiology.* 2020. PMID: 32909064
13. Das SK, Huang Y-Y, Li B, et al. Comparing cryoablation and microwave ablation for the treatment of patients with stage IIIB/IV non-small cell lung cancer. *Oncol Lett.* 2020;19(1):1031-41. PMID: 31885721
14. Aufranc V, Farouil G, Abdel-Rehim M, et al. Percutaneous thermal ablation of primary and secondary lung tumors: Comparison between microwave and radiofrequency ablation. *Diagn Interv Imaging.* 2019;100(12):781-91. PMID: 31402333
15. Vogl TJ, Eckert R, Naguib NN, et al. Thermal Ablation of Colorectal Lung Metastases: Retrospective Comparison Among Laser-Induced Thermotherapy, Radiofrequency Ablation, and Microwave Ablation. *AJR American journal of roentgenology.* 2016;207(6):1340-49. PMID: 27680945

16. Wolf FJ, Grand DJ, Machan JT, et al. Microwave ablation of lung malignancies: effectiveness, CT findings, and safety in 50 patients. *Radiology.* 2008;247(3):871-9. PMID: 18372457
17. Carrafiello G, Mangini M, Fontana F, et al. Complications of microwave and radiofrequency lung ablation: personal experience and review of the literature. *La Radiologia medica.* 2012;117(2):201-13. PMID: 22020434
18. He W, Hu XD, Wu DF, et al. Ultrasonography-guided percutaneous microwave ablation of peripheral lung cancer. *Clinical imaging.* 2006;30(4):234-41. PMID: 16814137
19. Little MW, Chung D, Boardman P, et al. Microwave ablation of pulmonary malignancies using a novel high-energy antenna system. *Cardiovascular and interventional radiology.* 2013;36(2):460-5. PMID: 22968596
20. Egashira Y, Singh S, Bandula S, et al. Percutaneous High-Energy Microwave Ablation for the Treatment of Pulmonary Tumors: A Retrospective Single-Center Experience. *Journal of vascular and interventional radiology : JVIR.* 2016;27(4):474-9. PMID: 26944360
21. Ko WC, Lee YF, Chen YC, et al. CT-guided percutaneous microwave ablation of pulmonary malignant tumors. *Journal of thoracic disease.* 2016;8(Suppl 9):S659-S65. PMID: 28066666
22. Healey TT, March BT, Baird G, et al. Microwave Ablation for Lung Neoplasms: A Retrospective Analysis of Long-Term Results. *Journal of vascular and interventional radiology : JVIR.* 2016. PMID: 27993505
23. Men M, Ye X, Fan W, et al. Short-Term Outcomes and Safety of Computed Tomography-Guided Percutaneous Microwave Ablation of Solitary Adrenal Metastasis from Lung Cancer: A Multi-Center Retrospective Study. *Korean journal of radiology.* 2016;17(6):864-73. PMID: 27833402
24. Zheng A, Ye X, Yang X, et al. Local Efficacy and Survival after Microwave Ablation of Lung Tumors: A Retrospective Study in 183 Patients. *Journal of vascular and interventional radiology : JVIR.* 2016;27(12):1806-14. PMID: 27789077
25. Acksteiner C, Steinke K. Percutaneous microwave ablation for early-stage non-small cell lung cancer (NSCLC) in the elderly: a promising outlook. *Journal of medical imaging and radiation oncology.* 2015;59(1):82-90. PMID: 25335916
26. Sun YH, Song PY, Guo Y, et al. Computed tomography-guided percutaneous microwave ablation therapy for lung cancer. *Genetics and molecular research : GMR.* 2015;14(2):4858-64. PMID: 25966260
27. Pusceddu C, Melis L, Sotgia B, et al. Usefulness of percutaneous microwave ablation for large non-small cell lung cancer: A preliminary report. *Oncol Lett.* 2019;18(1):659-66. PMID: 31289539
28. Wei Z, Ye X, Yang X, et al. Microwave ablation plus chemotherapy improved progression-free survival of advanced non-small cell lung cancer compared to chemotherapy alone. *Med Oncol.* 2015;32(2):464. PMID: 25572816
29. Li C, Wang J, Shao J-B, et al. Microwave ablation combined with chemotherapy improved progression free survival of IV stage lung adenocarcinoma patients compared with chemotherapy alone. *Thorac Cancer.* 2019;10(7):1628-35. PMID: 31243894
30. Chen B, Li W, Liu Y, et al. The efficacy and complications of computed tomography guided microwave ablation in lung cancer. *Ann Palliat Med.* 2020;9(5):2760-65. PMID: 32787355
31. Ni Y, Peng J, Yang X, et al. Multicentre study of microwave ablation for pulmonary oligorecurrence after radical resection of non-small-cell lung cancer. *Br J Cancer.* 2021;125(5):672-78. PMID: 34131307

32. Xu S, Bie ZX, Li YM, et al. A Comparative Study of Cavitary and Noncavitary Non-small Cell Lung Cancer Patients Treated with CT-Guided Microwave Ablation. *Journal of vascular and interventional radiology : JVIR.* 2021;32(8):1170-78. PMID: 34033905
33. Wu J, Sami S, Lajkosz K, et al. An Updated Systematic Review and Meta-Analysis on the Technical, Oncologic, and Safety Outcomes of Microwave Ablation in Patients with Renal Cell Carcinoma. *Journal of endourology / Endourological Society.* 2023. PMID: 37819699
34. Uhlig J, Strauss A, Rücker G, et al. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. *European radiology.* 2019;29(3):1293-307. PMID: 30255245
35. Katsanos K, Mailli L, Krokidis M, et al. Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours. *Cardiovascular and interventional radiology.* 2014;37(2):427-37. PMID: 24482030
36. Guan W, Bai J, Liu J, et al. Microwave ablation versus partial nephrectomy for small renal tumors: intermediate-term results. *Journal of surgical oncology.* 2012;106(3):316-21. PMID: 22488716
37. Martin J, Athreya S. Meta-analysis of cryoablation versus microwave ablation for small renal masses: is there a difference in outcome? *Diagn Interv Radiol.* 2013;19(6):501-7. PMID: 24084196
38. Yu J, Wang H, Cheng ZG, et al. A multicenter 10-year oncologic outcome of ultrasound-guided percutaneous microwave ablation of clinical T1 renal cell carcinoma: will it stand the test of time? *European radiology.* 2022;32(1):89-100. PMID: 34195888
39. Wilcox Vanden Berg RN, Calderon LP, LaRussa S, et al. Microwave ablation of cT1a renal cell carcinoma: oncologic and functional outcomes at a single center. *Clinical imaging.* 2021;76:199-204. PMID: 33964597
40. John JB, Anderson M, Dutton T, et al. Percutaneous microwave ablation of renal masses in a UK cohort. *BJU Int.* 2020. PMID: 32871034
41. An TJ, Arellano RS. Comparison of Safety and Efficacy of Percutaneous Microwave Ablation of Central Versus Peripheral Renal Cell Carcinoma. *Cardiovascular and interventional radiology.* 2020. PMID: 33078234
42. Acosta Ruiz V, Dahlman P, Brekkan E, et al. Microwave ablation of 105 T1 renal tumors: technique efficacy with a mean follow-up of two years. *Acta Radiol.* 2020:284185120956283. PMID: 32910687
43. Guo J, Arellano RS. Percutaneous Microwave Ablation of Category T1a Renal Cell Carcinoma: Intermediate Results on Safety, Technical Feasibility, and Clinical Outcomes of 119 Tumors. *AJR American journal of roentgenology.* 2021;216(1):117-24. PMID: 32603227
44. Aarts BM, Prevoo W, Meier MAJ, et al. Percutaneous Microwave Ablation of Histologically Proven T1 Renal Cell Carcinoma. *Cardiovascular and interventional radiology.* 2020;43(7):1025-33. PMID: 32052093
45. Shapiro DD, Wells SA, Best SL, et al. Comparing Outcomes for Patients with Clinical T1b Renal Cell Carcinoma Treated With Either Percutaneous Microwave Ablation or Surgery. *Urology.* 2020;135:88-94. PMID: 31585198
46. De Cobelli F, Papa M, Panzeri M, et al. Percutaneous Microwave Ablation Versus Cryoablation in the Treatment of T1a Renal Tumors. *Cardiovascular and interventional radiology.* 2020;43(1):76-83. PMID: 31451888
47. Zhou W, Herwald SE, McCarthy C, et al. Radiofrequency Ablation, Cryoablation, and Microwave Ablation for T1a Renal Cell Carcinoma: A Comparative Evaluation of

Therapeutic and Renal Function Outcomes. *Journal of vascular and interventional radiology : JVIR.* 2019;30(7):1035-42. PMID: 30956075
48. Yu J, Liang P, Yu XL, et al. US-guided percutaneous microwave ablation of renal cell carcinoma: intermediate-term results. *Radiology.* 2012;263(3):900-8. PMID: 22495684
49. Muto G, Castelli E, Migliari R, et al. Laparoscopic microwave ablation and enucleation of small renal masses: preliminary experience. *European urology.* 2011;60(1):173-6. PMID: 21531501
50. Bai J, Hu Z, Guan W, et al. Initial experience with retroperitoneoscopic microwave ablation of clinical T(1a) renal tumors. *Journal of endourology / Endourological Society.* 2010;24(12):2017-22. PMID: 20932080
51. Castle SM, Salas N, Leveillee RJ. Initial experience using microwave ablation therapy for renal tumor treatment: 18-month follow-up. *Urology.* 2011;77(4):792-7. PMID: 21324512
52. Guan W, Bai J, Hu Z, et al. Retroperitoneoscopic microwave ablation of renal hamartoma: middle-term results. *Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban.* 2010;30(5):669-71. PMID: 21063854
53. Han ZY, Liang P, Yu XL, et al. Ultrasound-guided percutaneous microwave ablation of sporadic renal angiomyolipoma: preliminary results. *Acta Radiol.* 2015;56(1):56-62. PMID: 24526757
54. Guo J, Arellano RS. Percutaneous Microwave Ablation of Stage T1b Renal Cell Carcinoma: Short-Term Assessment of Technical Feasibility, Short-Term Oncologic Outcomes, and Safety. *Journal of endourology / Endourological Society.* 2020;34(10):1021-27. PMID: 32498630
55. Yong C, Mott SL, Laroia S, et al. Outcomes of Microwave Ablation for Small Renal Masses: A Single Center Experience. *Journal of endourology / Endourological Society.* 2020;34(11):1134-40. PMID: 32611205
56. Wu X, Jiang Z, Liu J, et al. The efficacy and safety of microwave ablation versus conventional open surgery for the treatment of papillary thyroid microcarcinoma: a systematic review and meta-analysis. *Gland Surg.* 2022;11(6):1003-14. PMID: 35800741
57. Cui T, Jin C, Jiao D, et al. Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: A systematic review and meta-analysis. *European journal of radiology.* 2019;118:58-64. PMID: 31439259
58. Luo F, Huang L, Gong X, et al. Microwave ablation of benign thyroid nodules: 3-year follow-up outcomes. *Head Neck.* 2021;43(11):3437-47. PMID: 34459524
59. Honglei G, Shahbaz M, Farhaj Z, et al. Ultrasound guided microwave ablation of thyroid nodular goiter and cystadenoma: A single center, large cohort study. *Medicine (Baltimore).* 2021;100(34):e26943. PMID: 34449459
60. Xia B, Yu B, Wang X, et al. Conspicuousness and recurrence related factors of ultrasound-guided microwave ablation in the treatment of benign thyroid nodules. *BMC Surg.* 2021;21(1):317. PMID: 34344330
61. Javadov M, Karatay E, Ugurlu MU. Clinical and functional results of radiofrequency ablation and microwave ablation in patients with benign thyroid nodules. *Saudi Med J.* 2021;42(8):838-46. PMID: 34344807
62. Li X, Fan W, Zhang L, et al. CT-guided percutaneous microwave ablation of adrenal malignant carcinoma: preliminary results. *Cancer.* 2011;117(22):5182-8. PMID: 21523760

63. Gao Y, Zheng L, Liang P, et al. Evaluating the efficacy and safety of ultrasound-guided percutaneous microwave ablation for the treatment of adrenal metastasis. *J Cancer Res Ther.* 2020;16(5):1088-92. PMID: 33004752
64. Ni Y, Ye X, Yang X, et al. Microwave ablation as local consolidative therapy for patients with extracranial oligometastatic EGFR-mutant non-small cell lung cancer without progression after first-line EGFR-TKIs treatment. *Journal of cancer research and clinical oncology.* 2019:10.1007/s00432-019-3043-6. PMID: 31599340
65. Gennaro N, Sconfienza LM, Ambrogi F, et al. Thermal ablation to relieve pain from metastatic bone disease: a systematic review. *Skeletal Radiol.* 2019;48(8):1161-69. PMID: 30627778
66. Cazzato RL, de Rubeis G, de Marini P, et al. Percutaneous microwave ablation of bone tumors: a systematic review. *European radiology.* 2020. PMID: 33155107
67. Reis J, Chang Y, Sharma AK. Radiofrequency ablation vs microwave ablation for osteoid osteomas: long-term results. *Skeletal Radiol.* 2020;49(12):1995-2000. PMID: 32564104
68. Zhang X, Ye X, Zhang K, et al. Computed Tomography–Guided Microwave Ablation Combined with Osteoplasty for the Treatment of Bone Metastases: A Multicenter Clinical Study. *Journal of vascular and interventional radiology : JVIR.* 2021;32(6):861-68. PMID: 33771712
69. Cao XJ, Liu J, Zhu YL, et al. Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study. *J Clin Endocrinol Metab.* 2020. PMID: 33107573
70. Cao XJ, Wang SR, Che Y, et al. Efficacy and Safety of Thermal Ablation for Treatment of Solitary T1N0M0 Papillary Thyroid Carcinoma: A Multicenter Retrospective Study. *Radiology.* 2021;300(1):209-16. PMID: 33904775
71. Keane MG, Bramis K, Pereira SP, et al. Systematic review of novel ablative methods in locally advanced pancreatic cancer. *World journal of gastroenterology : WJG.* 2014;20(9):2267-78. PMID: 24605026
72. Liu M, Jin K, Sun J, et al. Postoperative ethmoid sinus mucoceles: Late complication of endoscopic ethmoidectomy and MWA management in outpatient. *Am J Otolaryngol.* 2021;42(5):103120. PMID: 34167833
73. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. v.4.2023. [cited 11/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf.
74. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143:e278S-313S. PMID: 23649443

CODES

Codes	Number	Description
CPT	19499	Unlisted procedure, breast
	32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral, radiofrequency
	32999	Unlisted procedure, lungs and pleura
	38589	Unlisted laparoscopy procedure, lymphatic system
	49999	Unlisted procedure, abdomen, peritoneum and omentum

	50592	Ablation, renal tumor(s), unilateral, percutaneous, radiofrequency
	53899	Unlisted procedure, urinary system
	60699	Unlisted procedure, endocrine system
HCPCS	C9751	Bronchoscopy, rigid or flexible, transbronchial ablation of lesion(s) by microwave energy, including fluoroscopic guidance, when performed, with computed tomography acquisition(s) and 3-d rendering, computer-assisted, image-guided navigation, and endobronchial ultrasound (ebus) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]) and all mediastinal and/or hilar lymph node stations or structures and therapeutic intervention(s)

Date of Origin: *October 2013*

Regence

Medical Policy Manual Surgery, Policy No. 193

Sacroiliac Joint Fusion

Effective: January 1, 2024

Next Review: June 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The sacroiliac (SI) joint is a strong weight bearing joint with a self-locking mechanism that provides stability with movement on the left and right side of the sacrum. Similar to other structures in the spine, it is assumed that the SI joint may be a source of low back pain but there are currently no reference standards for diagnosis. If conservative therapies fail to adequately treat symptoms, SI joint fusion may be used to stabilize the SI joint including open, percutaneous, and minimally invasive techniques.

MEDICAL POLICY CRITERIA

I. Sacroiliac joint fusion performed by an open procedure may be considered **medically necessary** when one of the following criteria is met:

   A. As an adjunct to sacrectomy or partial sacrectomy related to tumors involving the sacrum; or

   B. As an adjunct to the medical treatment of sacroiliac joint infection (e.g., osteomyelitis, pyogenic sacroiliitis)/sepsis; or

   C. As a treatment for severe traumatic injuries associated with pelvic ring fracture.

II. Sacroiliac joint fusion performed by an open procedure, for any other indication not listed above in Criterion I. is considered **not medically necessary**.

III. Minimally invasive fusion/stabilization of the sacroiliac joint may be considered **medically necessary** when ALL of the following criteria have been met:

A. Request is for a titanium triangular implant; and

B. Request is for an FDA-approved device; and

C. Clinical documentation that pain limits activities of daily living (ADL). ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required for daily functioning; and

D. Patients have undergone and failed a minimum 6 months of intensive physician-directed non-operative treatment that must include medication optimization, activity modification, and active therapeutic exercise targeted at the lumbar spine, pelvis, sacroiliac joint, and hip; and

E. There is at least 75% reduction of pain following an image-guided, contrast-enhanced intra-articular sacroiliac joint injection on 2 separate occasions; and

F. A trial of a therapeutic sacroiliac joint injection (i.e., corticosteroid injection) has been performed on at least one occasion (see Policy Guidelines); and

G. A thorough physical examination demonstrates findings consistent with sacroiliac joint disease including a positive response to a cluster of three provocative tests (e.g., thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test); and

H. Diagnostic imaging studies include ALL of the following:

1. Imaging of the sacroiliac joint indicates evidence of injury and/or degeneration; and

2. Imaging of the sacroiliac joint excludes the presence of destructive lesions (e.g., tumor, infection) or inflammatory arthropathy of the sacroiliac joint and rules out concomitant hip pathology; and

3. Advanced imaging of the lumbar spine (CT or MRI) is performed to rule out neural compression or other degenerative conditions that can be causing low back or buttock pain and excludes the presence of destructive lesions or inflammatory arthropathy of the sacroiliac joint.

IV. Minimally invasive fusion/stabilization of the sacroiliac joint for the treatment of back pain presumed to originate from the sacroiliac joint is considered **investigational** in all other scenarios including but not limited to when Criterion III is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

A successful trial of controlled diagnostic SI joint or lateral branch blocks consists of two separate positive blocks on different days with local anesthetic only (no steroids or other drugs), or a placebo-controlled series of blocks, under fluoroscopic guidance, that has resulted in a reduction in pain for the duration of the local anesthetic used (e.g., three hours longer with bupivacaine than lidocaine). There is no consensus on whether a minimum of 50% or 75% reduction in pain would be required to be considered a successful diagnostic block, although

evidence supports a criterion standard of 75% to 100% reduction in pain with dual blocks. No therapeutic intra-articular injections (i.e., steroids, saline, other substances) should be administered for a period of at least four weeks before the diagnostic block. The diagnostic blocks should not be conducted under intravenous sedation unless specifically indicated (e.g., the patient is unable to cooperate with the procedure).

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology including indication for procedure (diagnostic or treatment of specific condition) and whether procedure will be open or minimally invasive
- Documentation of specific conservative pain management including length of time utilized including rheumatologic evaluation when indicated
- Documentation of diagnostic blocks including agents used, duration of action and if completed under imaging guidance
- If request is for minimally invasive fusion/stabilization with a titanium triangular implant provide the following; documentation of specifically how pain limits ADLs, failure of minimum of six months of specific nonoperative therapy attempted, percentage of pain reduction achieved using the specific image guided injections listed above on two separate occasions, trial of injection has been performed at least once, absence of generalized pain behavior/disorders, documentation of location of pain on spine/joint, documentation per physical exam of location of pain including tenderness, positive response to at least three provocative tests and diagnostic imaging studies/reports completed.
- Documentation of specific device being utilized if applicable

CROSS REFERENCES

1. Percutaneous Vertebroplasty, Kyphoplasty, Sacroplasty, and Coccygeoplasty, Surgery, Policy No. 107
2. Lumbar Spinal Fusion, Surgery Policy No. 187

BACKGROUND

The sacroiliac (SI) joint is a joint between the sacrum and ilium of the pelvis. The SI joint is a strong weight bearing joint with a self-locking mechanism that provides stability with movement on the left and right side of the sacrum. Similar to other structures in the spine, it is assumed that the SI joint may be a source of low back pain.

Currently, there are no reference standards for the diagnosis of SI joint pain. SI joint pain is typically without any consistent, demonstrable radiographic or laboratory features and most commonly exists in the setting of morphologically normal joints. Clinical tests for SI joint pain may include various movement tests, palpation to detect tenderness, and pain descriptions by the patient. Research into sacroiliac joint pain has been inhibited by the lack of any criterion standard to measure its prevalence and against which various clinical examinations can be validated. Further confounding study of the SI joint is that multiple structures, such as posterior facet joints and lumbar discs, may refer pain to the area surrounding the SI joint.

There are many methods for the treatment of chronic SI joint pain including nonsurgical and surgical approaches. Conservative management may include nonsteroidal anti-inflammatory medications, prescription analgesics, spinal manipulation, physical therapy, a home exercise program, and evaluation and management of cognitive, psychological, or behavioral issues.

If conservative therapies fail to adequately treat symptoms, SI joint fusion may be used to stabilize the SI joint. Surgical approaches include open, percutaneous, and minimally invasive techniques. The open surgery technique involves the iliac crest bone and the sacrum being held together with plates and/or screws until fusion occurs between the two bones. The use of minimally invasive techniques to fuse the SI joint has increased over the last several years. Minimally invasive procedures use specially designed implants for the stabilization of the SI joint.

Some procedures have been referred to as SIJ fusion but may be more appropriately called fixation (this is because there is little to no bridging bone on radiographs). Devices for SIJ fixation/fusion that promote bone ingrowth to fixate the implants include a triangular implant (iFuse Implant System) and cylindrical threaded devices (Rialto, SImmetry, Silex, SambaScrew, SI-LOK). Some devices also have a slot in the middle where autologous or allogeneic bone can be inserted. This added bone is intended to promote fusion of the SIJ.

REGULATORY STATUS

Several percutaneous or minimally invasive fixation/fusion devices have received marketing clearance by the Food and Drug Administration. These include the Rialto™ SI Joint Fusion System (Medtronic), SIJ-Fuse (Spine Frontier), IFUSE® Implant System and iFuse-3D (SI Bone), SImmetry® Sacroiliac Joint Fusion System (Zyga Technologies), Silex™ Sacroiliac Joint Fusion System (XTANT Medical), SambaScrew® and FIREBIRD SI Fusion System (Orthofix), SImpact Sacroiliac Joint Fixation System (Life Spine), and the SI-LOK® Sacroiliac Joint Fixation System (Globus Medical). FDA Product Code: OUR.

Note: This policy does not address percutaneous sacroplasty which is addressed in the *Percutaneous Vertebroplasty and Kyphoplasty* policy (SUR107).

EVIDENCE SUMMARY

SI joint fusion performed by open procedure is considered standard of care to stabilize the sacroiliac joint due to trauma, infection, and tumors involving the sacrum. Therefore, the focus of the literature review is on the use of diagnostic blocks for the diagnosis of SI joint pain and the use of percutaneous or minimally invasive fusion techniques.

Due to the volume of published literature regarding minimally invasive sacroiliac joint fusion with varying study design and quality, the following is a summary of key references published to date. It is important to note that many of the systematic reviews include similar studies in addition to those studies being summarized below.

DIAGNOSTIC BLOCKS

The use of diagnostic blocks to evaluate SI joint pain builds on the experience of diagnostic block use in other joints to evaluate pain. Blinded studies with placebo controls (although difficult to conduct when dealing with invasive procedures) are ideally required for scientific validation of sacroiliac joint blocks, particularly when dealing with pain relief well-known to respond to placebo controls. In the typical evaluation of a diagnostic test, the results of SI

diagnostic block would then be compared with a criterion standard. However, there is no current criterion standard for SI joint injection. A search for systematic reviews, randomized controlled trials, and comparative studies on diagnostic blocks was conducted and is summarized below.

Systematic Reviews

In 2013, the American Society of Interventional Pain Physicians published an updated evidence review with guidelines on diagnosis of SIJ pain.[1] Various studies evaluating diagnostic blocks were reviewed in which the criteria for a positive test varied from 50% to 100% relief from either single or dual blocks. The most stringent criterion, 75% to 100% relief with dual blocks, was evaluated in seven studies. The prevalence of a positive test in the seven studies ranged from 10% to 44.4% in patients with suspected sacroiliac disease. The evidence for diagnostic sacroiliac intra-articular injections was considered to be good using 75% to 100% pain relief with single or dual blocks as the criterion standard.

A 2012 systematic review[2] evaluated the accuracy of diagnostic sacroiliac joint interventions. The methodological quality of the studies was evaluated and only the studies meeting at least 50% of the applicable appraisal inclusion criteria were included. A total of 17 studies met inclusion criteria with a range of diagnostic interventions and relief cutoff thresholds. Only one placebo-controlled study was identified with methodological limitations. The review concluded that there is good evidence for the use of controlled diagnostic local anesthetic blocks. Uncontrolled blocks had a false positive rate of approximately 20%. Overall, the systematic review concluded, based on what the authors determined to be good evidence, “there was no significant difference when 70% or greater relief is utilized as the criterion standard with dual blocks.” In addition, the systematic review concluded that “there is no evidence to support the use of ultrasound or landmark-guided injections for sacroiliac joint pain. These injections must be performed under fluoroscopic or radiologic guidance.” Limitations of this systematic review include the lack of high quality evidence, significant variation in interventions, and discrepancies in a gold standard to measure against.

A systematic review was commissioned by the American Pain Society and conducted by the Oregon Evidence-based Practice Center in 2009.[3] The systematic review concluded that no studies were identified that evaluated validity or utility of diagnostic sacroiliac joint block as a diagnostic procedure for low back pain with or without radiculopathy.

Randomized Controlled Trials

No RCTs identified after the above SRs were published.

Section Summary

Although there is no independent reference standard for the diagnosis of SIJ pain, SIJ blocks are considered the reference standard for the condition. The utility of this test ultimately depends on its ability to identify patients who benefit from treatment. Sacroiliac Joint Fusion

SACROILIAC JOINT FUSION

Systematic Reviews

Lingutla (2016) published a systematic review with meta-analysis evaluating SI joint fusion for low back pain where it has been determined that the cause of the pain is originating from the

sacroiliac joint and not the lumbar spine.[4] Six nonrandomized studies were included with a mean follow-up of 17.6 months. The authors concluded that all outcome measures showed a statistical improvement for alleviating pelvic girdle pain. However, the review consisted of nonrandomized studies with some methodological limitations. More research is needed for this patient population.

Zaidi (2015) conducted a systematic review of the evidence evaluating SI joint fusion interventions for treating SI joint pain or dysfunction.[5] A comprehensive literature search was conducted and the authors included five case series, eight retrospective studies, and three prospective studies with at least two patients (N=430). The mean duration of follow-up was 60 months with the most common pathology being SI joint degeneration/arthrosis followed by SI joint dysfunction, postpartum instability among other less common pathologies. Study participants reported satisfaction after the procedures which varied widely. The rates of reoperation for open surgery were 5% to 65% (mean 15%) and for minimally invasive 0% to 17% (mean 6%). Major complications ranged from 5% to 20% with one study reporting a 56% adverse event rate. The authors concluded that surgical intervention is beneficial for a subset of patients and that serious consideration of alternatives should be considered prior to surgery.

A 2012 systematic review found that the quality of evidence for surgical treatment (débridement, fusion) compared to injection treatment (corticosteroid, botulinum toxin, prolotherapy) for chronic sacroiliac pain was very low.[6] No studies were identified that directly compared surgery to injection therapy. Seven case series using a range of surgical techniques that evaluated a range of surgical treatments were included and summarized. The literature was considered heterogeneous and insufficient to evaluate the comparative effectiveness of surgical treatments compared to other treatments. Several surgical studies reported complications including but not limited to infections, nonunion, further surgery, and intraoperative fracture. Studies had small sample sizes and provided little information on determining successful fusion.

In 2010, Ashman[7] conducted a systematic review comparing fusion to denervation for chronic SI joint pain. Six case series on fusion were identified that evaluated a single treatment. As a result, no conclusions could be drawn for the comparative efficacy of the treatments.

Randomized Controlled Trials

No RCTs identified after the above SRs were published.

SIJ FUSION/FIXATION WITH A TRIANGULAR IMPLANT SYSTEM

Systematic Reviews

Chang (2022) published a systematic review of forty studies evaluating the use of minimally invasive SI joint fusion.[8] Minimally invasive SI joint fusion with the iFuse Implant System appeared to result in larger improvements in pain (two RCTs: MD for VAS -40.5 mm, 95% CI, -50.1 to -30.9; -38.1 mm, p<.0001) and larger improvements in physical function (mean difference in Oswestry Disability Index -25.4 points, 95% CI, -32.5 to -18.3; -19.8 points, p<.0001) compared to conservative management at six months. Improvements in pain and physical function for the RCTs appeared durable at one and two years of follow-up. Findings were similar in one CCS. The two RCTs also found significant improvements in QOL at six months and one year. AEs appeared higher in the fusion group at six months. The incidence of revision surgery varied by study; the highest was 3.8% at two years. Two CCSs compared the

effectiveness of alternative minimally invasive fusion procedures. One CCS compared iFuse to the Rialto SI Fusion System and reported no differences in pain, function, QOL, and revision surgeries from six months to one year. One CCS compared iFuse to percutaneous screw fixation and reported significantly fewer revisions among iFuse participants (mean difference -61.0%, 95% CI, -78.4% to -43.5%).

Hermans (2022) published a systematic review comparing minimally invasive joint fusion using titanium implants to conservative management in patients with SI joint dysfunction.[9] Three studies that included 388 patients were part of the review. The results from the pooled analysis showed that the fusion patients showed greater reduction in visual analog pain score and ODI outcomes compared to the ones who received conservative management. Adverse events reported across the studies were similar for both groups. The results of the study indicate that minimally invasive joint fusion is more effective than conservative management in patients with SIJ dysfunction.

Abbas (2022) published a systematic review evaluating the efficacy of SIJ fusion for low back pain caused by SIJ pathology.[10] Six studies were included with a total of 564 patients who received either SIJ fusion or conservative management. The results showed that the SIJ fusion patients had greater reductions in VAS and ODI outcomes compared to those receiving conservative management.

Tran (2019) published a systematic review comparing the effectiveness of minimally invasive joint fusion (e.g. utilizing the iFuse device) compared to screw-type surgeries. A total of twenty studies was pooled to calculate a standardized mean difference across pain, disability, and global/quality-of-life outcomes, including 14 studies evaluation the iFuse system and 7 studies evaluated cylindrical, threaded implants. Studies evaluating cylindrical threaded implants consisted of case series and cohort studies. Patients receiving these implants experienced significantly worse pain outcomes (p=0.03) compared to patients receiving iFuse, with a standardized mean difference of 1.28 and 2.04, respectively. A statistically significant difference in disability scores was reported between screw-type and iFuse implant groups (0.26 vs 1.68), with improved outcomes in the iFuse population. For global/quality-of-life outcomes, a statistically significant difference in scores was reported between screw-type and iFuse implants groups (0.60 vs 0.99 with improved outcomes in the iFuse population.

Heiney (2015) evaluated clinical outcomes and operative measures of minimally invasive sacroiliac joint fusion utilizing a lateral transarticular technique.[11] A total of 12 studies, including those for triangular implants were included. The authors concluded, for this particular technique, patients reported improvements in pain, disability, and quality of life scores.

Randomized Controlled Trials

Whang (2015) reported an industry-sponsored nonblinded RCT of the iFuse Implant System in 148 patients.[12] Twelve-month follow-up to this RCT was reported by Polly et al in 2015.[13] However, by 12 months, almost all patients in the control group had crossed over to SI JOINT fusion. Two-year follow-up of this trial was reported by Polly et al in 2016.[14] This last publication will be discussed in the case series section of this report. Trial inclusion was based on a determination of the SI JOINT as a pain generator from a combination of a history of SI JOINT-localized pain, positive provocative testing on at least three of five established physical tests, and at least a 50% decrease in SI JOINT pain after image-guided local anesthetic injection into the SI JOINT. The duration of pain before enrollment averaged 6.4 years (range,

0.47-40.7 years). A large proportion of subjects (37%) had previously undergone lumbar fusion, steroid SI JOINT infections (86%), and RFA (16%).

Patients were assigned 2:1 to minimally invasive SI joint fusion (n=102) or to nonsurgical management (n=46). Nonsurgical management included a stepwise progression of nonsurgical treatments, depending on individual patient choice. During follow-up, control patients received physical therapy (97.8%), intra-articular steroid injections (73.9%), and RFA of sacral nerve roots (45.7%). The primary outcome measure was six-month success rate, defined as the proportion of treated subjects with a 20-mm improvement in SI JOINT pain in the absence of severe device-related or neurologic adverse events or surgical revision. Patients in the control arm could crossover to surgery after six months. Baseline scores indicated that the patients were severely disabled, with VAS pain scores averaging 82.3 out of 100 and ODI scores averaging 61.9 out of 100 (0=no disability, 100=maximum disability).

At six months, success rates were 23.9% in the control group versus 81.4% in the surgical group (posterior probability of superiority >0.999). A clinically important (≥15-point) improvement in ODI score was found in 27.3% of controls compared with 75.0% of fusion patients. Measures of QOL (36-Item Short-Form Health Survey, EuroQol-5D) also improved to a greater extent in the surgery group. Of the 44 nonsurgical management patients still participating at six months, 35 (79.5%) crossed over to fusion. Compared to baseline, opioid use at six months decreased from 67.6% to 58% in the surgery group, and increased from 63% to 70.5% in the control group (p=0.082). At 12 months, opioid use was similar between groups (55% vs 52%, p=0.61). Although these results generally favored fusion, the trial is limited due to the high number of patients that crossed over from the control group to the fusion group. This limits the comparative long-term conclusions that can be drawn.

Sturesson (2016) reported another industry-sponsored nonblinded RCT of the iFuse Implant System in 103 patients.[15] Selection criteria were similar to those of the Whang trial, including at least 50% pain reduction on SI JOINT block. Mean pain duration was 4.5 years. Thirty-three percent of patients had undergone prior lumbar fusion. Nonsurgical management included physical therapy and exercises at least twice per week; interventional procedures (eg, steroid injections, RFA) were not allowed. The primary outcome was change in VAS pain score at six months.

Of 109 randomized subjects, six withdrew before treatment. All patient assigned to iFuse underwent the procedure, and follow-up at six months was in 49 of 51 patients in the control group and in all 52 patients in the iFuse group. At six months, VAS pain scores improved by 43.3 points in the iFuse group and by 5.7 points in the control group (p<0.001). ODI scores improved by 25.5 points in the iFuse group and by 5.8 points in the control group (p<0.001, between groups). QOL outcomes showed a greater improvement in the iFuse group than in the control group. Changes in pain medication use are not reported. Although these results favored fusion, with magnitudes of effect in a range similar to the Whang RCT, this trial was also not blinded and lacked a sham control. Outcomes were only assessed to six months. Six-month results for the Whang and Sturesson trials are shown in Table 1.

Table 1. Summary of 6-Month iFuse Results From Whang et al[12] and Sturesson et al[15]

Results	VAS Score		Success End Point		ODI Score		SF 36 PCS Score		EQ 5D TTO Index	
	Ctl	iFuse	Ctl	iFuse	Ctl	iFuse	Ctl	iFuse	Ctl	iFuse
Whang et al (2015)										
Baseline	82.2	82.3			61.1	62.2	30.8	30.2	0.47	0.44

Results	VAS Score		Success End Point		ODI Score		SF 36 PCS Score		EQ 5D TTO Index	
Follow-up	70.4	29.8	23.9%	81.4%[a]	56.4	31.9	32.0	42.8	0.52	0.72
Change	-12.1	-52.6[a]			-4.9	-30.3[a]	1.2	12.7	0.05	0.29
Sturesson et al (2016)										
Baseline	73.0	77.7								
Follow-up	67.8	34.4								
Change	-5.7	-43.3			-5.8	-25.5			0.11	0.37

The success end point was defined as a reduction in pain VAS score of ≥20, absence of device-related events, absence of neurologic worsening, and absence of surgical intervention.
Ctl: control; EQ-5D TTO: EuroQoL Time Tradeoff Index; ODI: Oswestry Disability Index; SF-36 PCS: 36-Item Short-Form Health Survey Physical Component Summary; VAS: visual analog scale.
[a] p<0.001.

Nonrandomized Studies

The Long Term Outcomes from INSITE and SIFI (LOIS) trial was a prospective single-arm study that enrolled patients who had participated in two of the studies described above for evaluation at three, four, and five years.[16] The primary success outcome, a reduction in VAS of at least 20 points in the absence of a serious device-related adverse event, neurologic worsening, or surgical revision, was obtained in 81.7% of patients at five years. The improvements in other clinical outcomes were maintained out to 5 years. Opioid use decreased over time, although the contribution of the opioid use agreement cannot be determined. Fifteen percent of patients were no working due to back pain. Radiolucencies suggesting implant failure were observed in 5% of cases and were associated with incorrect placement. Bridging bone was observed in 45% of sides at 12 months, 71% at 24 months, and 88% at 60 months.

The Study of Bone Growth in the Sacroiliac Joint after Minimally Invasive Surgery with Titanium Implants (SALLY) is a 5 year multicenter study that will assess non-inferiority of outcomes with a 3-D printed triangular implant as compared to the traditionally manufactured titanium coated implant.[17] Twelve month follow-up has been published for 46 of the 51 patients enrolled. The 6-month change in ODI met the non-inferiority margin, and secondary outcomes of pain, disability, and QOL were similar to those obtained in the INSITE, iMIA, and SIFI trials. Independent radiographic analysis showed bridging bone in 70% and 77% of sides imaged at 6 and 12 months, respectively, compared to 45% bridging bone in prior studies with the solid titanium coated implants. No breakage, migration, or subsidence was detected. However, there was no evidence that the increase in bridging bone led to an improvement in pain or functional outcomes compared to the milled implant at 12 months.

Two retrospective nonrandomized comparative studies were published in 2017. Vanaclocha (2017) found greater pain relief with SIJ fusion than with conservative management or SIJ denervation. [18] Spain and Holt (2017) reported a retrospective review of surgical revision rates following SIJ fixation with either surgical screws or the iFuse triangular implant. [19]Revision rates were lower with the iFuse device than observed with surgical screws.

Twelve-month results from the iMIA trial were reported by Dengler (2017).[20] Twenty-one patients in the conservative management group had little or no improvement in symptoms and crossed over to SIJ fusion after the 6-month visit. Fourteen (56%) of the 25 patients who remained in the conservative management group had at least a 20-point improvement in VAS back pain score (22.4% of patients assigned to conservative management). At 12 months, low back pain had improved by 42 points (SD=27.0) on a 100-point VAS in the SIJ fusion group compared with 14 (SD=33.4) points in the conservative management group (p<0.001). The

authors noted that there were methodological limitations including lack of blinding and subjective assessments of outcomes.

At 24 months back pain had improved by 45 points compared to 11 points in the control group, with 79% (37 of 47) of SIJ fusion patients achieving at least a 20 point improvement compared to 24% (11 of 46) of controls.[21] At 24 months there was an improvement of 26 points in ODI compared to 8 points in controls (p<0.001). Improvement of at least 20 points was observed in 64% of SIJ fusion group compared to 24% of the conservative management group.

Table 2. Extended Follow-Up From the INSITE and iMIA Trials

Outcome Measures	Baseline	6 Months (SD)	12 Months (SD)	24 Months (SD)
INSITE[22]				
Sacroiliac joint fusion pain score	82.3	29.8		26.7
Percent ≥20-point improvement pain				
Sacroiliac joint fusion ODI score	57.2	31.9		28.7
iMIA[20]				
Conservative management	73.0 (13.8)	67.8 (20.3)	58.9 (28.2)	
Leg pain				
Sacroiliac joint fusion	52.7 (31.5)	22.6 (25.1)	24.0 (27.8)	
Conservative management	55.6 (13.7)	50.2 (17.2)	46.9 (20.8)	
	57.5 (14.4)	32.0 (18.4)	32.1 (19.9)	

Adapted from Dengler et al (2017).[20]
ODI: Oswestry Disability Index.

Case Series With Good Reported Follow-Up Rates

Case series with good follow-up rates are more likely to provide valid estimates of outcomes. Principal results of the studies at 2- to 3-year follow-up are shown in Table 3.

Polly (2016) reported two-year outcomes from the RCT of SI JOINT fusion.[14] When reported, without an untreated control group, the study was a case series. Of 102 subjects originally assigned to SI JOINT fusion and treated, 89 (87%) were evaluated at two years. Although the clinical trial used a different composite end point, in this report, clinical outcomes were based on the amount of improvement in SI JOINT pain and in ODI scores. Improvement was defined as a change of 20 points in SI JOINT pain score and 15 points in ODI score. Substantial improvement was defined as a change in in 25 points in SI JOINT pain score or a score of 35 or less and an improvement of 18.8 points in ODI score. At 24 months, 83.1% and 82% had improvement and substantial improvement in SI JOINT pain score, and 68.2% and 65.9% had improvement and substantial improvement in ODI. By 24 months, the proportion taking opioids was reduced from 68.6% at baseline to 48.3%.

Results from a case series of 172 patients undergoing SI JOINT fusion reported to two years were published by Duhon (2016).[23, 24] Patients were formally enrolled in a single-arm trial (NCT01640353) with planned follow-up for 24 months. Success was defined as a reduction of VAS pain score of 20 mm (out of 100 mm), absence of device-related adverse events, absence of neurologic worsening, and absence of surgical reintervention. Enrolled patients had a mean VAS pain score of 79.8, a mean ODI score of 55.2, and had a mean pain duration of 5.1 years. At six months, 136 (80.5%) of 169 patients met the success end point, which met

the prespecified Bayesian probability of success rate. Mean VAS pain scores were 30.0 at six months and 30.4 at 12 months. Mean ODI scores were 32.5 at six months and 31.4 at 12 months. At two years, 149 (87%) of 172 patients were available for follow-up. VAS pain score at two years was 26.0 and ODI score was 30.9. Thus, 1-year outcomes were maintained at two years. Other outcomes (eg, QOL scores) showed similar maintenance or slight improvement compared to 1-year outcomes. Use of opioid analgesics decreased from 76.2% at baseline to 55% at two years. Over the 2-year follow-up, 8 (4.7%) patients required revision surgery.

Rudolph and Capobianco (2014) described 5-year follow-up for 17 of 21 consecutive patients treated at their institution between 2007 and 2009.[25] Of the four patients lost to follow-up, two had died and one had become quadriplegic due to severe neck trauma. For the remaining patients, mean VAS score (range, 0-10) improved from 8.3 before surgery to 2.4 at five years; 88.2% of patients had substantial clinical benefit, which was defined as a 2.5-point decrease in VAS score or a raw score less than 3.5. Mean ODI score at five years was 21.5. Imaging by radiograph and computed tomography showed intra-articular bridging in 87% of patients with no evidence of implant loosening or migration.

Rudolf (2012) retrospectively analyzed his first 50 consecutive patients treated with the iFuse Implant System.[26] There were 10 perioperative complications, including implant penetration into the sacral neural foramen (two patients) and compression of the L5 nerve (1 patient); these three patients required surgical retraction of the implant. At three years postsurgery, 1 patient required additional implants due to worsening symptoms. At a minimum of 24 months of follow-up (mean, 40 months), the treating surgeon was able to contact 45 patients. The mean pain score was two (1 to 10 scale), and 82% of patients had attained the minimal clinically important difference in pain score (defined as ≥ 2 of 10).

Case Series With Unknown Follow-Up Rates

The following case series did not report follow-up rates or study methodologies did not permit calculation of the complete number of patients treated.

Smith (2013) retrospectively compared open with minimally invasive SI JOINT fusion. Because all patients received fusion, this study should be interpreted as a case series, with attention paid to the minimally invasive fusion group.[27] Only patients with medical records documenting 12- or 24-month pain scales were included, resulting in 114 patients selected for the minimally invasive group. Losses to follow-up could not be determined. At 12 months, VAS pain scores decreased to a mean of 2.3 from a baseline of 8.1. At 24 months, mean VAS pain score was 1.7, but data for only 38 patients were analyzed. These improvements in VAS pain score were greater than those for open fusion, but conclusions of comparative efficacy should not be made given this type of study. Implant repositioning was performed in 3.5% of patients in the minimally invasive group.

A large (N=144) industry-sponsored, multicenter retrospective series was reported by Sachs et al in 2014.[28] Consecutive patients from 6 sites were included if preoperative and 12-month follow-up data were available. No information was provided on the total number of patients treated during the same time interval. Mean baseline pain score was 8.6. At a mean 16-month follow-up, VAS score was 2.7 (/10), an improvement of 6.1. Ten percent of patients reported an improvement of 1 point or less. Substantial clinical benefit, defined as a decrease in pain score by more than 2.5 points or a score of 3.5 or less, was reported in 91.9% of patients.

Sachs (2016) reported outcomes of 107 patients with a minimum follow-up of 3 years.[29] The number of potentially eligible patients was not reported, so the follow-up rate is unknown. Pain scores improved from a mean of 7.5 at baseline to 2.5 at a mean follow-up time of 3.7 years. ODI score at follow-up was 28.2, indicating moderate residual disability. Overall satisfaction rate was 87.9% (67.3% very satisfied, 20.6% somewhat satisfied). Revision surgery was reported in five (4.7%) patients. Without knowing the number of eligible patients, the validity of this study cannot be determined.

Table 3. Two- to 3-Year Outcomes of the iFuse Implant in Cohorts and Case Series

Studies and Outcomes	Mean Baseline Value	Mean 2- to 3-Year Value	Difference or % Achieving Outcome	Follow-Up Rate
Pain score (range, 0-10)	7.59	2.0	5.59	90% (45/50)
Duhon et al (2016)[23]				
	79.8		53.3	
Oswestry Disability Index score	55.2	30.9	24.5	
		40.7	8.9	
EQ-5D TTO score	0.43	0.71	0.27	
Pain score (range 0-10)	7.5	2.5		
		28.2		

All differences between baseline and 2- to 3-year values were statistically significant.
EQ-5D TTO Index: EuroQoL Time Tradeoff Index; SF-36: 36-Item Short-Form Health Survey.

Database Analysis

Schoell (2016) analyzed postoperative complications tracked in an administrative database of minimally invasive SIJ fusions to determine complications coded in postoperative claims. Using the Humana insurance database, patients with complications were identified using ICD-9 codes corresponding to a surgical complication within 90 days or 6 months if the codes were used for the first time. Of 469 patients, the overall incidence of complications was 13.2% at 90 days and 16.4% at 6 months. For specific complications, the infection rate was 3.6% at 90 days and the rate of complications classified as nervous system complications was 4.3%. Authors noted that the infection rate observed was consistent with the infection rates reported by Polly et al (2015), 20 but much higher than those reported for other types of minimally invasive spine procedures. The incidence of complications in this study may differ from those reported by registries. However, determining the true incidence of adverse events after procedures from either registries or insurance claims data can be difficult due to uncertainty about the completeness of reporting in registries and the accuracy of coded claims in claims databases.

Cher (2015) reported rates of implant revision using the Humana insurance database of procedures.[30] Between April 2009 and July 2014, 11,416 cases with the iFuse system took place. After minor adjustments of numbers to account for non-recommended uses and inability to match revision cases, the cumulative revision rate at 4 years was 3.54%. Overall, 24% of revision surgeries occurred in the first month and 63% occurred within the first 12 months. One-year revision rates fell over time (9.7% to 1.4% from 2009 to 2014).

Adverse Events

From 9/1/2016 to 12/8/2017 a total of 47 MAUDE database injury reports were identified

(product code OUR). Many reports were for revisions needed and/or user error/wrong placement e.g. too deep, wrong size device, with a few noting infection or hematoma.

From January 2010 through August 2016, a total of 438 MAUDE database injury reports were identified (product code OUR): 355 mentioned revision, 188 malposition, 32 radicular pain, 24 impingement or impingement, and 14 infection.

Summary

For individuals who SIJ pain who receive SIJ fusion/fixation with a triangular implant, the evidence includes two non-blinded RCTs of minimally invasive fusion and 2 case series with more than 85% follow-up at 2 to 3 years. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. Both RCTs reported superior short-term results for fusion, however, a preferable design for assessing pain outcomes would be independent, blinded assessment of outcomes or, when feasible, a sham-controlled trial. Longer term follow-up from these RCTs indicated that the results obtained at six months persist to two years. Two additional cohort studies or case series, with sample sizes ranging from 45 to 149 patients and low dropout rates (<15%), have also shown reductions in pain and disability at two years. One small case series showed outcomes that persisted to five years. The cohort studies and case series are consistent with the durability of treatment benefit. Analysis of an insurance database reported an overall incidence of complications to be 16.4% at six months and cumulative revision rate at four years of 3.54%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SIJ FUSION/FIXATION WITH A CYLINDRICAL THREADED IMPLANT

Systematic Reviews

No systematic reviews identified for SIJ Fusion/Fixation with a Cylindrical Threaded Implant that are not already addressed.

Randomized Controlled Trials

Rappoport (2017) reported on an industry-sponsored prospective study of SIJ fusion with a cylindrical threaded implant (SI-LOK).[31] The study included 32 patients with a diagnosis of SIJ dysfunction who had failed nonoperative treatment, including medication, physical therapy, and therapeutic injections. A diagnostic injection was performed to confirm the source of pain to the SIJ. The procedure included drilling to prepare for screw insertion and implantation of three screws, at least one of which was slotted. The slotted screws were packed with autogenous bone graft from the drill reamings. Pain and disability scores were reduced following device implantation, and revisions within the first 12 months of the study were low (n=2). Follow-up will continue through two years

Table 4. Pain and Disability Scores After Implantation With a Cylindrical Threaded Implant

Outcome Measures	Baseline	3 Months (SD)	6 Months (SD)	12 Months (SD)	p
Low back pain	55.8 (26.7)	28.5 (21.6)	31.6 (26.9)	32.7 (27.4)	<0.01
Left leg pain	40.6 (29.5)	19.5 (22.9)	16.4 (25.6)	12.5 (23.3)	<0.01
Right leg pain	40.0 (34.1)	18.1 (26.3)	20.6 (25.4)	14.4 (21.1)	<0.05
Oswestry Disability Index	55.6 (16.1)	33.3 (16.8)	33.0 (16.8)	34.6 (19.4)	<0.01

Adapted from Rappoport et al (2017).[31]

Summary

There is limited evidence on fusion of the SIJ with devices other than the triangular implant. One-year results from a prospective cohort of 32 patients who received a cylindrical slotted implant showed reductions in pain and disability similar to results obtained for the triangular implant. However, there is uncertainty in the health benefit of SIJ fusion/fixation with this implant design. Therefore, controlled studies with a larger number of patients and longer follow-up are needed to evaluate this device.

PRACTICE GUIDELINE SUMMARY

NORTH AMERICAN SPINE SOCIETY

The North American Spine Society (NASS) published coverage recommendations for percutaneous sacroiliac joint fusion in 2015.[32] NASS indicated that there was relatively moderate evidence. In the absence of high-level data, policies reflect the multidisciplinary experience and expertise of the committee members in order to present reasonable standard practice indications in the United States. NASS recommended coverage when all of the following criteria are met:

1. "[Patients] have undergone and failed a minimum 6 months of intensive nonoperative treatment that must include medication optimization, activity modification, bracing and active therapeutic exercise targeted at the lumbar spine, pelvis, SI JOINT and hip including a home exercise program.
2. Patient's report of typically unilateral pain that is caudal to the lumbar spine (L5 vertebra), localized over the posterior SI JOINT, and consistent with SI JOINT pain.
3. A thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, ie, at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) in the absence of tenderness of similar severity elsewhere (eg, greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.
4. Positive response to a cluster of 3 provocative tests (eg, thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test). Note that the thrust test is not recommended in pregnant patients or those with connective tissue disorders.
5. Absence of generalized pain behavior (eg, somatoform disorder) or generalized pain disorders (eg, fibromyalgia).
6. Diagnostic imaging studies that include ALL of the following:
    a. Imaging (plain radiographs and a CT [computed tomography] or MRI [magnetic resonance imaging]) of the SI joint that excludes the presence of destructive lesions (eg, tumor, infection) or inflammatory arthropathy that would not be properly addressed by percutaneous SI JOINT fusion.
    b. Imaging of the pelvis (AP [anteroposterior] plain radiograph) to rule out concomitant hip pathology.
    c. Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain.
    d. Imaging of the SI joint that indicates evidence of injury and/or degeneration.

7. At least 75% reduction of pain for the expected duration of the anesthetic used following an image-guided, contrast-enhanced intra-articular SI JOINT injection on 2 separate occasions.
8. A trial of at least one therapeutic intra-articular SI JOINT injection (ie, corticosteroid injection)."

INTERNATIONAL SOCIETY FOR THE ADVANCEMENT OF SPINE SURGERY

The International Society for the Advancement of Spine Surgery (ISASS) published a policy statement on minimally invasive sacroiliac joint fusion. These recommendations were updated in 2016.[33] ISASS lists criteria for determining a patient's eligibility regarding minimally invasive SI joint fusion. However, the statement has several limitations including but not limited to the literature review methods are not transparent, there is no formal assessment of the quality of the evidence, and there is not a clear link between the recommendations and supporting evidence. ISASS recommendations state that patients who have all of the following criteria may be eligible for minimally invasive SI JOINT fusion:

- "Significant SI joint pain … or significantly limitations in activities of daily living because of pain from the SI joint(s).
- "SI joint pain confirmed with … at least three positive physical provocation examination maneuvers that stress the SI joint.
- "Confirmation of the SI joint as a pain generator with ≥ 75% acute decrease in pain immediately following fluoroscopically guided diagnostic intra-articular SI joint block using local anesthetic.
- "Failure to respond to at least six months of non-surgical treatment consisting of non-steroidal anti-inflammatory drugs and/or … one or more of the following: … physical therapy…. Failure to respond means continued pain that interferes with activities of daily living and/or results in functional disability;
- "Additional or alternative diagnoses that could be responsible for the patient's ongoing pain or disability have been considered, investigated and ruled out."

AMERICAN SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS (ASIPP)

The ASIPP guidelines published in 2013 have a recommendation for diagnostic sacroiliac joint injections which were based on a systematic review of the evidence.[1] The guideline indicates that sacroiliac joint blocks appear to be the evaluation of choice to provide appropriate diagnosis, due to the inability to make the diagnosis of sacroiliac joint-mediated pain with noninvasive tests. The ASIPP guidelines conclude and recommend the following for diagnostic sacroiliac joint blocks:

- The evidence for diagnostic intraarticular sacroiliac joint injections is good with 75% to 100% pain relief as the criterion standard with controlled local anesthetic or placebo blocks, and fair due to the limitation of the number of studies with 50% to 74% relief with a dual block.

- Controlled sacroiliac joint blocks with placebo or controlled comparative local anesthetic blocks are recommended when indications are satisfied with suspicion of sacroiliac joint pain.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS TASK FORCE ON CHRONIC PAIN MANAGEMENT AND THE AMERICAN SOCIETY OF REGIONAL ANESTHESIA AND PAIN MEDICINE PRACTICE

In 2010, the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine Practice updated their guidelines for chronic pain management.[34] The guidelines recommend that diagnostic sacroiliac joint injections or lateral branch blocks may be considered for the evaluation of patients with suspected sacroiliac joint pain.

AMERICAN PAIN SOCIETY (APS)

The 2009 practice guidelines from the APS were based on a systematic review that was commissioned by the APS and conducted at the Oregon Evidence-based Practice Center.[3, 35] The APS guideline states that there is insufficient evidence to evaluate the validity or utility of diagnostic sacroiliac joint block as a diagnostic procedure for low back pain with or without radiculopathy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

NICE guidance was published in April 2017 on minimally invasive SIJ fusion surgery for chronic sacroiliac pain.[36] The recommendations included:

1.1 “Current evidence on the safety and efficacy of minimally invasive sacroiliac (SI) joint fusion surgery for chronic SI pain is adequate to support the use of this procedure…..

1.2 Patients having this procedure should have a confirmed diagnosis of unilateral or bilateral SI joint dysfunction due to degenerative sacroiliitis or SI joint disruption.

1.3 This technically challenging procedure should only be done by surgeons who regularly use image-guided surgery for implant placement. The surgeons should also have had specific training and expertise in minimally invasive SI joint fusion surgery for chronic SI pain.

SUMMARY

Sacroiliac joint fusion or fixation performed by open procedure is considered standard of care for traumatic injuries, tumors involving the sacrum, and SI joint infection/sepsis as outlined in the Medical Policy Criteria and therefore may be considered medically necessary. Sacroiliac joint fusion performed by an open procedure for any other indication is considered not medically necessary.

There is enough research to show that minimally invasive fusion/stabilization of the sacroiliac joint using an FDA-approved titanium triangular implant improves health outcomes. Additionally, clinical guidelines based on research recommend the use of minimally invasive fusion/stabilization of the sacroiliac joint using a titanium triangular implant. Therefore, minimally invasive fusion/stabilization of the sacroiliac joint using an FDA-approved titanium triangular implant may be considered medically necessary when policy criteria are met.

There is not enough research to show that minimally invasive fusion/stabilization of the sacroiliac joint using any other device or when policy criteria are not met improves health

outcomes including but not limited to the use of a non-FDA approved device or a device that is not a titanium triangular implant. Therefore, minimally invasive fusion/stabilization of the sacroiliac joint using any other device including but not limited to a non-FDA approved device or a device that is not a titanium triangular implant or when policy criteria are not met is considered investigational.

REFERENCES

1. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain physician.* 2013;16(2 Suppl):S49-283. PMID: 23615883
2. Simopoulos TT, Manchikanti L, Singh V, et al. A systematic evaluation of prevalence and diagnostic accuracy of sacroiliac joint interventions. *Pain physician.* 2012;15(3):E305-44. PMID: 22622915
3. Chou R, Atlas SJ, Stanos SP, et al. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976).* 2009;34(10):1078-93. PMID: 19363456
4. Lingutla KK, Pollock R, Ahuja S. Sacroiliac joint fusion for low back pain: a systematic review and meta-analysis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2016;25(6):1924-31. PMID: 26957096
5. Zaidi HA, Montoure AJ, Dickman CA. Surgical and clinical efficacy of sacroiliac joint fusion: a systematic review of the literature. *Journal of neurosurgery Spine.* 2015;23(1):59-66. PMID: 25840040
6. Spiker WR, Lawrence BD, Raich AL, et al. Surgical versus injection treatment for injection-confirmed chronic sacroiliac joint pain. *Evid Based Spine Care J.* 2012;3(4):41-53. PMID: 23526911
7. Ashman B, Norvell DC, Hermsmeyer JT. Chronic sacroiliac joint pain: fusion versus denervation as treatment options. *Evid Based Spine Care J.* 2010;1(3):35-44. PMID: 22956926
8. Chang E, Rains C, Ali R, et al. Minimally invasive sacroiliac joint fusion for chronic sacroiliac joint pain: a systematic review. *The spine journal : official journal of the North American Spine Society.* 2022;22(8):1240-53. PMID: 35017057
9. Hermans SMM, Droeghaag R, Schotanus MGM, et al. Minimally Invasive Sacroiliac Joint Fusion vs Conservative Management in Patients With Sacroiliac Joint Dysfunction: A Systematic Review and Meta-Analysis. *International journal of spine surgery.* 2022;16(3):472-80. PMID: 35772982
10. Abbas A, Du JT, Toor J, et al. The efficacy of primary sacroiliac joint fusion for low back pain caused by sacroiliac joint pathology: a systematic review and meta-analysis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2022. PMID: 35768617
11. Heiney J, Capobianco R, Cher D. A systematic review of minimally invasive sacroiliac joint fusion utilizing a lateral transarticular technique. *International journal of spine surgery.* 2015;9:40. PMID: 26273558
12. Whang P, Cher D, Polly D, et al. Sacroiliac joint fusion using triangular titanium implants vs. non-surgical management: six-month outcomes from a prospective randomized controlled trial. *International journal of spine surgery.* 2015;9:6. PMID: 25785242

13. Polly DW, Cher DJ, Wine KD, et al. Randomized controlled trial of minimally invasive sacroiliac joint fusion using triangular titanium implants vs nonsurgical management for sacroiliac joint dysfunction: 12-month outcomes. *Neurosurgery.* 2015;77(5):674-91. PMID: 26291338
14. Polly D, Swofford J, Whang P, et al. Two-year outcomes from a randomized controlled trial of minimally invasive sacroiliac joint fusion vs non-surgical management for sacroiliac joint dysfunction. *International journal of spine surgery.* 2016;10:22. PMID:
15. Sturesson B, Kools D, Pflugmacher R, et al. Six-month outcomes from a randomized controlled trial of minimally invasive SI joint fusion with triangular titanium implants vs conservative management. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2016. PMID: 27179664
16. Whang PG, Darr E, Meyer SC, et al. Long-Term Prospective Clinical And Radiographic Outcomes After Minimally Invasive Lateral Transiliac Sacroiliac Joint Fusion Using Triangular Titanium Implants. *Medical devices (Auckland, NZ).* 2019;12:411-22. PMID: 31576181
17. Patel V, Kovalsky D, Meyer SC, et al. Prospective Trial of Sacroiliac Joint Fusion Using 3D-Printed Triangular Titanium Implants. *Medical devices (Auckland, NZ).* 2020;13:173-82. PMID: 32607011
18. Vanaclocha V, Herrera JM, Saiz-Sapena N, et al. Minimally Invasive Sacroiliac Joint Fusion, Radiofrequency Denervation, and Conservative Management for Sacroiliac Joint Pain: 6-Year Comparative Case Series. *Neurosurgery.* 2017. PMID: 28431026
19. Spain K, Holt T. Surgical Revision after Sacroiliac Joint Fixation or Fusion. *International journal of spine surgery.* 2017;11:5. PMID: 28377863
20. Dengler JD, Kools D, Pflugmacher R, et al. 1-Year Results of a Randomized Controlled Trial of Conservative Management vs. Minimally Invasive Surgical Treatment for Sacroiliac Joint Pain. *Pain physician.* 2017;20(6):537-50. PMID: 28934785
21. Dengler J, Kools D, Pflugmacher R, et al. Randomized Trial of Sacroiliac Joint Arthrodesis Compared with Conservative Management for Chronic Low Back Pain Attributed to the Sacroiliac Joint. *The Journal of bone and joint surgery American volume.* 2019;101(5):400-11. PMID: 30845034
22. Polly DW, Swofford J, Whang PG, et al. Two-year outcomes from a randomized controlled trial of minimally invasive sacroiliac joint fusion vs non-surgical management for sacroiliac joint dysfunction. *International journal of spine surgery.* 2016;10:28. PMID: 27652199
23. Duhon BS, Bitan F, Lockstadt H, et al. Triangular titanium implants for minimally invasive sacroiliac joint fusion: 2-year follow-up from a prospective multicenter trial. *International journal of spine surgery.* 2016;10:13. PMID: 27162715
24. Duhon BS, Cher DJ, Wine KD, et al. Triangular titanium implants for minimally invasive sacroiliac joint fusion: a prospective study. *Global spine journal.* 2016;6(3):257-69. PMID: 27099817
25. Rudolf L, Capobianco R. Five-year clinical and radiographic outcomes after minimally invasive sacroiliac joint fusion using triangular implants. *The open orthopaedics journal.* 2014;8:375-83. PMID: 25352932
26. Rudolf L. Sacroiliac Joint Arthrodesis-MIS Technique with Titanium Implants: Report of the First 50 Patients and Outcomes. *The open orthopaedics journal.* 2012;6:495-502. PMID: 23284593

27. Smith AG, Capobianco R, Cher D, et al. Open versus minimally invasive sacroiliac joint fusion: a multi-center comparison of perioperative measures and clinical outcomes. *Ann Surg Innov Res.* 2013;7(1):14. PMID: 24172188
28. Sachs D, Capobianco R, Cher D, et al. One-year outcomes after minimally invasive sacroiliac joint fusion with a series of triangular implants: a multicenter, patient-level analysis. *Medical devices (Auckland, NZ).* 2014;7:299-304. PMID: 25210479
29. Sachs D, Kovalsky D, Redmond A, et al. Durable intermediate-to long-term outcomes after minimally invasive transiliac sacroiliac joint fusion using triangular titanium implants. *Medical devices (Auckland, NZ).* 2016;9:213-22. PMID: 27471413
30. Cher DJ, Reckling WC, Capobianco RA. Implant survivorship analysis after minimally invasive sacroiliac joint fusion using the iFuse Implant System((R)). *Medical devices (Auckland, NZ).* 2015;8:485-92. PMID: 26648762
31. Rappoport LH, Luna IY, Joshua G. Minimally Invasive Sacroiliac Joint Fusion Using a Novel Hydroxyapatite-Coated Screw: Preliminary 1-Year Clinical and Radiographic Results of a 2-Year Prospective Study. *World neurosurgery.* 2017;101:493-97. PMID: 28216399
32. North American Spine Society (NASS). NASS coverage policy recommendations: Percutaneous sacroiliac joint fusion. [cited 06/12/2023]. 'Available from:' https://www.spine.org/ProductDetails?productid=%7b9EAC3FC6-AF81-E611-851E-005056AF031E%7d.
33. International Society for the Advancement of Spinal Surgery (ISASS). ISASS policy 2016 update- minimally invasive sacroilliac joint fusion. [cited 06/12/2023]. 'Available from:' https://www.spine.org/Product-Details?productid=%7b9EAC3FC6-AF81-E611-851E-005056AF031E%7d.
34. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology.* 2010;112(4):810-33. PMID: 20124882
35. Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976).* 2009;34(10):1066-77. PMID: 19363457
36. (NICE) NIfHaCE. National Institute for Health and Care Excellence (NICE). Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain [IPG578]. [cited 08/16/2022]. 'Available from:' https://www.nice.org.uk/guidance/ipg578.

CODES

Codes	Number	Description
CPT	~~0775T~~	~~Arthrodesis, sacroiliac joint, percutaneous, with image guidance, includes placement of intra-articular implant(s) (eg, bone allograft[s], synthetic device[s])~~ (Deleted 01/01/2024)
	~~0809T~~	~~Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, placement of transfixing device(s) and intraarticular implant(s), including allograft or synthetic device(s)~~ (Deleted 01/01/2024)
	22899	Unlisted procedure, spine
	27096	Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed

Codes	Number	Description
	27278	Arthrodesis, sacroiliac joint, percutaneous, with image guidance, including placement of intra-articular implant(s) (eg, bone allograft[s], synthetic device[s]), without placement of transfixation device
	27279	Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device
	27280	Arthrodesis, sacroiliac joint, open, including obtaining bone graft, including instrumentation, when performed
	27299	Unlisted procedure, pelvis or hip joint
HCPCS	None	

Date of Origin: *December 2014*

Regence

Medical Policy Manual Surgery, Policy No. 195

Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation

Effective: March 1, 2024

Next Review: November 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Left atrial appendage (LAA) closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in atrial fibrillation.

MEDICAL POLICY CRITERIA

I. The use of the WATCHMAN or Amplatzer Amulet device for percutaneous left atrial appendage closure may be considered **medically necessary** for the prevention of stroke in patients with atrial fibrillation when the following criteria are met:
   A. There is an increased risk of stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc score and systemic anticoagulation therapy is recommended; and
   B. Clinical documentation that the patient is suitable for short-term anticoagulation but unable to take long-term oral anticoagulation.

II. The use of any other device for left atrial appendage closure or when Criterion I. is not met is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

The balance of risks and benefits associated with implantation of the Watchman device for stroke prevention, as an alternative to systemic anticoagulation with warfarin, must be made on an individual basis.

Bleeding is the primary risk associated with systemic anticoagulation. A number of risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in patients with atrial fibrillation treated with warfarin (Pisters et al, 2010). Scores range from 0 to 9, based on a number of clinical characteristics (see Table PG1).

Risk of major bleeding in patients with scores of 3, 4, and 5 has been reported at 3.74 per 100 patient-years, 8.70 per 100 patient-years, and 12.5 per 100 patient-years, respectively. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratio, or differential dose selections of oral anticoagulants or aspirin (January et al, 2014).

Table PG1. Clinical Components of the HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristics	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile international normalized ratios	1
E	Elderly (>65 y)	1

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could our impact review and decision outcome:

- History and Physical/Chart Notes
- Documentation of FDA approved device to be utilized
- Documentation that supports an increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc score and systemic anticoagulation therapy is recommended
- Documentation long-term risks of systemic anticoagulation outweigh the risks of the device implantation

CROSS REFERENCES

None

BACKGROUND

Stroke is the most serious complication of atrial fibrillation (AF). The estimated incidence of

stroke in untreated patients with AF is 5% per year. Stroke associated with AF is primarily embolic in nature, tends to be more severe than the typical ischemic stroke, and causes higher rates of mortality and disability. As a result, stroke prevention is one of the main goals of AF treatment.

Stroke in AF occurs primarily as a result of thromboembolism from the left atrium. The lack of atrial contractions in AF leads to blood stasis in the left atrium, and this low flow state increases the risk for thrombosis. The area of the left atrium with the lowest blood flow in AF, and therefore the highest risk of thrombosis, is the left atrial appendage (LAA). The LAA is the region responsible for an estimated 90% of left atrial thrombi.

The main treatment for stroke prevention in AF is anticoagulation, which has proven efficacy. The risk for stroke among patients with AF is stratified on the basis of several factors. A commonly used score, the CHADS2 score, assigns 1 point each for the presence of heart failure, hypertension, age 75 years or older, diabetes, or prior stroke or transient ischemic attack. The CHADS2-VASc score includes sex, more age categories, and the presence of vascular disease, in addition to the risk factors used in the CHADS2 score. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban, and apixaban, have recently received U.S. Food and Drug Administration (FDA) approval for stroke prevention in nonvalvular AF and have demonstrated noninferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, there is an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments, as well as lifestyle changes. Other anticoagulants e.g. apixaban and dabigatran do not require monitoring. However, unlike warfarin, the antithrombotic effects of these anticoagulants are not always reversible with hemostatic drugs. Guidelines from the American College of Chest Physicians recommend the use of oral anticoagulation for patients with AF who are at high risk of stroke (i.e., CHADS2 score ≥2), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.[1]

Bleeding is the primary risk associated with systemic anticoagulation. A number of risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin.[2] The score ranges from 0 to 9, based on a number of clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios (INRs), age, and drug/alcohol use. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of the patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin.[3]

Surgical removal, or exclusion, of the LAA is often performed in patients with AF who are undergoing open heart surgery for other reasons. Percutaneous LAA closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in AF. The devices may prevent stroke by occluding the LAA, thus preventing thrombus formation.

Several versions of LAA occlusion devices have been developed. The WATCHMAN™ left atrial appendage system (Boston Scientific, Maple Grove, MN) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system,

using venous access and transseptal puncture to enter the left atrium. Following implantation, patients are anticoagulated with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Lariat® Loop Applicator is a suture delivery device that is intended to close a variety of surgical wounds in addition to left atrial appendage closure. The Cardioblate® closure device developed by Medtronic is currently being tested in clinical studies. The Amplatzer® cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but not LAA closure device. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion device (eV3, Plymouth, MN) has also been evaluated in research studies but has not received FDA approval.

REGULATORY STATUS

In 2009, the WATCHMAN™ Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was originally considered by the FDA for approval based on the results the results of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) randomized controlled trial (RCT). The device underwent three panel reviews before it was approved by FDA through the premarket approval process in March 2015. This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with nonvalvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder (Abbott) received FDA approval in 2021 through the premarket approval process based on results from the Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial (Amulet IDE Trial).[4]

The Atriclip™ LAA Exclusion System was cleared for marketing by the FDA through the 510(k) process. The FDA indicates the device is indicated for the occlusion of the heart's left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial as well as thoracotomy (single or multiple).[5]

At least one other device has been studied for LAA occlusion, but are not approved in the US for percutaneous closure of the LAA. In 2006, the Lariat® Loop Applicator device (SentreHEART, Redwood City, CA), a suture delivery system, was cleared for marketing by the FDA through the 510(k) process. The intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture.

EVIDENCE SUMMARY

The standard treatment for stroke prevention in atrial fibrillation is anticoagulation, which has proven effectiveness. In order to determine the safety and effectiveness of left atrial

appendage (LAA) closure devices for the prevention of stroke in atrial fibrillation, large, well-designed randomized controlled trials (RCTs) that compare LAA to no therapy (patients with a prohibitive risk for oral anticoagulation), oral anticoagulation, or open surgical repair are needed. For chronic conditions such as atrial fibrillation, RCTs with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects.

The evidence on the efficacy of LAA closure devices consists of numerous nonrandomized studies of various occlusion devices, and two published RCTs of the WATCHMAN™ device that compared LAA closure with warfarin anticoagulation. The evidence for each device is summarized separately since the devices are not similar in design and may have unique considerations.

WATCHMAN™ DEVICE

The review of the evidence related to the efficacy of the WATCHMAN™ device is based, in part, on a Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014, which evaluated use of the WATCHMAN™ device for patients who were eligible and ineligible for anticoagulation therapy and determined that it does not meet Technology Evaluation Criteria.[6] In addition, the PROTECT-AF and the PREVAIL RCTs evaluated the WATCHMAN™ device. The PROTECT-AF study by Holmes reported outcomes for 18 months of follow-up.[7] Noninferiority criteria were met and then the results of the final analysis were published by Reddy at a mean follow-up of 2.3 years.[8] The FDA reviewed the trial data in 2009 but the data was at a slightly earlier time point than the Holmes analyses. The FDA revealed several concerns during their review that were not reported by the peer reviewed published evidence.[9] As a result, the FDA in coordination with the trial sponsors, developed the PREVAIL trial which had different entry criteria. Study participants from the PROTECT-AF trial were included in the analysis of the PREVAIL trial if they met inclusion criteria. The quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. BCBSA TEC assessment reports the following regarding the quality of the PROTECT-AF and PREVAIL trials:

> “Subject characteristics were balanced between groups. Losses to follow-up in the PROTECT-AF trial were not reported in peer-reviewed publications, and, according to FDA documents, appear to be unbalanced between treatment groups. Losses to follow-up are not clearly reported in FDA documents on the PREVAIL trial, but also appear to be unbalanced between treatment groups. Patients receiving the WATCHMAN™ device underwent more intensive surveillance for thrombosis after device implantation, and continued anticoagulation if concerns about thrombosis arose. Although this was part of the treatment protocol, it makes determinations of efficacy less certain, because there could be a benefit to imaging surveillance alone.”

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

Jaiswal (2023) published a systematic review of three RCTs comparing the WATCHMAN device to the Amplatzer Amulet device in patients having percutaneous LAAC.[10] A total of 2150 patients were included and results showed that the odds of experiencing procedure-related complications was significantly higher in the Amulet device group (OR 1.80 [1.21-2.67], p <0.001). The odds of all-cause mortality (OR, 0.75 (95% CI: 0.49–1.16), *p* = .20), stroke (OR, 0.79 [0.47–1.34], *p* = .39), systemic/pulmonary embolism (OR, 1.34 [0.30–6.04], *p* = .70), and major bleeding (OR, 1.10 [0.83–1.48], *p* = .50) were comparable between the two devices. The odds of device related thrombus (OR, 0.72 [0.46–1.14], *p* = .17) was comparable between both

the group of patients, however the incidence of peri device leak was significantly lower in AA group (OR, 0.41 [0.26–0.66], $p < .001$) compared with WATCHMAN group of patients.

Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014 evaluated the use of the WATCHMAN™ device for patients who were eligible and ineligible for anticoagulation therapy and determined that the WATCHMAN™ device did not meet Technology Evaluation Criteria. Although the WATCHMAN™ device and other LAA closure devices would ideally represent an alternative to oral anticoagulation for the prevention of stroke in patients with AF, during the postimplantation period, the device may be associated with increased thrombogenicity and, therefore, anticoagulation is used during the periprocedural period. Most studies evaluating the WATCHMAN™ device have included patients who are eligible for anticoagulation. There are two main RCTs for the WATCHMAN™ device and the quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. The TEC assessment made the following conclusions about the use of LAA closure in patients without contraindications to anticoagulation:

> "We identified two randomized controlled trials (RCTs) and one case series evaluating the WATCHMAN™ device. The RCTs were noninferiority trials and compared LAAC with anticoagulation. The first trial showed a lower rate of a composite outcome (stroke, death, and embolism) in patients receiving LAAC and met noninferiority criteria compared with anticoagulation, but FDA review noted problems with patient selection, potential confounding with other treatments, and losses to follow-up. The second trial, which incorporated the first trial's results as a discounted informative prior in a Bayesian analysis, showed similar rates of the same composite outcome but did not meet noninferiority criteria. The second trial met its second principal outcome noninferiority criteria in one of two analyses and a performance goal for short-term complication rate. When assessing the results of both trials, the relative performance of LAAC and anticoagulation is uncertain."[6]

In addition, the BCBSA TEC concluded that the evidence is insufficient to make conclusions about improvement in net health outcomes compared to established alternatives.

There are several meta-analyses but the most rigorous is a patient level meta-analysis by Holmes. Holmes (2015) reported results of a patient-level meta-analysis that included data from the industry-sponsored PROTECT AF and PREVAIL trials.[11] The PROTECT AF and PREVAIL registries were designed to include patients with similar baseline characteristics as their respective RCTs. The meta-analysis included a total of 2,406 patients, 1,877 treated with the WATCHMAN™ device and 382 treated with warfarin alone. Mean patient follow-up durations were 0.58 years and 3.7 years, respectively, for the PREVAIL continued access registry and the PROTECT AF continued access registry. In a meta-analysis of 1,114 patients treated in the RCTs, compared with warfarin, LAA closure met the study's noninferiority criteria for the primary composite efficacy end point of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2; p=0.22). All-cause stroke rates did not differ significantly between groups (1.75 per 100 patient-years for LAA closure vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7; p=0.94). However, LAA closure–treated patients had higher rates of ischemic stroke (1.6 events/100 patient-years vs 0.9 events/100 patient-years; HR=1.95, p=0.05) when procedure-related strokes were included, but had lower rates of hemorrhagic stroke (0.15

events/100 patient-years vs 0.96 events/100 patient-years; HR=0.22; 95% CI, 0.08 to 0.61; p=0.004).

A second patient-level meta-analysis of the two RCTs evaluated bleeding outcomes.[12] There were a total of 54 episodes of major bleeding, with the most common types being gastrointestinal (GI) bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the WATCHMAN™ group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio (RR) of 0.96 (95% CI, 0.66 to 1.40; p=0.84). However, there was a reduction in bleeding risk for the WATCHMAN™ group past the initial periprocedural period. For bleeding events occurring more than seven days postprocedure, the event rates were 1.8 per 100 patient-years in the WATCHMAN™ group compared with 3.6 per 100 patient-years in the anticoagulation group (RR=0.49; 95% CI, 0.32 to 0.75; p=0.01). For bleeding events occurring more than six months post procedure (the time at which antiplatelet therapy is discontinued for patients receiving the WATCHMAN™ device), the event rates were 1.0 per 100 patient-years in the WATCHMAN™ group compared with 3.5 per 100 patient-years in the anticoagulation group (RR=0.28; 95% CI, 0.16 to 0.49; p<0.001).

Randomized Controlled Trials

The first RCT published was the PROTECT AF study,[7] which was a randomized, unblinded trial that evaluated the noninferiority of an LAA closure device compared with warfarin for stroke prevention in AF. The trial randomized 707 patients from 59 centers in the United States and Europe to the WATCHMAN™ device or warfarin treatment in a 2:1 ratio. Mean follow-up was 18±10 months. The primary efficacy outcome was a composite end point of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite end point of excessive bleeding (intracranial or gastrointestinal [GI] bleeding) and procedure-related complications (pericardial effusion, device embolization, and procedure-related stroke). There were noted limitations to this study including inclusion of patients with low stroke risk (CHADS2 scores of 1), high rates of adjunctive antiplatelet therapy use in both groups, and generally poor compliance with warfarin therapy in the control group.

The primary efficacy outcome occurred at a rate of 3.0 per 100 patient years in the LAA closure group compared with 4.9 per 100 patient years in the warfarin group (rate ratio [RR], 0.62; 95% credible interval [CrI], 0.35 to 1.25). Based on these outcomes, the probability of noninferiority was greater than 99.9%. For the individual components of the primary outcome, cardiovascular/unexplained death and hemorrhagic stroke were higher in the warfarin group. In contrast, ischemic stroke was higher in the LAA closure group at 2.2 per 100 patient years compared with 1.6 per 100 patient years in the warfarin group (RR=1.34; 95% CrI, 0.60 to 4.29).

The primary safety outcome occurred more commonly in the LAA closure group, at a rate of 7.4 per 100 patient years compared with 4.4 per 100 patient years in the warfarin group (RR=1.69; 95% CrI, 1.01 to 3.19). The excess in adverse event rates for the LAA closure group was primarily the result of early adverse events associated with placement of the device. The most frequent type of complication related to LAA closure device placement was pericardial effusion requiring intervention, which occurred in 4.8% of patients (22/463).

Longer term follow-up from the PROTECT AF study was reported by Reddy (2013).[13] At a mean follow-up of 2.3 years, the results were similar to the initial report. The relative risk for the composite primary outcome in the WATCHMAN™ group compared with anticoagulation was 0.71, and this met noninferiority criteria with a confidence of greater than 99%. Complications were more common in the WATCHMAN™ group, with an estimated rate of 5.6%/year in the WATCHMAN™ group compared with 3.6%/year in the warfarin group. Outcomes through four years of follow-up were reported by Reddy et al in 2014.[14] Mean follow-up was 3.9 years in the LAA closure group and 3.7 years in the warfarin group. In the LAA closure group, warfarin was discontinued in 345 of 370 patients (93.2%) by the 12 month follow-up evaluation. During the follow-up period, the relative risk for the composite primary outcome in the WATCHMAN™ group compared with anticoagulation was 0.60 (8.4% in the device group vs 13.9% in the anticoagulation group; 95% CrI, 0.41 to 1.05), which met the noninferiority criteria with a confidence of greater than 99.9%. Fewer hemorrhagic strokes occurred in the WATCHMAN™ group (0.6% vs 4.0%; RR=0.15; 95% CrI, 0.03 to 0.49), and fewer cardiovascular events occurred in the WATCHMAN™ group (3.7% vs 0.95%; RR=0.40; 95% CrI, 0.23 to 0.82). Rates of ischemic stroke did not differ significantly between groups, but WATCHMAN™ group patients had lower all-cause mortality than anticoagulation group patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=0.04).

Alli (2013) reported quality-of-life parameters, as measured by change in scores on the Short-Form 12-Item Health Survey from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF study.[15] For the subset of PROTECT AF subjects included in the present analysis, at baseline, control group subjects had a higher mean CHADS2 score (2.4 vs 2.2; p=0.052) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%; p=0.028). For subjects in the WATCHMAN™ group, the total physical score improved in 34.9% and was unchanged in 29.9%; for those in the warfarin group, the total physical score improved in 24.7% and was unchanged in 31.7% (p=0.01).

A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the WATCHMAN™ device to address some of the limitations of the PROTECT AF study, including its inclusion of patients with low stroke risk (CHADS2 scores of 1) and generally poor compliance with warfarin therapy in the control group. Results from the PREVAIL trial were initially presented in FDA documentation, and published in peer-reviewed form by Holmes et al in 2014.[11] In the PREVAIL trial, 461 subjects enrolled at 41 sites were randomized in a 2:1 fashion to either the WATCHMAN™ device or control, which consisted of either initiation or continuation of warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0. Subjects had nonvalvular AF and required treatment for prevention of thromboembolism based on a CHADS2 score of two or higher (or ≥1 with other indications for warfarin therapy based on American College of Cardiology/American Heart Association/European Society of Cardiology guidelines) and were eligible for warfarin therapy. In the device group, warfarin and low-dose aspirin were continued until 45 days postprocedure; if a follow-up echocardiogram at 45 days showed occlusion of the LAA, warfarin therapy could be discontinued. Subjects who discontinued warfarin were treated with aspirin and clopidogrel for six months post device implantation and with 325 mg aspirin indefinitely after that.

Three noninferiority primary efficacy end points were specified: (1) occurrence of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism (18-month rates); (2) occurrence of late ischemic stroke and systemic embolization (beyond seven days postrandomization, 18-month rates); and (3) occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or

major endovascular intervention (eg, pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) occurring within seven days of the procedure or by hospital discharge, whichever was later. The 18-month event rates were determined using Bayesian statistical methods to integrate data from the PROTECT-AF study. All patients had a minimum follow-up of six months. For randomized subjects, mean follow-up was 11.8 months and median follow-up was 12.0 months (range, 0.03-25.9 months).

The first primary end point, the 18-month modeled RR between the device and control groups was 1.07 (95% CrI, 0.57 to 1.89). Because the upper bound of the 95% CrI was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary end point of late ischemic stroke and systemic embolization, the 18-month RR between the device and control groups was 1.6 (95% CrI, 0.5 to 4.2), with an upper bound of the 95% CrI above the preset noninferiority margin of 2.0. The rate difference between the device and control groups was 0.005 (95% CrI, -0.019 to 0.027). The upper bound of the 95% CrI was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary end point, major safety issues, the noninferiority criterion was met.

Reddy (2017) published a study on the five-year outcomes after left atrial appendage closure, for patients who participated in the PREVAIL and/or PROTECT AF trials.[16] When evaluating the five-year findings the authors stated that if procedure related strokes are excluded, ischemic stroke and systemic embolism differences did not vary significantly (HR: 1.40; 95% CI: 0.76 to 2.59; p = 0.28). But, hemorrhagic stroke was significantly reduced with left atrial appendage closure (HR: 0.20; 95% CI: 0.07 to 0.56; p = 0.0022). The authors go on to state patients enrolled in the studies had to be able to take oral anticoagulants; thus, the results do not tell you anything about patients unable to take oral anticoagulants. Since the PREVAIL and/or PROTECT AF trials, novel oral anticoagulants have become routinely prescribed and have not been compared to left atrial appendage closure. They stated additional studies are needed to compare left atrial appendage closure to other oral anticoagulants and to determine outcomes for patients unable to take oral anticoagulants. There are studies underway. It is important to note that there is potential conflict of interest with several authors.

Nonrandomized Studies

Saw (2017) evaluated safety and effectiveness of the WATCHMAN™ for 106 patients who cannot take anticoagulants and who had nonvalvular atrial fibrillation.[17] 97.2% of the patients had successful LAA closure, with one device embolization, one implant being placed too deep, and one cardiac perforation requiring repair prior to device implantation. The major combined safety event rate was 1.9% (one death and one device embolization). Follow-up occurred 210 ± 182 days, noting two transient ischemic events. The authors stated that their early experience is that the WATCHMAN™ is safe and effective for patients who cannot be on anticoagulation therapy, but that there were study limitations including a small sample size, varied antithrombotic therapy and device surveillance, and both the device and events were not adjudicated. Additional studies must evaluate how the Watchman™ device impacts healthcare outcomes.

Main (2016) evaluated follow-up transesophageal (TEE) studies for how often device related thrombus (DRT) occurred in patients in the PROTECT-AF trial.[18] In all, 93 follow-up TEEs in 35 patients (33 at 45-day follow-up, 33 at six-month follow-up, and 27 at one-year follow-up) were assessed. The assessment process included a three-phase adjudication (an interactive

training program, an interpretation process, development of DRT criteria, and a final determination of DRTs related to the Watchman™ device). This assessment found device related DRTs in 5.7% of the patients, with DRTs not as common at 45 days, when patients continued on Warfarin. The authors noted study limitations, including but not limited the fact that event adjudication studies tend to underestimate events that occur, the TEE studies varied in clinical quality, and anticoagulant routine data was not completely documented. In addition, there is potential conflict of interest identified in the article.

A number of small published case series are primarily intended to establish safety and feasibility of the device.[19-23] A larger case series of 143 patients from Europe was published in 2011.[21] The case series reported successful implantation in 96% (137/143) of patients and serious complications in 7.0% of patients (10/143). Complications included stroke (n=3), device embolization (n=2), and pericardial effusion (n=5). Another larger case series was reported by Reddy et al[22], primarily focusing on the adverse event rate from a registry of 460 patients who received the WATCHMAN™ device. Serious pericardial effusion occurred in 2.2% of patients, and there were no deaths or periprocedural strokes reported. Matsuo et al reported results from a case series of 179 patients who underwent LAA closure at a single center, most (n=172) of whom received a WATCHMAN™ device.[24] Device deployment was successful in 98.9% of patients. The overall complication rate was 11.2%; major complications occurred in 3.3% (tamponade in two cases; possible transient ischemic attack [TIA] in one case; device dislocation in three cases). At 45-day follow-up, 99.4% of patients (164/166) had closure of the LAA.

Reddy (2016) evaluated adverse events for the WATCHMAN™ since it was FDA approved.[25] Adverse events were identified by procedural data collected by the manufacturer clinical specialist present during surgery. Implantation was deemed successful in 95% of consecutive cases (3,653 out of 3,822 total). The complications included 39 pericardial tamponades (1.02%; 24 treated percutaneously, 12 surgically and 3 fatal), three procedure-related strokes (0.078%), nine device embolizations (0.24%; 6 requiring surgical removal), and three procedure-related deaths (0.078%).

Bonnet published safety and efficacy data for the WATCHMAN™ device from a small single center registry study.[26] There were 23 total patients (mean CHA2DS2-VASc score: 5). The procedural success rate was 95.7% (95% confidence interval: 77.3-100.0) and the reported efficacy was 90.9% (95% confidence interval: 71.0-98.7). No adverse events were reported during or after hospitalization.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.[27] The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attach. There were no episodes of definitive stroke recorded or reported. However, there were twenty-six leaks ≥1 mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

There is uncertainty about the role of the WATCHMAN™ device in patients with AF who have absolute contraindications to oral anticoagulants. Reddy et al[8] conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAA closure with the WATCHMAN™ device in patients with nonvalvular AF with a CHADS2 score 1 or higher who were considered ineligible for warfarin. Postimplantation, patients received 6 months of

clopidogrel or ticlopidine and lifelong aspirin therapy. Thirteen patients (8.7%) had a procedure- or device-related serious adverse event, most commonly pericardial effusion (three patients). Over a mean 14.4 months of follow-up, all-cause stroke or systemic embolism occurred in four patients.

Chun (2013) compared the WATCHMAN™ device with the Amplatzer cardiac plug among patients with nonvalvular AF in a prospective cohort study, who were at high risk for stroke and had a contraindication to or were not willing to accept oral anticoagulants.[28] Eighty patients were assigned to LAA occlusion with the WATCHMAN™ or the Amplatzer device. After device implantation, either preexisting oral anticoagulation therapy or dual platelet inhibition with aspirin and clopidogrel was continued for six weeks. A follow-up transesophageal echocardiogram was performed at six weeks postprocedure; if a device-related thrombus had formed, patients received intensive antithrombotic therapy for six weeks. Aspirin was continued indefinitely for all patients. The primary end point of successful device implantation occurred in 98% of patients. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the two groups. At a median 364 days of follow-up, there were no cases of stroke/TIA or other bleeding complications.

The EWOLUTION WATCHMAN™ registry is intended to evaluate procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the WATCHMAN™ device at 47 centers in 13 countries. A publication from the EWOLUTION registry in 2016 reported on 30-day outcomes of device implantation in 1,021 patients.[29] The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate-to-high risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow postprocedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Network Analyses

Sahay (2017) performed a network meta-analysis to evaluate the safety and effectiveness of LAAC versus other strategies to prevent stroke in AF patients.[30] Nineteen RCTs with 87,831 patients were evaluated. The authors stated that although LAAC was found to be better than anticoagulant therapy and similar to novel anticoagulants, the results should be carefully analyzed.

Bajaj (2016) conducted a network meta-analysis of published RCTs evaluating multiple novel oral anticoagulants and left atrial appendage closure devices (WATCHMAN™) which have been tested against dose-adjusted vitamin K antagonists for stroke prophylaxis in non-valvular atrial fibrillation.[31] At the time of the analysis, there were no direct comparisons of these strategies from RCTs. Six RCTs were included in the analysis (N=59,627). Safety and efficacy outcomes were evaluated for six treatment strategies. The analysis showed that all prophylaxis strategies had similar rates of ischemic stroke. The authors also reported that in a cluster analyses, assessing safety and efficacy, apixaban, edoxaban and dabigatran ranked best followed by vitamin K antagonists and rivaroxaban, whereas the WATCHMAN™ left atrial

appendage closure device ranked last. All of these strategies had different safety outcomes. The authors concluded that more RCTs are needed that directly compare treatment strategies.

Tereshchenko (2016) published a network meta-analysis that included 21 RCTs (96,017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) in which the safety and efficacy of novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the WATCHMAN™ device were evaluated.[32] The primary efficacy outcome was the combination of stroke and systemic embolism and the primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. The authors concluded that "in comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60-0.95]), VKA (0.38 [0.29-0.49]), apixaban (0.31 [0.22-0.45]), dabigatran (0.29 [0.20-0.43]), edoxaban (0.38 [0.26-0.54]), rivaroxaban (0.27 [0.18-0.42]), and the WATCHMAN™ device (0.36 [0.16-0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68-0.99]; VKA: 0.69 [0.57-0.85]; apixaban: 0.62 [0.50-0.78]; dabigatran: 0.62 [0.50-0.78]; edoxaban: 0.62 [0.50-0.77]; rivaroxaban: 0.58 [0.44-0.77]; and the WATCHMAN™ device: 0.47 [0.25-0.88])."

Section Summary

The evidence for the use of the WATCHMAN™ device for stroke prevention in patients with nonvalvular atrial fibrillation who are candidates for oral anticoagulation mainly includes two noninferiority RCTs (PROTECT-AF and PREVAIL) and patient-level meta-analysis of these trials. Both RCTs compare the WATCHMAN™ device to anticoagulation and report on composite outcomes. The first RCT reported noninferiority between the two groups for a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism up to four years of follow-up. However, there are documented issues with patient selection criteria (i.e., population low risk for stroke), losses to follow-up, and inconsistency between the two groups in the use of other treatments that may have impacted the findings. The second RCT did not demonstrate noninferiority for the same composite outcome as the first trial (stroke, cardiovascular/unexplained death, or systemic embolism). However, the trial reported noninferiority of the WATCHMAN™ device to warfarin for late ischemic stroke and systemic embolization. The meta-analysis of the two trials reported a periprocedural risk of ischemic stroke with the WATCHMAN™ device and a lower risk of hemorrhagic stroke over the long term.

The published RCTs and meta-analysis report mixed results for the primary composite outcome and risk of safety events. In addition, the two RCTs have methodological limitations that may impact not only the RCT but also the meta-analysis findings which includes unblinding, differing stroke risk among study participants, loss of patients to follow-up, and poor compliance to Warfarin in the comparison groups. The current evidence base does not consistently demonstrate a net improvement in health outcomes (balance of benefit and harms) compared with established treatments for preventing stroke in patients with AF who are eligible to receive systemic anticoagulation.

The evidence for patients where the use of oral anticoagulants is not feasible consists of small nonrandomized studies with methodological limitations. These studies report on the placement of the device but many of them do not report on the *comparative* efficacy and safety of LAA closure in preventing strokes in this population. More high quality, comparative evidence is needed.

AMPLATZER AMULET DEVICE

Randomized Controlled Trials

Two randomized noninferiority trials (SWISS-APERO and Amulet IDE, described below) have been reported comparing the Amplatzer Amulet and Watchman devices, but neither included an anticoagulant group. A third trial (PRAGUE-17) compared either the Amulet or Watchman device with anticoagulants, but did not report subgroup analysis according to the device.

SWISS-APERO Trial

The Comparison of Amulet Versus Watchman/FLX Device in Patients Undergoing Left Atrial Appendage Closure (SWISS-APERO) trial conducted by Galea (2022) compared the Amulet and Watchman devices in 221 participants with non-valvular AF.[33] The enrolled participants were at high risk for stroke (mean CHA2DS2-VASc score 4.3; 39% had a history of prior stroke) and bleeding (mean HAS-BLED score 3.1; 88% had a history of bleeding requiring medical evaluation). Participants were primarily male (70%) and mean age was 77 years. Outcome assessment focused on successful closure, based on a composite outcome of either treatment group crossover during the LAAC procedure or residual LAA patency at 45 days post-intervention, based on CT angiography. The study found no difference in treatment between groups in the composite outcome (RR, 0.97; 95% CI 0.80 to 1.16). Major procedure-related complications were more common with the Amulet versus the Watchman device (9.0% vs. 2.7%; p=.047) There were six deaths during the trial, including two in the Amulet group (1.8%) and four in the Watchman group (3.6%; p=.409). Limitations of the study include the lack of an anticoagulant control group and the short duration of follow-up, although planned trial follow-up is ongoing. In addition, the actual Watchman device used was changed during the course of the trial due to a new device (Watchman FLX) version becoming available.

Amulet IDE Trial

Lakkireddy (2021) reported the results of the Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial (Amulet IDE) comparing the Amulet and Watchman devices.[34] The study enrolled 1,878 patients with non-valvular AF at high-risk for stroke (mean CHA2DS2-VASc score 4.5 and 4.7) and bleeding (mean HAS-BLED score 3.2 and 3.3). The mean age of enrolled patients was 75 years and 59% were male; race and ethnicity were not reported. Twenty-eight percent of enrolled participants had a history of major bleeding and 19 percent had a history of stroke. The primary efficacy endpoint was a composite that included ischemic stroke or systemic embolism, while the safety analysis included a primary composite outcome of all-cause mortality, major bleeding or procedure-related complications. Duration of follow-up was 18 months for efficacy outcomes and 12 months for safety outcomes. After 18 months, there was no difference in the composite efficacy outcome between the Amulet and Watchman devices (HR, 0.00; 95% CI, -1.55 to 1.55). Results were consistent in showing no difference between groups when considering ischemic stroke and systemic embolism as individual outcomes. There was also no difference between Amulet and Watchman groups for a secondary composite outcome that included any stroke, systemic embolism or sudden cardiac death (HR, -2.12; 95% CI, -4.45 to 0.21), nor were there differences between groups when these outcomes were considered individually. In terms of safety, there was no difference between the Amulet and Watchman groups for the composite safety outcome at 12 months (HR, -0.14; 95% CI, -3.42 to 3.13). When outcomes were considered separately, there was also no difference between the Amulet and Watchman groups for all-cause mortality or major bleeding. Procedure-related complications were more likely to occur with the Amulet versus

the Watchman devices (HR, 1.86; 95% CI, 1.11 to 3.12). Follow-up is planned to continue through 2024.

PRAGUE-17 Trial

The PRAGUE-17 trial found that the use of either the Watchman device or the Amplatzer Amulet was noninferior to direct oral anticoagulants for the primary composite endpoint that included ischemic or hemorrhagic stroke, TIA, systemic embolism, clinically significant bleeding, significant peri-procedural or device-related complications, or cardiovascular mortality in high-risk patients with AF.[35] Four year outcomes of the PRAGUE-17 trial were published (2022) and showed that LAAC remains noninferior to DOACs for preventing major cardiovascular, neurological, or bleeding events. Furthermore, nonprocedural bleeding was significantly reduced with LAAC.[36]

Section Summary: Amplatzer Amulet

Two RCTs compared the Amulet and Watchman devices, one of which was a short-term trial that assessed periprocedural outcomes at 45 days. The second trial comparing the Amulet and Watchman devices found the Amulet device to be noninferior to the Watchman device after 18-months follow-up for a composite efficacy outcome that included ischemic stroke or systemic embolism and for a composite safety outcome that included all-cause mortality, major bleeding or procedure-related complications. The primary mechanism of action endpoint of device closure at 45 days was observed in 98.9% of Amulet subjects and 96.8% of Watchman subjects. The 97.5% lower confidence bound was 0.41%, which was greater than the predefined non-inferiority margin of -3% ($p<0.0001$). Therefore, device closure with the Amulet device was non-inferior to the Watchman device.

One additional RCT evaluated the use of either the Amplatzer Amulet or Watchman device versus anticoagulants; subgroup analyses according to the device were not performed. After up to 4 years of follow-up, the study found LAA closure with either the Watchman or Amulet was noninferior to anticoagulants for a composite outcome that included stroke, TIA, systemic embolism, clinically significant bleeding, significant periprocedural or device-related complications, or cardiovascular mortality. The summary of the clinical evidence provides a reasonable assurance that the Amulet device is effective for reducing the risk of thrombus embolization from the LAA in select patients with non-valvular atrial fibrillation.

LARIAT® DEVICE

The available evidence on the efficacy of the Lariat device for LAA closure consists of a number of small case series.

Litwinowicz (2018) published a non-randomized, non-comparative single-center study of 139 patients undergoing LAAC with the LARIAT® device.[37] The study's primary outcomes were risk of thromboembolism, severe bleeding, and mortality with an average follow-up time of 4.2 years. The results of the study indicated that the rate of thromboembolisms is 0.6% and the severe bleeding rate was 0.8%. The reported mortality rate was 1.6%. The authors concluded that LAAC using this device is a safe and effective treatment for stroke prevention and bleed risk reduction in this population. The authors also noted the significant limitations with this study including the lack of control group, variability in post-procedure anticoagulation, and relying on calculated stroke or bleeding risks for analyses.

Gianni (2016) published a retrospective multicenter study of 98 patients who underwent LAA ligation with the LARIAT® device.[38] How many times and what the clinical implications of a leak were assessed. A transesophageal echocardiography assessed leaks during the procedure, at six and 12 months and after thromboembolic events. Leaks were detected in 5%, 15%, and 20% respectfully in patients at the three evaluation periods. The authors stated that because incomplete occlusion can occur, appropriate long-term surveillance should be performed, along with the addition of anticoagulant therapy or percutaneous transcatheter closure as needed.

A SR of published studies on the Lariat device was published in 2016.[39] No RCTs were identified. Five case series were selected, with a total of 309 patients (range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and seven (2.3%) patients required urgent cardiac surgery. The reviewers also searched the MAUDE database for adverse events and found 35 unique reports. Among the 35 reported complications, there were five deaths and 23 cases of emergency cardiac surgery.

Individual case series continue to be published, including a large case series of 712 consecutive patients from 18 U.S. hospitals.[40] This series reported a procedural success rate of 95% and complete closure in 98%. There was one death and emergent cardiac surgery was required in 1.4%.

A large case series was reported by Price (2014) in a retrospective multicenter study of early outcomes after use of the Lariat device.[41] This study included 154 patients with a median CHADS2 score of 3. Device success, defined as suture deployment and a residual shunt less than 5 mm, was achieved in 94% of patients. Procedural success, defined as device success and no major complication (death, MI, stroke, major bleeding, or emergency surgery) at hospital discharge, was achieved in 86% of patients. Fifteen patients (10%) had at least one major periprocedural complication, and 10% had significant pericardial effusion. Of the 134 patients (87%) who had out-of-hospital outcome data available, the composite out-of-hospital outcome of death, MI, or stroke occurred in four patients (2.9%).

Gianni (2016) published a retrospective, multicenter study including 98 consecutive patients which evaluated the incidence and clinical implications of leaks (acute incomplete occlusion, early and late reopening) following LAA ligation with the LARIAT device.[38] Leaks were detected in 5 (5%), 14 (15%), and 19 (20%) patients at the three time points. A total of five patients developed neurological events (four strokes and one transient ischemic attack). Three occurred late and were associated with small leaks (< 5mm). The authors concluded that “incomplete occlusion of the LAA after LARIAT ligation is relatively common and may be associated with thromboembolic events.

Bartus (2013) reported results of a case series that enrolled 89 patients with AF and either a contraindication to warfarin or previous warfarin failure.[42] A total of 85 of 89 (96%) had successful left atrial ligation, and 81 of 89 (91%) had complete closure immediately. There were three access-related complications, two cases of severe pericarditis postoperatively, one late pericardial effusion, and two cases of unexplained sudden death. There were two late strokes, which the authors did not attribute to an embolic source. At 1-year follow-up, complete closure was documented by echocardiography in 98% of available patients (n=65). In a smaller, earlier series from the same research group,[43] 13 patients were treated with the Lariat device, 11 of whom were treated as part of percutaneous radiofrequency ablation for AF. One of the 11 procedures was terminated due to unsuccessful placement, and the other 10

procedures were successful, with complete closure verified on echocardiography. There was one procedural complication in which the snare could not be removed and were retrieved by thoracoscopy.

Stone (2013) reported outcomes for 27 patients with AF, a high stroke risk (CHADS2 score ≥2), and contraindications or intolerance to anticoagulation who underwent percutaneous LAA ligation with the Lariat device.[44] Acute procedural success was 92.6%; periprocedural complications included 3 cases of pericarditis and 1 periprocedural stroke associated with no long-term disability. A follow-up transesophageal echo was performed in 22 patients at an average of 45 days postprocedure, which demonstrated successful LAA exclusion in all 22. Follow-up was for an average of four months, during which time one stroke and no deaths occurred.

Massumi (2013)[45] reported on 21 patients with AF and contraindications to anticoagulation. A total of 20 of 21 patients had successful atrial closure, which was documented by echocardiography to be intact at a mean follow-up of 96 days. No patients had a stroke during a mean follow-up of approximately one year. Complications were reported in 5 of 21 patients. One patient had right ventricular perforation and tamponade requiring surgical intervention. One patient developed pleuroperidicarditis that required multiple drainage procedures. Three additional patients developed pericarditis within 30 days of the procedure.

Section Summary

The current studies on the Lariat device are limited to small nonrandomized studies. While these studies report high procedural success, interpretation is limited due to methodological limitations such as small sample size, lack of randomized treatment allocation, and lack of a control group for comparison. Larger-scaled trials are needed to confirm the efficacy and safety of the Lariat device.

AMPLATZER® CARDIAC PLUG DEVICE

Cruz-Gonzales (2020), in their retrospective registry study, aimed to evaluate the safety and efficacy of LAA occlusion for patients with nonvalvular AF with prior stroke or TIA despite anticoagulant therapy (resistant stroke [RS]).[46] They assessed data from the Amplatzer Cardiac Plug multicenter registry on 1047 consecutive patients with nonvalvular AF undergoing LAA occlusion. There were no significant differences in baseline characteristics between the 2 groups. The RS group had a significantly higher mean CHA2-DS2-VASc score (5.5±1.5 in the RS group vs. 4.6±1.6 in the non-stroke group) and HAS-BLED score (3.9±1.3 vs. 3.1±1.2). There were no significant differences between groups in procedural success or periprocedural major safety events. At one-year follow-up, the observed annual rate of stroke of TIA was 2.6% in the RS group and 1.2% for the non-stroke group.

Additional available evidence on use of the Amplatzer device for left atrial occlusion consists of a number of case series, most of which included less than 40 patients.[19, 47-51] Another case series, Nietlispach, attempted LAA occlusion in 152 patients from a single institution.[52] Amplatzer Cardiac Plugs were used in 120 patients and nondedicated devices were used in 32 patients. Short-term complications occurred in 9.8% of patients (15/152). Longer-term adverse outcomes occurred in 7% of patients including two strokes, one peripheral embolization, and four episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients.

Berti (2016) evaluated consecutive, high-risk patients (n=110) with non-valvular atrial fibrillation and contraindications to oral anticoagulants.[53] There was a mean follow-up of 30±12 months. Procedures were performed using the Amplatzer Cardiac Plug or Amulet. Berti reports procedural success (technical success without major procedure-related complications) was achieved in 96.4%. The rate of major procedural complications was 3.6% (three cases of pericardial tamponade requiring drainage and one case of major bleeding). The annual rate of ischemic stroke and other thromboembolic events were 2.2% and 0%, respectively. The annual rate for major bleeding was 1.1%.

Additional case series of patients treated with the Amplatzer device were published including patients from different countries.[19, 27, 47, 48, 54-56] Many of the case series reported high procedural success, as well as various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Several studies have reported the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest study reported outcomes, up to four years postprocedure, for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device.[57] Patients had a median CHA2DS2-VASc score of 4 and were generally considered at high risk for bleeding complications. Postprocedural antithrombotic therapy was tailored to the patient's individual risk profile, but the authors described that, generally, short-term dual antiplatelet therapy (1-2 months) and subsequent indefinite single antiplatelet therapy were prescribed after successful device implantation. Procedural success occurred in 93.3%, and three major procedure-related complications (two cases of cardiac tamponade, one case of pericardial effusion requiring drainage or surgery) occurred. Over a mean follow-up of 680 days, observed annual rates of ischemic strokes and any thromboembolic events were 0.8% and 2.5%, respectively.

Meerkin (2013) reported outcomes for 100 patients with AF, a CHADS2 score of 2 or higher, and a contraindication to oral warfarin who were treated with the Amplatzer device at a single institution.[58] All patients were treated with heparin during the procedure; they were maintained on clopidogrel for one month postprocedure and daily aspirin indefinitely. Successful deployment occurred in all patients. There were two significant periprocedural complications, including one pericardial effusion with tamponade and one case of acute respiratory distress with pulmonary edema.

Wiebe (2014) reported results of a retrospective cohort of 60 patients with nonvalvular AF who had a CHADS2-VASc score of at least 1 and contraindications to warfarin anticoagulation who underwent percutaneous LAA closure with the Amplatzer device.[50] Contraindications to warfarin included contraindications as defined in the warfarin product label, a history of severe bleeding while receiving anticoagulant therapy, as well as a history of bleeding tendencies in the absence of anticoagulation or blood dyscrasia, along with patients who were unable to maintain a stable INR and those with a known hypersensitivity to warfarin or a high-risk of falling who were also included. Patients received heparin during the closure procedure; they were maintained on clopidogrel for 3 months postprocedure and daily aspirin indefinitely. Device implantation was successful in 95% of patients. Over a median follow-up of 1.8 years, no patients experienced a stroke. The rate of major bleeding complications was 1.9%/year of follow-up.

Urena (2013) reported results from a similar cohort of 52 patients with nonvalvular AF who had a CHADS2-VASc score of at least 2 and contraindication to oral anticoagulation therapy who

underwent percutaneous LAA closure with the Amplatzer device.[51] Device implantation was successful in all but one patient. There were no periprocedural strokes or death. Over the follow-up period (mean, 20 months), rates of death, stroke, and systemic embolism were 5.8% (3/52), 1.9% (1/52), and 0%, respectively.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.[27] The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attach. There were no episodes of definitive stroke recorded or reported. However, there were twenty-six leaks ≥1 mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

Other smaller case series of patients with contraindication to oral anticoagulation include studies by Danna,[47] which included 37 patients and reported a 1-year stroke rate of 2.94%, and Horstmann,[59] which included 20 patients and reported no episodes of strokes over a mean follow-up of 13.6 months.

Gloekler (2015)[60] compared outcomes for nonvalvular AF patients treated with the first-generation Amplatzer cardiac plug (n=50) and those treated with the second-generation Amulet device (n=50) in a retrospective analysis of prospectively collected data. There were no significant differences between devices in terms of safety outcomes.

Section Summary

All of the nonrandomized studies report high procedural success, but also report various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

PLAATO DEVICE

Bayard (2010) reported on 180 patients with nonrheumatic atrial fibrillation and a contraindication to warfarin and who were treated with the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device.[61] Placement was successful in 90% of patients. Two patients died within 24 hours of the procedure (1.1%), and six patients had cardiac tamponade (3.3%), with two required surgical drainage. During a follow-up of 129 patient-years, three strokes were reported for a rate of 2.3% per year. Other case reports and small case series report complications, including multiple reports of thrombus formation at the site of device placement.[61, 62]

Section Summary

The nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

ATRICLIP DEVICE

Ad (2015) reported on 24 patients that received the Atriclip PRO. Ninety five percent of patients had nonparoxysmal AF.[63] The clip did not deploy in one patient but the procedural success was 95%. Another study reported on 30 procedures for the Atriclip.[64] The device was

successfully placed in 28 of the 30 patients and the study didn't report any adverse events at follow-up. A multicenter study reported on a total of 71 patients receiving the Atriclip device.[65] Safety of the device was assessed at 30 days and there was a three month follow-up for efficacy. One patient was not able to receive the Atriclip device but procedural success was confirmed in 67 of 70 patients. Significant adverse events were reported in 34 of 70 patients. There was no adverse events from the device itself and no perioperative mortality. At the three month follow-up, one patient passed away and 60 of 61 patients still had successful occlusion.

Section Summary

Nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

EVALUATIONS OF MULTIPLE DEVICES

Hanif (2017) published a SR of RCTs to compare the risk of stroke in patients with left atrial appendage occlusion (LAAO) versus anticoagulant, antiplatelet, or placebo therapy.[66] The impact on operative time, major bleeding, and mortality were assessed. Although LAAO was found to be better than anticoagulant therapy for stroke and mortality, the authors stated the evidence had methodological limitations.

Health Quality Ontario (2017) performed a SR evaluating both clinical and cost effectiveness of left atrial appendage closure devices versus novel anticoagulants e.g. dabigatran or versus Warfarin.[67] .Five studies compared novel anticoagulants to Warfarin and two compared left atrial appendage closure to Warfarin. The authors concluded that moderate quality evidence indicates left atrial appendage closure is as effective as novel oral anticoagulants for patients with nonvalvular AF, but is cost effective only for patients who cannot take anticoagulants.

Lempereur (2017) published a SR evaluating device associated thrombosis (DAT) for the Watchman™, Amplatzer™ Cardiac Plug (ACP), and Amulet devices from 2008-2015.[68] Thirty studies were included. The mean frequency of DAT after LAAO was 3.9% for all devices (82/2118). The reported frequency of DAT six weeks after implant was similar for WM and ACP/Amulet (2.0 versus 2.6%, respectively, $P = 0.60$). The reported frequency of events did not appear to change over time. The conclusion was that DAT was an infrequent complication of LAAO as it occurs mostly in the early post procedure, and there is a low rate of neurological complications. But, the authors stated their review had limitations including lack of a standard definition for DAT amongst studies and that the review was based only on published data. Therefore unpublished, underreported and/or underdiagnosed DATs would impact the review outcomes. Additional larger multicenter studies are needed to determine risks, complications, and treatment efficacy of LAAO.

Wei (2016) published a SR evaluating two RCTs (PROTECT AF and PREVAIL) and 36 observational studies on the safety and effectiveness of left atrial appendage occlusion (LAAO) devices.[69] The systems mainly involved in the studies included PLAATO, the Amplatzer® Cardiac Plug device, and WATCHMAN™. Other devices such as nondedicated Amplatzer® occluders, and WaveCrest® were also reviewed. Procedure failure was 0.02 (95% CI: 0:02-0.03), with no heterogeneity amongst studies. All-cause mortality was 0.03 (95% CI: 0.02-0.03) and cardiac/neurological mortality was 0 (95% CI: 0.00-0.01), with low pooled results and no heterogeneity amongst studies. The frequency of stroke/transient ischemic attack was 0.01 (95% CI: 0.01-0.01), with no heterogeneity amongst studies. The frequency of thrombus on devices was 0.01 (95% CI: 0.01-0.02), with no heterogeneity amongst studies. Major

hemorrhagic event complications were 0.01 (95% CI: 0.00-0.01), with no heterogeneity amongst studies. Of the devices, most did not differ in the frequency of events except all-cause mortality and cardiac/neurological mortality was higher for the PLAATO group and thrombus occurred more often in the ACP group and less often in the PLATTO group. The authors stated LAAO is safe and effective and there is a low rate of failure, for patients not able to be on long-term anticoagulant therapy. However, the authors stated their study had limitations, including but not limited to the definition of safety and effectiveness varied amongst studies, there were only two RCTs, two large studies did not report cardiac or neurological death frequencies, and the data on specific devices was not always easy to assess.

Li (2016) published a SR to report how effective and safe LAAO devices were for greater than one year, when compared to novel oral anticoagulants (NOACs).[70] They evaluated six RCTs and 27 observational studies. The authors stated the RCTs showed that LAAO was not better than NOACs for stroke prevention (odds ratio 0.86), but did show LAAO patients had less hemorrhagic events at follow-up. An analysis of the observational studies showed that LAAO patients had a lower rate of both thromboembolic events (1.8 per 100 patient-years versus 2.4 events per 100 patient-years) and major bleeding (2.2 events per 100 patient-years versus 2.5 events per 100 patient-years). During longer follow-up periods patients with LAAO had less thromboembolic events (2.1, 1.8, and1.0 events per 100 person-years for 1, 1-2, and > 2 years respectively). The authors stated the SR had limitations, including but not limited to different follow-up durations between LAAO and NOAC groups and number of patients who received LAAO was less than those receiving NOACs. They stated additional studies with consistent homogeneity could assess healthcare outcomes and assist in confirming this study's findings.

Xu conducted a comprehensive literature search for studies evaluating patients after receiving an occlusion device.[25] Studies were included if they had at least 10 patients followed for at least six months. Twenty five total studies were included with only two RCTs and the rest were cohort studies (N= 2,779). Xu performed a meta-analysis of stroke events and adverse events after patients received an occlusion device. Xu reported that the adjusted incidence rate of stroke was 1.2/100 person-years (PY) (95% confidence interval [CI], 0.9-1.6/100 PY) and the ischemic and hemorrhagic stroke rates were 1.1/100 PY (95% CI, 0.8-1.4/100 PY) and 0.2/100 PY (95% CI, 0.1-0.3/100 PY), respectively. Additionally, the combined efficacy outcomes (stroke or transient ischemic attacks [TIAs], systemic embolism, or cardiovascular death) was 2.7/100 PY (95% CI, 1.9- 3.4/100 PY). The most common adverse events were major bleeding and pericardial effusions at a rate of 2.6% (95% CI, 1.5%-3.6%) and 2.5% (95% CI, 1.8%-3.2%), respectively.

Sahay conducted a SR of the evidence with a network meta-analysis of all RCTs (N=19) with a total of 87,831 patients.[71] The network analysis evaluated the safety and efficacy of left atrial appendage closure compared to other strategies for stroke prevention in atrial fibrillation.[71] The network meta-analysis includes direct and indirect comparisons for these various treatment strategies. The analysis compared treatment strategies to warfarin as a common comparator group. The authors reported that "…using warfarin as the common comparator revealed efficacy benefit favoring LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67, p<0.001; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52, p<0.001) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91, p=0.0018; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86, p=0.017) and similar to NOAC (mortality: HR 0.76,= 95% CI 0.50 to 1.16, p=0.211; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92, p=0.969)." The rates for major bleeding were comparable. The authors further note that caution should be taken in interpreting these results

as more studies are needed to further substantiate the findings especially in light of the wide confidence intervals.

Betts (2016) evaluated the feasibility and long term efficacy of LAAO using a retrospective multicenter registry (July 2009-November 2014).[72] The devices included the WATCHMAN™ (63%), Amplatzer™ Cardiac Plug (34.7%), Lariat (1.7%) and Coherex WaveCrest (0.6%). A total of 371 patients were included and the overall procedure success was 92.5% with major adverse events in 3.5% of patients. The authors reported "an annual 90.1% relative risk reduction (RRR) for ischemic stroke, an 87.2% thromboembolic events RRR, and a 92.9% major bleeding RRR were observed, if compared with the predicted annual risks based on CHADS2, CHA2DS2-Vasc, and HAS-BLED scores, respectively, over a follow-up period of 24.7 ± 16.07 months. In addition, the authors reported higher success rates and a reduction in acute major complications in the second half of recruitment.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY, HEART RHYTHM SOCIETY, AND SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

In 2015, the American College of Cardiology (ACC), Heart Rhythm Society (HRS), and Society for Cardiovascular Angiography and Interventions published an overview of the integration of percutaneous LAA closure devices into the clinical practice of patients with AF.[73] The overview was organized around questions related to the sites of care delivery for LAA closure devices, training for proceduralists, necessary follow-up data collection, identification of appropriate patient cohorts, and reimbursement. The statement provides general guidelines for facility and operator requirements, including the presence of a multidisciplinary heart team, for centers performing percutaneous LAA closures. The statement does not provide specific recommendations about the indications and patient populations appropriate for percutaneous LAA closure.

AMERICAN COLLEGE OF CARDIOLOGY, THE AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY[3, 74]

The 2019 ACC/AHA/HRS focused update of the 2014 guidelines on the management of patients with AF recommends surgical occlusion of the LAA with the WATCHMAN device as an alternative to long-term anticoagulation therapy (Class IIB, Level of Evidence: B-NR).

AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP)

2018 American College of Chest Physicians guidelines (updated from 2012) recommend that CHA2DS2VASc be used to evaluate stroke risk, and patients initially identified as having a low stroke risk should not be given antithrombotic therapy. In addition, they recommend bleeding risk assessments be given to every patient at every patient contact and that "potentially modifiable bleeding risk factors" should be the initial focus.

SUMMARY

There is enough research to show that the WATCHMAN or Amplatzer Amulet device for left atrial appendage closure results in improved health outcomes for the prevention of stroke in patients with atrial fibrillation. Clinical guidelines based on evidence recommend the use of

the WATCHMAN device for left atrial appendage closure in certain patients. Therefore, the use of the WATCHMAN or Amplatzer Amulet device for left atrial appendage closure may be considered medically necessary for the prevention of stroke in patients with atrial fibrillation who are at an increased risk of stroke.

There is not enough research to show that left atrial appendage closure devices improve health outcomes when policy criteria are not met. No evidence-based practice guidelines recommend the use of devices other than the WATCHMAN or Amplatzer Amulet device. Therefore, the use of left atrial appendage closure devices is investigational when policy criteria are not met including the use of devices other than the WATCHMAN or Amplatzer Amulet device.

REFERENCES

1. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-75S. PMID: 22315271
2. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138:1093-100. PMID: 20299623
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2014. PMID: 24682347
4. Food and Drug Administration- Amulet Approval. [cited 1/9/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200049A.pdf.
5. Food and Drug Administration. [cited 1/9/2024]. 'Available from:' http://www.accessdata.fda.gov/cdrh_docs/pdf14/K142120.pdf.
6. Center BBATE. BlueCross BlueShield Association Technology Evaluation Center. Percutaneous Left Atrial Appendage Closure Therapy for the Prevention of Stroke. [cited 1/9/2024]. 'Available from:' https://bluewebportal.bcbs.com/documents/2574832/6316047/29_5.pdf/7f77d82e-a105-4308-b5b1-6191f6c54fd1.
7. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet.* 2009;374(9689):534-42. PMID: 19683639
8. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *Journal of the American College of Cardiology.* 2013;61(25):2551-6. PMID: 23583249
9. Administration FaD. Food and Drug Administration. FDA Executive Summary P130013 Boston Scientific Watchman Left Atrial Appendage Closure Therapy. [cited 1/9/2024]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013S016.

10. Jaiswal V, Ang SP, Shrestha AB, et al. Amplatzer amulet versus watchman device for percutaneous left atrial appendage closure: A systematic review and meta-analysis. *Medicine.* 2023;102(26):e34185. PMID: 37390240
11. Holmes DR, Jr., Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *Journal of the American College of Cardiology.* 2014;64(1):1-12. PMID: 24998121
12. Price MJ, Reddy VY, Valderrabano M, et al. Bleeding Outcomes After Left Atrial Appendage Closure Compared With Long-Term Warfarin: A Pooled, Patient-Level Analysis of the WATCHMAN Randomized Trial Experience. *JACC Cardiovascular interventions.* 2015;8(15):1925-32. PMID: 26627989
13. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation.* 2013;127(6):720-9. PMID: 23325525
14. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA.* 2014;312:1988-98. PMID: 25399274
15. Alli O, Doshi S, Kar S, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology.* 2013;61(17):1790-8. PMID: 23500276
16. Reddy VY, Doshi SK, Kar S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *Journal of the American College of Cardiology.* 2017;70(24):2964-75. PMID: 29103847
17. Saw J, Fahmy P, Azzalini L, et al. Early Canadian Multicenter Experience With WATCHMAN for Percutaneous Left Atrial Appendage Closure. *Journal of cardiovascular electrophysiology.* 2017;28(4):396-401. PMID: 28128883
18. Main ML, Fan D, Reddy VY, et al. Assessment of Device-Related Thrombus and Associated Clinical Outcomes With the WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients With Atrial Fibrillation (from the PROTECT-AF Trial). *The American journal of cardiology.* 2016;117(7):1127-34. PMID: 26993976
19. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2012;79(5):794-800. PMID: 21542102
20. Montenegro MJ, Quintella EF, Damonte A, et al. Percutaneous occlusion of left atrial appendage with the Amplatzer Cardiac PlugTM in atrial fibrillation. *Arquivos brasileiros de cardiologia.* 2012;98(2):143-50. PMID: 22286325
21. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2011;77(5):700-6. PMID: 20824765
22. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation.* 2011;123:417-24. PMID: 21242484

23. Swaans MJ, Post MC, Rensing BJ, et al. Percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation.* 2012;20(4):161-6. PMID: 22231152
24. Matsuo Y, Sandri M, Mangner N, et al. Interventional closure of the left atrial appendage for stroke prevention. *Circ J.* 2014;78:619-24. PMID: 24419803
25. Reddy VY, Gibson DN, Kar S, et al. Post-FDA Approval, Initial US Clinical Experience with Watchman Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation. *Journal of the American College of Cardiology.* 2016. PMID: 27816552
26. Bonnet G, Salaun E, Pankert M, et al. Initial experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation: A single-centre registry. *Archives of cardiovascular diseases.* 2016. PMID: 27594651
27. Figini F, Mazzone P, Regazzoli D, et al. Left atrial appendage closure: A single center experience and comparison of two contemporary devices. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2016. PMID: 27567013
28. Chun KR, Bordignon S, Urban V, et al. Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: a prospective single-center experience. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2013;10(12):1792-9. PMID: 23973952
29. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J.* 2016;37:2465-74. PMID: 26822918
30. Sahay S, Nombela-Franco L, Rodes-Cabau J, et al. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials. *Heart.* 2017;103(2):139-47. PMID: 27587437
31. Bajaj NS, Kalra R, Patel N, et al. Comparison of Approaches for Stroke Prophylaxis in Patients with Non-Valvular Atrial Fibrillation: Network Meta-Analyses of Randomized Controlled Trials. *PLoS One.* 2016;11:e0163608. PMID: 27706224
32. Tereshchenko LG, Henrikson CA, Cigarroa J, et al. Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis. *Journal of the American Heart Association.* 2016;5(5). PMID: 27207998
33. Galea R, De Marco F, Meneveau N, et al. Amulet or Watchman Device for Percutaneous Left Atrial Appendage Closure: Primary Results of the SWISS-APERO Randomized Clinical Trial. *Circulation.* 2022;145(10):724-38. PMID: 34747186
34. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE): A Randomized, Controlled Trial. *Circulation.* 2021;144(19):1543-52. PMID: 34459659
35. Osmancik P, Tousek P, Herman D, et al. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). *Am Heart J.* 2017;183:108-14. PMID: 27979034
36. Osmancik P, Herman D, Neuzil P, et al. 4-Year Outcomes After Left Atrial Appendage Closure Versus Nonwarfarin Oral Anticoagulation for Atrial Fibrillation. *Journal of the American College of Cardiology.* 2022;79(1):1-14. PMID: 34748929
37. Litwinowicz R, Bartus M, Burysz M, et al. Long term outcomes after left atrial appendage closure with the LARIAT device-Stroke risk reduction over five years follow-up. *PLoS One.* 2018;13(12):e0208710. PMID: 30566961
38. Gianni C, Di Biase L, Trivedi C, et al. Clinical Implications of Leaks Following Left Atrial Appendage Ligation With the LARIAT Device. *JACC Cardiovascular interventions.* 2016;9(10):1051-7. PMID: 27198686

39. Chatterjee S, Herrmann HC, Wilensky RL, et al. Safety and Procedural Success of Left Atrial Appendage Exclusion With the Lariat Device: A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database. *JAMA Intern Med.* 2015;175:1104-9. PMID: 25938303
40. Lakkireddy D, Afzal MR, Lee RJ, et al. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: Results from a US multicenter evaluation. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2016;13(5):1030-6. PMID: 26872554
41. Price MJ, Gibson DN, Yakubov SJ, et al. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. *Journal of the American College of Cardiology.* 2014;64(6):565-72. PMID: 25104525
42. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *Journal of the American College of Cardiology.* 2013;62(2):108-18. PMID: 23062528
43. Bartus K, Bednarek J, Myc J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2011;8(2):188-93. PMID: 21050893
44. Stone D, Byrne T, Pershad A. Early results with the LARIAT device for left atrial appendage exclusion in patients with atrial fibrillation at high risk for stroke and anticoagulation. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2015;86(1):121-7. PMID: 23765504
45. Massumi A, Chelu MG, Nazeri A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *The American journal of cardiology.* 2013;111(6):869-73. PMID: 23312129
46. Cruz-González I, González-Ferreiro R, Freixa X, et al. Left atrial appendage occlusion for stroke despite oral anticoagulation (resistant stroke). Results from the Amplatzer Cardiac Plug registry. *Rev Esp Cardiol (Engl Ed).* 2020;73(1):28-34. PMID: 31036510
47. Danna P, Proietti R, Sagone A, et al. Does left atrial appendage closure with a cardiac plug system reduce the stroke risk in nonvalvular atrial fibrillation patients? A single-center case series. *Pacing and clinical electrophysiology : PACE.* 2013;36(3):347-53. PMID: 23252940
48. Lopez-Minguez JR, Eldoayen-Gragera J, Gonzalez-Fernandez R, et al. Immediate and One-year Results in 35 Consecutive Patients After Closure of Left Atrial Appendage With the Amplatzer Cardiac Plug. *Revista espanola de cardiologia.* 2013;66(2):90-7. PMID: 22939161
49. Streb W, Szymala M, Kukulski T, et al. Percutaneous closure of the left atrial appendage using the Amplatzer Cardiac Plug in patients with atrial fibrillation: evaluation of safety and feasibility. *Kardiologia polska.* 2013;71(1):8-16. PMID: 23348528
50. Wiebe J, Bertog S, Franke J, et al. Safety of percutaneous left atrial appendage closure with the amplatzer cardiac plug in patients with atrial fibrillation and contraindications to anticoagulation. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2014;83(5):796-802. PMID: 24327462
51. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *Journal of the American College of Cardiology.* 2013;62(2):96-102. PMID: 23665098

52. Nietlispach F, Gloekler S, Krause R, et al. Amplatzer left atrial appendage occlusion: single center 10-year experience. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2013;82(2):283-9. PMID: 23412815
53. Berti S, Pastormerlo LE, Rezzaghi M, et al. Left atrial appendage occlusion in high-risk patients with non-valvular atrial fibrillation. *Heart.* 2016. PMID: 27492943
54. Guerios EE, Schmid M, Gloekler S, et al. Left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation. *Arquivos brasileiros de cardiologia.* 2012;98(6):528-36. PMID: 22584492
55. Kefer J, Vermeersch P, Budts W, et al. Transcatheter left atrial appendage closure for stroke prevention in atrial fibrillation with Amplatzer cardiac plug: the Belgian Registry. *Acta cardiologica.* 2013;68(6):551-8. PMID: 24579432
56. Streb W, Szymala M, Kukulski T, et al. Percutaneous closure of the left atrial appendage using the Amplatzer Cardiac Plug in patients with atrial fibrillation: evaluation of safety and feasibility. *Kardiologia polska.* 2013;71:8-16. PMID: 23348528
57. Santoro G, Meucci F, Stolcova M, et al. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 2014. PMID: 25354761
58. Meerkin D, Butnaru A, Dratva D, et al. Early safety of the Amplatzer Cardiac Plug for left atrial appendage occlusion. *International journal of cardiology.* 2013;168(4):3920-5. PMID: 23890886
59. Horstmann S, Zugck C, Krumsdorf U, et al. Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. *Neurology.* 2014;82:135-8. PMID: 24319042
60. Gloekler S, Shakir S, Doblies J, et al. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. *Clinical research in cardiology : official journal of the German Cardiac Society.* 2015;104(8):656-65. PMID: 25736061
61. Bayard YL, Omran H, Neuzil P, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 2010;6(2):220-6. PMID: 20562072
62. Cruz-Gonzalez I, Martin Moreiras J, Garcia E. Thrombus formation after left atrial appendage exclusion using an Amplatzer cardiac plug device. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2011;78(6):970-3. PMID: 21523900
63. Ad N, Massimiano PS, Shuman DJ, et al. New Approach to Exclude the Left Atrial Appendage During Minimally Invasive Cryothermic Surgical Ablation. *Innovations (Philadelphia, Pa).* 2015;10(5):323-27. PMID: 26523825
64. Mokracek A, Kurfirst V, Bulava A, et al. Thoracoscopic Occlusion of the Left Atrial Appendage. *Innovations (Philadelphia, Pa).* 2015;10(3):179-82. PMID: 26181584
65. Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg.* 2011;142(5):1002-9, 09 e1. PMID: 21906756
66. Hanif H, Belley-Cote EP, Alotaibi A, et al. Left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation: a systematic review and network meta-

analysis of randomized controlled trials. *The Journal of cardiovascular surgery.* 2017. PMID: 28215062
67. Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment. *Ontario health technology assessment series.* 2017;17(9):1-106. PMID: 28744335
68. Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: A systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2017;90(5):E111-E21. PMID: 28145040
69. Wei Z, Zhang X, Wu H, et al. A meta-analysis for efficacy and safety evaluation of transcatheter left atrial appendage occlusion in patients with nonvalvular atrial fibrillation. *Medicine.* 2016;95(31):e4382. PMID: 27495048
70. Li X, Wen SN, Li SN, et al. Over 1-year efficacy and safety of left atrial appendage occlusion versus novel oral anticoagulants for stroke prevention in atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials and observational studies. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2016;13(6):1203-14. PMID: 26724488
71. Sahay S, Nombela-Franco L, Rodes-Cabau J, et al. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials. *Heart.* 2016. PMID: 27587437
72. Betts TR, Leo M, Panikker S, et al. Percutaneous left atrial appendage occlusion using different technologies in the United Kingdom: A multicenter registry. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2016. PMID: 27651124
73. Masoudi FA, Calkins H, Kavinsky CJ, et al. 2015 ACC/HRS/SCAI Left Atrial Appendage Occlusion Device Societal Overview. *Journal of the American College of Cardiology.* 2015;66(13):1497-513. PMID: 26133570
74. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart rhythm : the official journal of the Heart Rhythm Society.* 2019;16(8):e66-e93. PMID: 30703530

CODES

Codes	Number	Description
CPT	33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation
	33267	Open exclusion of left atrial appendage any method
	33268	Open exclusion of left atrial appendage performed at the time of other sternotomy or thoracotomy procedure
	33269	Thoracoscopic exclusion of left atrial appendage
	93799	Unlisted cardiovascular service or procedure
HCPCS	None	

Date of Origin: *December 2011*

Regence

Medical Policy Manual Surgery, Policy No. 201

Transcatheter Aortic Valve Implantation for Aortic Stenosis

Effective: July 1, 2023

Next Review: March 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transcatheter aortic valve implantation (also known as transcatheter aortic valve replacement) is an alternative to open valve replacement surgery for patients with aortic stenosis and to nonsurgical therapy for patients with a prohibitive risk for surgery.

MEDICAL POLICY CRITERIA

I. For patients with native valve aortic stenosis, transcatheter aortic valve implantation with an U.S. Food and Drug Administration (FDA)-approved transcatheter heart valve system may be considered **medically necessary** when all of the following criteria (A. – D.) are met:

   A. New York Heart Association heart failure class II, III, or IV symptoms; and

   B. Left ventricular ejection fraction greater than 20%; and

   C. Aortic valve is not unicuspid or bicuspid; and

   D. Severe aortic stenosis, defined as any one or more of the following:

      1. An aortic valve area of less than or equal to 1 cm^2, or

      2. An aortic valve area index of less than or equal to 0.6 cm^2/m^2, or

3. A mean aortic valve gradient greater than or equal to 40 mmHg, or
4. A peak aortic-jet velocity greater than or equal to 4.0 m/s.

II. For patients with a bioprosthetic aortic valve, transcatheter aortic valve replacement (i.e., valve-in-valve) with an FDA-approved transcatheter heart valve system (e.g., Edwards SAPIEN™ or Medtronic CoreValve System™) may be considered **medically necessary** when all of the following criteria (A. – D.) are met:

A. Failure of a surgical bioprosthetic aortic valve (stenosed or insufficient); and

B. New York Heart Association heart failure class II, III, or IV symptoms; and

C. Left ventricular ejection fraction greater than 20%; and

D. There is clinical documentation that the patient is either of the following:

1. Not a candidate for open surgery, or
2. At high risk for open surgery, defined as either of the following, as documented by the ordering provider:
   a. Society of Thoracic Surgeons predicted operative risk score of 8% or higher (see Policy Guidelines), or
   b. An expected mortality risk of 15% or higher for open surgery

III. Transcatheter aortic valve implantation or replacement is considered **investigational** when Criteria I. or II. is not met, including for all other indications and for non-FDA-approved devices.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

For the use of the SAPIEN or CoreValve devices, severe aortic stenosis is defined by the presence of one or more of the following criteria:

- An aortic valve area of less than or equal to 1 cm^2
- An aortic valve area index of less than or equal to 0.6 cm^2/m^2
- A mean aortic valve gradient greater than or equal to 40 mmHg
- A peak aortic-jet velocity greater than or equal to 4.0 m/s.

The Society of Thoracic Surgeons risk calculator can be found at http://riskcalc.sts.org/stswebriskcalc/calculate.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments
- The name of the valve system to be implanted

- Documentation of aortic valve stenosis (e.g., valve area, mean aortic valve gradient)
- In the case of valve-in-valve implantation, documentation that supports determination that patient is not a candidate or is high-risk for open surgery

CROSS REFERENCES

None

BACKGROUND

AORTIC STENOSIS

Aortic stenosis is defined as narrowing of the aortic valve opening, resulting in obstruction of blood flow from the left ventricle into the ascending aorta. Progressive calcification of the aortic valve is the most common etiology in North America and Europe, while rheumatic fever is the most common etiology in developing countries.[1] Congenital abnormalities of the aortic valve, most commonly a bicuspid or unicuspid valve, increase the risk of aortic stenosis, but aortic stenosis can also occur in a normal aortic valve. Risk factors for calcification of a congenitally normal valve mirror those for atherosclerotic vascular disease, and include advanced age, male gender, smoking, hypertension, and hyperlipidemia.[1] Thus, the pathogenesis of calcific aortic stenosis is thought to be similar to that of atherosclerosis, i.e., deposition of atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification.

The natural history of aortic stenosis involves a long asymptomatic period, with slowly progressive narrowing of the valve until the stenosis reaches the severe stage. At this stage, symptoms of dyspnea, chest pain, and/or dizziness/syncope often occur, and the disorder progresses rapidly.

Aortic stenosis does not cause substantial morbidity or mortality when the disease is mild or moderate in severity. By the time it becomes severe, there is an untreated mortality rate of approximately 50% within two years.[2] Open surgical replacement of the diseased valve with a bioprosthetic or mechanical valve is an effective treatment for reversing aortic stenosis, and artificial valves have demonstrated good durability for up to 20 years.[2] However, these benefits are accompanied by perioperative mortality of approximately 3% to 4% and substantial morbidity,[2] both of which increase with advancing age.

Many patients with severe, symptomatic aortic stenosis are poor operative candidates. Approximately 30% of patients presenting with severe aortic stenosis do not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities.[3] For patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of aortic stenosis but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes.[4] Balloon valvuloplasty can improve symptoms and increase flow across the stenotic valve but is associated with high rates of complications such as stroke, myocardial infarction, and aortic regurgitation. Also, restenosis can occur rapidly, and there is no improvement in mortality.

Transcatheter Aortic Valve Implantation

Transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), has been developed in response to this unmet need and was originally intended as an alternative for patients for whom surgery was not an option due to prohibitive surgical risk or for patients at high-risk for open surgery. The procedure is performed percutaneously, most often through the transfemoral artery approach. It can also be done through the subclavian artery approach and transapically using mediastinoscopy. Balloon valvuloplasty is first performed to open the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve and is then expanded and secured to the underlying aortic valve annulus. The procedure is performed on the beating heart without cardiopulmonary bypass.

REGULATORY STATUS

Multiple manufacturers have transcatheter aortic valve devices with FDA approval:

- Edwards SAPIEN Transcatheter Heart Valve System™ (Edwards Lifesciences)
    - Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX
    - Edwards SAPIEN XT Transcatheter Heart Valve (model 9300TFX) and accessories
    - SAPIEN 3 THV System, a design iteration
    - SAPIEN 3 Ultra THV System, a design iteration
      Note: In August 2019, FDA issued a recall for the Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System (Recall event ID: 83293) due to "reports of burst balloons which have resulted in significant difficulty retrieving the device into the sheath and withdrawing the system from the patient during procedures".

- Medtronic CoreValve System™ (Medtronic CoreValve)
    - Medtronic CoreValve Evolut R System™ (design iteration for valve and accessories)
    - Medtronic CoreValve Evolut PRO System™ (design iteration for valve and accessories, includes porcine pericardial tissue wrap)
    - Medtronic CoreValve Evolut PRO+ System™ (design iteration)

- LOTUS Edge™ Valve System (Boston Scientific)

  Note: In January 2021, Boston Scientific Corporation announced a global, voluntary recall of all unused inventory of the LOTUS Edge™ Valve System due to complexities associated with the product delivery system.[5] There are no safety concerns for patents who have the LOTUS Edge™ Valve System currently implanted. Boston Scientific has chosen to retire the entire LOTUS product platform immediately rather than develop and reintroduce an enhanced delivery system. All related commercial, clinical, research and development, and manufacturing activities will cease.

- Portico™ with FlexNav™ (Abbott Medical)

Other transcatheter aortic valve systems are under development. The following repositionable valves are under investigation:

- JenaValve™ (JenaValve Technology); designed for transapical placement

EVIDENCE SUMMARY

TAVI OUTCOMES IN PATIENTS AT PROHIBITIVE RISK FOR OPEN SURGERY

Systematic Reviews

Systematic reviews assessing whether TAVI improves outcomes for patients who are not suitable candidates for open surgery consist of summaries of case series. A systematic review sponsored by the Agency for Healthcare Research and Quality (2010, archived) evaluated 84 publications (total n=2,375 patients).[6] Implantation was successful in 94% of patients overall, with higher success rates reported in more recent publications. The aggregate 30-day survival was 89% across all studies. Adverse event rates were reported in the larger case series, with an estimated 30-day rate of major cardiovascular adverse event and stroke of 8%.

A systematic review by Figulla (2011) included studies that enrolled symptomatic patients with severe aortic stenosis who had a mean age of 75 years or older, reported on 10 or more patients, and had a follow-up duration of 12 months or more.[7] Twelve studies met these criteria and were compared with a group of 11 studies that treated severe aortic stenosis with nonsurgical therapy. The procedural success in these studies ranged from 86% to 100%, and the 30-day mortality ranged from 5.3% to 23%. The combined mean survival rate at one year was 75.9% (95% confidence interval [CI] 73.3% to 78.4%). This one-year survival rate compared favorably with medical therapy, which was estimated to be 62.4% (95% CI 59.3% to 65.5%).

Randomized Controlled Trials

<u>SAPIEN and SAPIEN XT</u>

The Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve (PARTNER) randomized controlled trial (RCT) was a pivotal multicenter trial of TAVI performed in the United States, Canada, and Germany, using the SAPIEN™ system. Leon (2010) reported on trial results for patients with severe aortic stenosis who were not candidates for open surgery, referred to as the PARTNER B trial.[8] To be classified as unsuitable for open surgery, patients had to have a predicted probability of 50% or higher for death or a serious irreversible condition at 30 days postsurgery. This probability was determined by two surgeon investigators using clinical judgment and the Society of Thoracic Surgery (STS) Risk Score. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as unsuitable for surgery. A total of 3,105 patients were screened for aortic valve surgery, and 12% of them were included in the cohort of patients deemed unsuitable for surgery.

In the trial, 358 patients were randomized to TAVI or usual care. TAVI was performed by the transfemoral approach under general anesthesia. Standard therapy was determined by treating clinicians. In most cases (83.8%), standard treatment included balloon valvuloplasty of the aortic valve. A small number of patients (6.7%) underwent open surgical valve replacement, despite the high risk, and another 2.2% of patients underwent TAVI at a center outside the United States not participating in the trial. The primary outcome was death from any cause during the trial (median follow-up 1.6 years). A coprimary endpoint was the composite of time to death from any cause or time to repeat hospitalization related to aortic stenosis or TAVI. Secondary endpoints were cardiovascular mortality, New York Heart Association (NYHA) functional class, the rates of hospitalizations due to aortic stenosis or

TAVI, the six-minute walk test (6MWT), valve performance as measured by echocardiography, and procedural complications (e.g., myocardial infarction [MI], stroke, acute kidney injury [AKI], vascular complications, bleeding).

The mean age of enrolled patients was 83.2 years. Some baseline imbalances in the patient population indicated that the standard therapy group might have had a higher severity of illness. Standardized scores of surgical risks were higher in the standard therapy group. The logistic EuroSCORE was significantly higher in the standard therapy group than in the TAVI group (30.4 vs. 26.4, p=0.04), and the STS score was numerically higher but was not statistically significant (12.1 vs. 11.2, respectively, p=0.14). Significantly more patients in the standard therapy group had chronic obstructive pulmonary disease (52.5% vs. 41.3%, p=0.04) and atrial fibrillation (48.8% vs. 32.9%, p=0.04), and there was a nonsignificant trend for more patients in the standard therapy group having a lower ejection fraction (51.1% vs. 53.9%) and frailty, as determined by prespecified criteria (28.0% vs. 18.1%), all respectively.

Death from any cause at one year after enrollment was lower for the TAVI group (30.7% vs. 49.7%, p<0.001). This represents a 19% absolute risk reduction, a 38.2% relative risk (RR) reduction, and a number needed to treat of 5.3 to prevent one death over a one-year follow-up. Most secondary outcomes also favored the TAVI group. Cardiovascular death was lower in the TAVI group (19.6% vs. 44.1%, p<0.001). The composite of all-cause mortality and repeat hospitalizations was reached by 42.5% of the patients in the TAVI group compared with 70.4% in the standard therapy group. Symptoms and functional status were also superior in the TAVI group. The percentage of patients in NYHA class I or II at one year was higher for the TAVI group (74.8% vs. 42.0%, p<0.001), and there was a significant improvement in the 6MWT for the TAVI group but not for the standard therapy group (between-group comparisons not reported). Subgroup analysis did not report any significant differences in outcomes according to clinical and demographic factors.

Complication rates were higher for the TAVI group. Stroke or transient ischemic attack (TIA) at one year was more than twice as frequent for the TAVI group (10.6% vs. 4.5%, p=0.04). Major bleeding and vascular complications occurred in a substantial percentage of patients undergoing TAVI (22.3% vs. 11.2%, p=0.007) and were significantly higher than in the standard therapy group (32.4% vs. 7.3%, p<0.001).

Quality of life (QoL) outcomes from this trial were reported by Reynolds (2011), and were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score, the 12-Item Short-Form Health Survey (SF-12), and the EuroQoL (EQ-5D).[9] The number of participants who completed the QoL measures was not clearly reported; estimates from graphical representation show that between 149 and 170 patients in the TAVI group and 138 and 157 patients in the medical therapy group completed baseline QoL measures. At follow-up time points of 30 days, six months, and 12 months, change in the QoL scores was greater for the TAVI group. At 30 days, the mean difference in the KCCQ score was 13.3 points (95% CI 7.6 to 19.0, p<0.001). This mean difference increased at later time points to 20.8 points (95% CI 14.7 to 27.0, p<0.001) at six months and to 26.0 points (95% CI 18.7 to 33.3, p<0.001) at 12 months. Changes in the SF-12 and EQ-5D measures showed similar patterns.

Two-year outcomes from the PARTNER trial were reported by Makkar (2012).[10] Mortality at two years was 43.3% in the TAVI group compared with 68.0% in the medical therapy group (hazard ratio [HR] 0.58, 95% CI 0.36 to 0.92, p=0.02). Cardiovascular mortality was also lower

with TAVI (31.0%) than with medical therapy (62.4%, p<0.001). The rate of hospitalization over the two-year period was lower with TAVI (35.0%) than with medical therapy (72.5%, p<0.001).

Svensson (2014) reported detailed mortality outcomes for both arms of the PARTNER trial: the PARTNER B RCT (previously described), which compared surgical repair with TAVI in prohibitive surgical risk patients, and the PARTNER A RCT, which compared surgical repair with TAVI in high surgical risk patients (described next).[11] For the 358 patients considered inoperable and enrolled in the PARTNER B trial, 237 patients had died at last follow-up. Those randomized to standard therapy exhibited an early peak in mortality that was higher than those randomized to TAVI, and that persisted beyond six months. Compared with standard therapy, the estimated net lifetime benefit added by transfemoral TAVI was 0.50 years (90% CI 0.30 to 0.67).

Kapadia (2014) reported on three-year outcomes for 358 prohibitive-risk patients randomized to standard therapy or TAVI in the PARTNER trial, along with all outcomes (early and long-term) for randomized inoperable PARTNER patients, including 91 subjects in the randomized PARTNER continued-access study.[12] Analysis of the pooled randomized patients was anticipated in the study protocol. At the three-year follow-up for the pivotal trial subjects, all-cause mortality was 54.1% in the TAVI group and 80.9% in the standard therapy group (HR 0.53, 95% CI 0.41 to 0.68, p<0.001). The incidence of stroke was higher in the TAVI group (15.7%) than in the standard therapy group at three years (5.5%, HR 3.81, 95% CI 1.26 to 6.26, p=0.012). However, at three years, the incidence of the composite of death or stroke was significantly lower in the TAVI group (57.4% vs. 80.9%, HR 0.60, 95% CI 0.46 to 0.77, p<0.001). Survivors at three years who had undergone TAVI were more likely to have NYHA class I or II symptoms than those who had received standard therapy. In the pooled sample, at the two- and three-year follow-ups, mortality was lower for patients who had undergone TAVI than in those who had standard therapy (at two years: 44.8% vs. 64.3%, at three years: 54.9% vs. 78.0%, all p<0.001).

Webb (2015) reported on a multicenter RCT comparing a newer-generation SAPIEN XT system with the original SAPIEN system in 560 patients with severe, symptomatic aortic stenosis considered at prohibitive risk for open surgery.[13] The trial used a noninferiority design; for its primary endpoint, a composite of all-cause mortality, major stroke, and rehospitalization at one year in the intention-to-treat population, the RR between the SAPIEN and SAPIEN XT groups was 0.99 (p<0.002), which met the criteria for noninferiority.

Kapadia (2019) reported an analysis of stroke risk and its association with QoL after surgical aortic valve replacement (SAVR) versus TAVR from a propensity-matched study of 1,204 pairs of patients in the PARTNER trials.[14] The analysis focused only on as-treated SAVR and transfemoral TAVR. The incidence of stroke by 30 days was 5.1% in SAVR versus 3.7% in TAVR; incidence of 30-day major stroke was 3.9% versus 2.2% (p=0.018). In both groups, risk of stroke peaked in the first post-procedure day but then remained low out to 48 months. Major stroke was associated with a decline in QoL as measured by the KCCQ at one year.

Huded (2022) reported on rehospitalization rates from the PARTNER trial, finding no effect modification by transcatheter versus surgical aortic valve replacement.[15]

Nonrandomized Studies

Many case series of TAVI have been published in the last 10 years, most of which have included patients that were not candidates for open surgery. However, the selection process

for TAVI has largely been subjective, with the expert opinion of the surgeons and/or cardiologists as the main factor determining suitability for open surgery. As a result, there may be overlap in these series with patients who are surgical candidates, but the distinction cannot be gleaned easily from the reported studies.

Some of the larger and/or prospective case series are discussed next, including the series reporting on the pivotal trials leading to devices' approvals.

CoreValve Extreme Risk Study

Popma (2014) published results of the CoreValve Extreme Risk Study pivotal trial, which was designed to evaluate the CoreValve self-expanding valve among patients with severe aortic stenosis who were considered to be at extreme risk (NYHA class ≥II) for SAVR.[16] A patient was judged to be at extreme risk if two cardiac surgeons and one interventional cardiologist at the clinical site estimated a 50% or greater risk for mortality or irreversible morbidity at 30 days with surgical repair. The study's primary endpoint was the 12-month rate of all-cause mortality or major stroke in the "attempted implant" population. This population included all patients who underwent a documented valve implant via an iliofemoral approach. The study defined an objective performance goal of 43% for all-cause mortality or major stroke at 12 months postprocedure. This goal was based on two sources: (1) a weighted meta-analysis of seven balloon aortic valvuloplasty studies, which yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% CI 34.0% to 51.4%); and (2) an adjusted estimate based on the lower 95% confidence bound of 43% in the standard therapy arm of inoperable patients in the PARTNER trial.

There were 489 patients included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study before treatment, six of whom did not complete the procedure with iliofemoral access). The Kaplan-Meier estimate of the primary endpoint (all-cause mortality or major stroke) was 26.0% (upper bound of 95% CI 29.9%), which was lower than the prespecified performance goal of 43% ($p<0.001$). The rate of all-cause mortality at one year following enrollment was 24.3%, while the rate of major stroke at 12 months was 4.3%. These rates are comparable or better than those seen in the TAVI arm of the PARTNER pivotal trial, although patients in the PARTNER pivotal trial had a higher baseline STS score (12.1% in the PARTNER trial vs. 10.3% in the CoreValve Extreme Risk trial).

Two-year results from the CoreValve study were reported by Yakubov (2015).[17] The Kaplan-Meier estimate of all-cause mortality or major stroke was 38.0% (upper bound of 95% CI 42.6%). The incremental rates between years one and two were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke. Baron (2017) reported on three-year results of the QoL data.[18] The QoL improvements following TAVR were largely sustained through three years with clinically meaningful (≥10 points) improvements in the KCCQ overall summary score at three years observed in greater than 83.0%. At five years of follow-up, the Kaplan-Meier rate of death or major stroke was 72.6%, and the KCCQ remained improved compared with pre-TAVI scores.[19]

Osnabrugge (2015) reported on health status outcomes for the 471 patients who underwent TAVI via the transfemoral approach.[20] On average, general and disease-specific QoL scores both showed substantial improvements after TAVI. However, 39% of patients had a poor outcome at six months (22% death, 16% very poor QOL, 1.4% QoL declined).

Reardon (2014) reported on outcomes for the group of patients enrolled in the CoreValve study who received the device through an approach other than the iliofemoral.[21] Inclusion criteria and procedures were the same as for the primary CoreValve Extreme Risk Trial. One hundred fifty patients with prohibitive iliofemoral anatomy were included and received the CoreValve device through an open surgical approach via the subclavian artery (n=70) or a direct aortic approach via a median hemisternotomy or right thoracotomy (n=80). Included patients were elderly (mean age 81.3 years) and significantly symptomatic, with 92% of subjects having NYHA class III or IV heart disease. At 30 days postprocedure, 23 (15.3%) patients met the primary endpoint of all-cause mortality or major stroke; of the 23 patients, 17 (11.3%) died, and 11 (7.5%) experienced a major stroke. At 12 months postprocedure, 59 (39.4%) patients met the primary endpoint; of those, 54 (36%) died, and 13 (9.1%) experienced a major stroke. The 30-day mortality of 11.3% was higher than that reported in the studies of TAVI using a transfemoral or an iliofemoral approach (PARTNER B RCT and the CoreValve Extreme Risk Pivotal Trial) but similar to the 30-day mortality reported by the patients treated with a transapical approach (PARTNER A trial).

Post-approval Registries

Mack (2013) reported on outcomes after TAVI from 224 hospitals participating in the Edwards SAPIEN device post-FDA approval registry.[22] From November 2011 to May 2013, the registry included 7,710 patients who underwent TAVI placement, of whom 1,559 (20%) patients were considered inoperable and 6,151 (80%) were considered high-risk but operable. Of those considered inoperable, 1,139 underwent device placement via transfemoral access, while 420 underwent device placement via nontransfemoral access. In-hospital mortality was 5.4% and 7.1% for the inoperable patients who underwent TAVI via transfemoral and nontransfemoral access, respectively. Thirty-day clinical outcomes were reported for 694 inoperable patients; of those, 30-day mortality was 6.7% and 12.6% for patients who underwent TAVI via transfemoral and nontransfemoral access, respectively.

Additional Case Series

The prospective nonrandomized Treatment of Aortic Stenosis With a Self-Expanding Transcatheter Valve: the International Multi-Centre ADVANCE study had central adjudication of endpoints and adverse events to evaluate the CoreValve implants in individuals with severe symptomatic aortic stenosis who were considered inoperable or at higher risk for SAVR.[23] The study enrolled 1,015 patients, of whom 996 were implanted, most (88.4%) by the iliofemoral approach, with 9.5% and 2.1% by the subclavian and direct aortic approaches, respectively. For the study's primary endpoint of major adverse cardiac and cerebrovascular events (MACCE; a composite of all-cause mortality, MI, stroke, or reintervention), rates were 8.0% (95% CI 6.3% to 9.7%) at 30 days and 21.2% (95% CI 18.4% to 24.1%) at 12 months. The all-cause mortality rate was 4.5% (95% CI 3.2% to 5.8%) at 30 days and 17.9% (95% CI 15.2% to 20.5%) at 12 months. Overall, strokes occurred in 3.0% (95% CI 2.0% to 4.1%) at 30 days and in 4.5% (95% CI 2.9% to 6.1%) at 12 months. A new permanent pacemaker was implanted in 26.3% (95% CI 23.5% to 29.1%) and in 29.2% (95% CI 25.6% to 32.7%) of patients at 30-day and 12-month follow-ups, respectively. Patients were grouped into three categories of surgical risk based on logistic EuroSCORE values (≤10%, >10% to ≤20%, and >20%). Thirty-day survival did not differ significantly across risk groups, but 12-month rates of MACCE, all-cause mortality, cardiovascular mortality, and death from any cause or major stroke were higher for higher surgical risk patients.

The two largest series included in the Agency for Healthcare Research and Quality review[6] (described previously) reported on 646 patients treated with the CoreValve[24] and 339 patients treated with the SAPIEN valve.[25] The CoreValve study by Piazza (2008) was notable in that it used more objective patient selection criteria than is common in this literature.[24] Their criteria for eligibility included: (1) logistic EuroSCORE of 15% or higher, (2) age of 75 or older, or (3) age of 65 or older with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns, or radiation precluding open surgery, or body mass index of 18 kg/m^2 or less. Procedural success was 97%, and 30-day survival was 92%. The 30-day combined rate of death, MI, or stroke was 9.3%. The Canadian study by Rodes-Cabau (2010) used the SAPIEN valve.[25] This study had subjective inclusion criteria, relying on the judgment of the participating surgeons to determine eligibility for TAVI. The procedural success rate was 93.3%, and the 30-day mortality was 10.4%. The authors also reported a mortality rate of 22.1% at a median follow-up of eight months.

Additional series have described experiences with TAVI in European centers. Zahn (2011), in a large case series from Germany, reported on 697 patients treated with the CoreValve system.[26] Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series from Italy included 663 patients treated with the CoreValve device.[27] Procedural success was 98%, and mortality at one year was 15%.

Section Summary: TAVI Outcomes in Patients at Prohibitive Risk for Open Surgery

Numerous case series have demonstrated the feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at one year for TAVI compared with standard therapy. Subsequent publications from this same trial reported that the mortality benefit was maintained at two years and that QoL was improved for the TAVI group. Baseline between-group differences were present, indicating that the TAVI group may have been healthier. While these differences are unlikely to account for the degree of mortality benefit reported, they may have resulted in an overestimation of the mortality benefit. The CoreValve Extreme Risk Study pivotal trial also demonstrated mortality rates much lower than the prespecified performance goal and comparable or better than those seen in the TAVI arm of the PARTNER pivotal trial.

The benefit in mortality was accompanied by an increased stroke risk as well as substantial increases in vascular complications and major bleeding. There is also uncertainty concerning the generalizability of these results because patient selection was primarily determined by the cardiovascular surgeons and/or cardiologists. It is not known whether this type of decision making is reliable across the range of practicing clinicians.

TAVI OUTCOMES IN PATIENTS AT HIGH RISK FOR OPEN SURGERY

Systematic Reviews

A meta-analysis of four RCTs was published by Panoulas (2018) to determine whether sex differences had any impact on mortality rates for TAVI and SAVR.[28] The four RCTs comprised of 3,758 patients (2,052 men, 1,706 women); all patients had severe aortic stenosis. The study revealed that among women undergoing TAVI, a significantly lower mortality rate was found than in women undergoing SAVR at the one-year mark; in fact, women undergoing TAVI were found to have a 31% lower mortality rate than women undergoing SAVR, again at the one-year

mark (odds ratio [OR] 0.68, 95% CI 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVR versus men undergoing SAVR. An updated meta-analysis by Dagan (2021) identified eight RCTs including 8,040 patients (41.4% female).[29] Similar results were found to the 2018 analysis with lower one-year mortality and improved safety with TAVI compared with SAVR in women.

Villablanca (2016) reported on a meta-analysis and meta-regression of long-term outcomes (more than one year) of TAVI compared with SAVR for severe aortic stenosis.[30] Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO.[30] The review was limited to studies comparing TAVI with surgical repair, with subgroup analyses for high- and intermediate-risk patients. Overall, four RCTs (n=3,806 patients) and 46 observational studies (n=40,441 patients) were included, with a median follow-up of 21.4 months. Two of the RCTs were conducted in high-risk patients and are described in detail below (PARTNER 1[31] and CoreValve High Risk Trial[32]). Results from the subgroup analyses focused on high-risk patients are shown in Table 1.

Table 1. TAVI Versus Surgical Repair in High-Risk Patients

Outcomes	TAVI[a]	Surgical Repair[a]	RR for TAVI vs. Surgical Repair (95% CI)	I^2, %
30-day postprocedure mortality	508/8,552 (5.9%)	804/29,323 (2.7%)	1.02 (0.76 to 1.36)	72.3
All-cause mortality	3,625/8,803 (41.1%)	5,438/29,450 (18.6%)	1.16 (0.87 to 1.53)	96.6
Stroke incidence	191/4,293 (4.4%)	213/4,348 (4.9%)	0.79 (0.66 to 0.95)	0
Myocardial infarction incidence	57/2,820 (2.0%)	59/2,746 (2.1%)	0.91 (0.64 to 1.29)	21.5
Vascular complication incidence	203/2,489 (8.2%)	35/2,682 (1.3%)	5.5 (2.42 to 12.4)	67.5
Residual regurgitation incidence	268/2,831 (9.5%)	36/2,823 (1.3%)	6.3 (4.55 to 8.71)	0
Requirement for permanent pacemaker incidence	527/3,449 (15.3%)	236/3,653 (6.4%)	1.68 (0.94 to 3.00)	83.2
New-onset AF incidence	165/1,192 (13.8%)	376/1,281 (29.4%)	0.38 (0.26 to 0.55)	64.6
Major bleeding incidence	321/2,074 (15.4%)	416/2,298 (18.1%)	0.73 (0.65 to 0.83)	24.2
Acute kidney injury incidence	294/3,446 (8.5%)	396/3,528 (11.2%)	0.73 (0.53 to 1.01)	68.4

Adapted from Villablanca (2016).[30]
AF: atrial fibrillation; CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.
[a] Values are n/N (%).

Earlier systematic reviews focused largely on nonrandomized comparative studies because only one RCT had been published at the time of the reviews (the PARTNER trial). Panchal (2013) reported on results from a meta-analysis of 17 studies that included 4,659 patients: 2,267 treated with TAVI and 2,392 treated with open surgery.[33] Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality, which was higher by a mean of 3.7 points compared with patients undergoing open surgery. On combined analysis, there were no differences between groups for 30-day mortality, mortality at longest follow-up, cardiovascular mortality, MI, stroke, or TIA. Patients in the open surgery group had a higher incidence of major bleeding complications (RR 1.42, 95% CI 1.20 to 1.67, p<0.001). In a similar meta-analysis (2013) that included 17 studies reporting on 4,873

patients, there were no differences between TAVI and open surgery in early mortality (OR 0.92, 95% CI 0.70 to 1.2) or mid-term mortality, defined as between three months and three years (HR 0.99, 95% CI 0.83 to 1.2).[34]

Randomized Controlled Trials

SAPIEN PARTNER A Trial

Smith (2011) published results from the cohort of patients in the PARTNER trial of the SAPIEN valve who were at high-risk for open surgery, but still suitable candidates.[35] The inclusion and exclusion criteria were generally the same as those for the prior cohort, except that these patients were classified as high-risk for surgery rather than unsuitable for surgery. For high-risk, patients had to have a predicted perioperative mortality of 15% or higher, as determined by a cardiac surgeon and cardiologist using clinical judgment. An STS Risk Score of 10 or higher was included as a guide for high-risk, but an STS Risk Score threshold was not a required criterion for enrollment. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as high-risk for surgery. A total of 3,105 patients were screened for aortic valve surgery, and 22.5% of them were included in the cohort of patients deemed high-risk for surgery.

There were 699 patients randomized to TAVI or surgical aortic valve repair. The primary hypothesis was that TAVI was noninferior to open AVR, using a one-sided noninferiority boundary of 7.5% absolute difference in mortality at one year. Patients were first evaluated to determine if they were eligible for TAVI via the transfemoral approach. Four hundred ninety-two patients were eligible for transfemoral TAVI; the remaining 207 were categorized as the transapical placement cohort. Within each cohort (transfemoral and transapical), patients were randomized to surgical aortic valve repair (n=351) or TAVI (n=348).

The primary outcome was death from any cause at one-year follow-up. A second powered endpoint was noninferiority at one year for patients undergoing TAVI by the transfemoral approach. Secondary endpoints were cardiovascular mortality, NYHA functional class, rehospitalizations, 6MWT, valve performance as measured by echocardiography, and procedural complications (MI, stroke, AKI, vascular complications, bleeding). Mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographic and clinical characteristics were generally well-balanced, except for a trend toward an increased percentage of patients in the TAVI group with a creatinine level greater than 2.0 mg/dL (11.1% vs. 7.0%, p=0.06).

Death from any cause at one year following enrollment was 24.2% for the TAVI group and 26.8% for the open AVR group (between-group difference, p=0.44). The upper limit of the 95% CI for the between-group difference was a 3.0% excess mortality in the TAVI group, which was well within the noninferiority boundary of 7.5%. Thus, the criterion of noninferiority was met (p=0.001). For the subgroup of patients who underwent TAVI by the transfemoral approach, results were similar, with 22.2% mortality in the TAVI group and 26.4% mortality in the open AVR group (p=0.002 for noninferiority). The secondary outcomes of cardiovascular mortality (14.3% vs. 13.0%, p=0.63) and rehospitalizations (18.2% vs. 15.5%, p=0.38) did not differ significantly between the TAVI and the open AVR groups, respectively. The percentage of patients in NYHA class I or II at one year was similar between groups at one year, as was an improvement on the 6MWT. On subgroup analysis, there was a significant effect for sex, with women deriving greater benefit than men (p=0.045), and a significant effect for prior coronary

artery bypass graft, with patients who had not had prior coronary artery bypass graft deriving greater benefit in the TAVI group.

Certain complication rates showed significant differences between groups. Stroke or TIA at one year was higher for the TAVI group (8.3% vs. 4.3%, respectively, p=0.04). Vascular complications occurred in 18.0% of patients undergoing TAVI compared with 4.8% in the open AVR group (p=0.01), and major vascular complications were also higher in the TAVI group (11.3% vs. 3.5%, p=0.01). On the other hand, major bleeding was more common in the open group (25.7%) compared with the TAVI group (14.7%, p=0.01).

Five-year results from the PARTNER trial were reported by Mack (2015).[31] At five-year follow-up, in the intention-to-treat population, the risk of death from any cause did not differ significantly between patients treated with TAVI (67.8%) and those treated with surgical repair (62.4%, HR 1.04, 95% CI 0.86 to 1.24, p=0.76). As reported in the original PARTNER trial findings, moderate or severe aortic regurgitation – primarily paravalvular regurgitation – was more common among TAVI-treated patients. Among TAVI-treated patients, the presence of aortic regurgitation was associated with increased five-year mortality risk (72.4% for moderate or severe aortic regurgitation vs. 56.6% for mild aortic regurgitation or less, p=0.003).

Reynolds (2012) published QoL results from the PARTNER A trial.[36] QOL outcomes were evaluated using the KCCQ summary score, the SF-12, and the EQ-5D. Of 699 patients in the trial, 628 completed baseline QoL measures. Patients in both the TAVI group and the SAVR group demonstrated significant improvements in all QoL measures over the 12 months following treatment. The TAVI group had superior improvement at one month on the KCCQ (mean difference 9.9, 95% CI 4.9 to 14.9, p<0.001), but this difference was no longer present at 6 or 12 months. A similar pattern of results was reported for the SF-12 and EQ-5D measures.

Genereux (2014) published a follow-up study from the PARTNER A trial reporting on bleeding complications.[37] Using an as-treated approach, this analysis included 313 patients treated with surgical repair, 240 patients treated with transfemoral TAVI, and 104 patients treated with transapical TAVI. Seventy-one (22.7%) patients treated with surgery had major bleeding complications within 30 days of the procedure, compared with 27 (11.3%) of those treated with transfemoral TAVI and 9 (8.8%) of those treated with transapical TAVI (p<0.001).

U.S. CoreValve High-Risk Study

Adams (2014) published results of the U.S. CoreValve High Risk Study.[38] This RCT compared SAVR with TAVI using the CoreValve device in patients who had severe aortic stenosis and were considered at increased risk of death during surgery. The study randomized 795 patients in a 1:1 ratio to TAVI or open AVR. Patients were considered to be at “increased surgical risk” if two cardiac surgeons and one interventional cardiologist estimated that the risk of death within 30 days of surgery was 15% or more and that the risk of death or irreversible complications within 30 days after surgery was less than 50%. The primary analysis was based on the as-treated population, which included all patients who underwent attempted implantation. For the study’s primary outcome, the rate of death from any cause at one year was lower in the TAVI group (14.2%) than in the surgical group (19.1%, absolute risk reduction, 4.9%, upper boundary of 95% CI -0.4%, which was less than the predefined noninferiority margin of 7.5%-point difference between groups, noninferiority, p<0.001, superiority, p=0.04). Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVI group than in the surgical group: at 30 days, major

vascular complications occurred in 5.9% of the TAVI group compared with 1.7% of the surgical group (p=0.003), while permanent pacemaker implantation was required in 19.8% of the TAVI group compared with 7.1% of the surgical group (p<0.001). In contrast to the PARTNER trial, the TAVI group did not have a higher rate of any stroke at one year postprocedure (8.8%) than the surgical group (12.6%, p=0.10).

Two-year follow-up results from the U.S. CoreValve High Risk Study were published by Reardon (2015).[32] At that point, the mortality benefits seen with TAVI were maintained.

A three-year follow-up analysis was reported by Deeb (2016), which found sustained improvements in the TAVI-treated group for all-cause mortality, stroke, and MACCE compared with the surgical group.[39] At three years, 37.3% (n=142) of TAVI-treated patients experienced all-cause mortality or stroke, which was significantly less than the 46.7% (n=160) of surgical patients for the same outcome (p=0.006). In the TAVI group, MACCE was observed in 40.2% (n=153) of patients; in the surgical group, MACCE occurred in 47.9% (n=164) of patients (p=0.025). Other outcomes that were improved in the TAVI group compared with surgery were life-threatening or disabling bleeding, AKI, aortic valve area, and mean aortic valve gradient. More TAVI-treated patients required implantation of a pacemaker (28.0%) than did surgical patients (14.5%, p<0.001); also, more patients in the TAVI group (6.8%) had moderate atrial regurgitation than in the surgery group (0.0%) at three years. The authors noted the improvement in mean aortic valve gradient for both cohorts (TAVR 7.62 mmHg vs. SAVR 11.40 mmHg, p<0.001).

Additional analyses of the U.S. CoreValve High Risk Study have focused on the impact of patient and prosthesis mismatch[40] and health status.[41]

Conte (2017) analyzed both periprocedural and early complications (0-3 days and 4-30 days postoperative, respectively) in patients from the U.S. CoreValve High Risk Study.[42] There were no statistically significant differences in all-cause mortality, stroke, MI, or major infection in either the periprocedural period (0-3 days) or between 4 and 30 days postprocedure. Major vascular complication rate within three days was significantly higher with TAVR (6.4% vs. 1.4%, p=0.003). Life-threatening or disabling bleeding (12.0% vs. 34.0%, p<0.001), encephalopathy (7.2% vs. 12.3%, p=0.02), atrial fibrillation (8.4% vs. 18.7%, p<0.001), and AKI (6.1% vs. 15.0%, p<0.001) were significantly higher with SAVR.

Gleason (2019) reported five-year follow-up of the CoreValve High Risk Trial and estimated similar five-year survival (55.3% for TAVR vs. 55.4% for SAVR) and stroke rates (12.3% for TAVR versus 13.2% for SAVR) in high-risk patients. Valve reintervention were uncommon; freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR.[43]

REPRISE III

The Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System–Randomized Clinical Evaluation (REPRISE III) trial was an RCT comparing two different TAVR platforms: the mechanically expanded Lotus valve (which was discontinued in January 2021) and self-expanding CoreValve. Thirty-day and one-year results were reported in the Summary of Safety and Effectiveness compiled by the FDA and two-year results were published by Reardon (2019).[44 45] The trial enrolled 912 patients (n=607 in Lotus, n=305 in CoreValve) with high/extreme risk and severe, symptomatic aortic stenosis between September 2014, and December 2015 at 55 centers in North America, Europe, and Australia. An early-generation CoreValve device was used. Follow-up is scheduled to continue for up to

five years. Patients were required to have an STS-prom risk score of ≥8% or another indicator of high or extreme risk. The mean age was 83 years and the mean STS-PROM score was 6.8%. The primary safety outcome was a composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 AKI, or major vascular complications at 30 days. The primary effectiveness outcome was a composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation at one year. At 30 days, the incidence of the primary safety outcome was 20% versus 17% for Lotus versus CoreValve (risk difference [RD] 3.1%, 95% CI -2.3 to 8.5) and met the criteria for noninferiority. All of the individual components of the 30-day primary safety outcome were similar between the two groups. The incidence of the primary effectiveness outcome was 16% versus 26% in Lotus versus CoreValve (RD -10.2%, 95% CI -16.3 to 4.0) and met the criteria for noninferiority. At two years, all-cause death was 21% vs. 22.5% with Lotus versus CoreValve (HR 0.94, 95% CI 0.69 to 1.26) and all-cause mortality or disabling stroke was 23% vs. 27% with Lotus versus CoreValve (HR 0.81, 95% CI 0.61 to 1.07). Placement of a new permanent pacemaker was more common in the Lotus group (42% vs. 26%, HR 1.9, 95% CI 1.4 to 2.5). Valve thrombosis was also more common in the Lotus group (3% vs. 0%). Repeated procedures were more common in the CoreValve group (0.6% vs. 2.9%, HR 0.19, 95% CI 0.05 to 0.70), as was valve migration (0.0% vs. 0.7%) and embolization (0.0% vs. 2.0%).

PORTICO IDE

The Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption (PORTICO IDE) trial enrolled patients with severe aortic stenosis at high or extreme surgical risk.[46] Patients were randomized to a Portico valve (n=381) or another FDA-approved valve (n=369). The primary efficacy endpoint was a composite of all-cause mortality and stroke at one year, and the primary safety endpoint was a composite of all-cause mortality, disabling stroke, life-threatening bleeding, AKI, or major vascular complications. Overall, the mean age was 83 years with females comprising 52.7% of patients. Additional demographic characteristics were not reported. The primary efficacy endpoint at one year was similar between groups (14.8% in the Portico group vs. 13.4% with other valves, absolute difference 1.5%, 95% CI -3.6 to 6.5). For the composite safety endpoint at 30 days, the event rate was higher with the Portico valve (13.8% vs 9.6%, absolute difference 4.2%, 95% CI -0.4 to 8.8). At two years, the rates of death or disabling stroke were similar between groups.

Nonrandomized Studies

Since the publication of the pivotal RCTs and systematic reviews described previously, a number of nonrandomized studies have compared surgical with TAVR.[47-49] Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.

Section Summary: TAVI Outcomes in Patients at High Risk for Open Surgery

The most direct evidence related to the use of TAVI compared to SAVR for aortic stenosis in patients who are at high but not prohibitive risk of surgery comes from two industry-sponsored RCTs. The PARTNER RCT in high-risk patients who were eligible for SAVR reported no differences between TAVI and open AVR in terms of mortality at one year and most major secondary outcomes. The noninferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality. The reported mortality for the TAVI group was lower than that for the open group, although not significantly better. QoL was also similar at one year between the TAVI and AVR groups. Stroke and TIA were significantly more common for the TAVI

group, occurring at a rate of almost two times that reported for open surgery. Other secondary outcomes were similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern about the generalizability of results because the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. The U.S. CoreValve High Risk Study reported that TAVI was noninferior to open surgical repair. Although unlike the PARTNER A trial, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group. Follow-up analyses of the U.S. CoreValve High Risk Study showed sustained improvements in the TAVI group for the outcome of all-cause mortality and a number of secondary outcomes. The incidence of pacemaker implantation continued to be higher in TAVI-treated patients.

The Portico valve was compared with other FDA-approved valves. Although more safety events were noted at 30 days, the valves had comparable outcomes at two years.

TAVI OUTCOMES IN PATIENTS AT INTERMEDIATE RISK OR LOW RISK FOR OPEN SURGERY

Systematic Reviews

Several systematic reviews and meta-analyses were published in 2017 through 2020,[50-63] including many overlapping RCTs and observational studies.

In a Cochrane review, Kolkailah (2019) evaluated the literature on TAVI versus SAVR for severe aortic stenosis in patients with low surgical risk.[64] The review included four studies (n=2,818) and one ongoing study. Results revealed that there is probably little or no difference between TAVI and SAVR with regard to the following short-term outcomes: all-cause mortality (RR 0.69, 95% CI 0.33 to 1.44), stroke (RR 0.73, 95% CI 0.42 to 1.25), myocardial infarction (RR 0.82, 95% CI 0.42 to 1.58), and cardiac death (RR 0.71, 95% CI 0.32 to 1.56). TAVI may potentially reduce the risk of short-term hospitalization as well (RR 0.64, 95% CI 0.39 to 1.06) and result in an increased risk of permanent pacemaker implantation (RR 3.65, 95% CI 1.50 to 8.87). TAVI reduces the risk of atrial fibrillation (RR 0.21, 95% CI 0.15 to 0.3), AKI (RR 0.3, 95% CI 0.16 to 0.58), and bleeding (RR 0.31, 95% CI 0.16 to 0.62) compared to SAVR.

Garg (2017) published a systematic review and meta-analyses that included RCTs and prospective observational studies comparing TAVI with SAVR published between January 2000 and March 2017 including low-to-intermediate surgical risk patients with severe aortic stenosis.[52] Five RCTs (n=4,425 patients) were included and are discussed in the following section. The meta-analytic results pooling the RCTs are shown in Table 2.

Table 2. TAVI Versus Surgical Repair in Low- or Intermediate-Risk Patients

Outcomes	TAVI	Surgical Repair	RR for TAVI vs. Surgical Repair (95% CI)	p	I^2
30-day mortality	3.1	3.0	1.04 (0.73 to 1.47)	0.84	0
Stroke incidence	7.3	8.1	0.91 (0.74 to 1.11)	0.35	0
Acute kidney injury incidence	1.8	4.7	0.38 (0.26 to 0.54)	<0.001	0
Myocardial infarction incidence	3.1	3.1	1.00 (0.71 to 1.41)	1.00	0
Major vascular complication incidence	7.3	3.2	3.09 (1.51 to 6.35)	0.002	66
Requirement for permanent pacemaker incidence	20.0	7.9	3.10 (1.44 to 6.66)	0.004	92

Adapted from Garg (2017).[52]
Values are percent unless other noted.
CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.

Zhou (2016) reported on a meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery.[65] Seven studies were included: three RCTs (Nordic Aortic Intervention Trial [NOTION; 2015],[66]Transapical Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis [STACCATO; 2012],[67] Leon [2016][68]) and four observational studies (total n=6,214 patients, 3,172 [51.0%] treated with TAVI). The main meta-analytic results are summarized in Table 3. Importantly, this review included a meta-analytic result for mortality at one year.

Table 3. TAVI Versus Surgical Repair in Low- or Intermediate-Risk Patients

Outcomes	TAVI	Surgical Repair	RR for TAVI vs. Surgical Repair (95% CI)	p	I^2
Short-term postprocedure mortality	2.59	3.94	0.63 (0.37 to 1.08)	0.09	56
Short-term cardiovascular mortality	1.96	3.15	0.51 (0.23 to 1.15)	0.11	68
Acute kidney injury incidence	1.92	4.8	0.34 (0.17 to 0.67)	0.002	61
Stroke incidence	3.57	4.90	0.72 (0.56 to 0.92)	0.01	42
Myocardial infarction incidence	0.7	1.7	0.51 (0.23 to 0.69)	<0.001	10
Major vascular complication incidence	7.2	3.6	3.54 (1.42 to 8.81)	0.006	86
Requirement for permanent pacemaker incidence	11.9	6.1	2.79 (1.49 to 5.23)	0.001	88
All-cause mortality (one year)	10.1	12.2	0.82 (0.58 to 1.16)	0.26	67

Adapted from Zhou (2016).[65]
Values are percent unless other noted.
CI: confidence interval; OR: odds ratio; TAVI: transcatheter aortic valve implantation.

Earlier systematic reviews came to similar conclusions.[69 70] Siemieniuk (2016) also reported on a systematic review and meta-analysis comparing TAVI with surgical repair in patients at low- or intermediate-risk of open surgery, with the aim of evaluating valve durability and need for reinterventions.[71]

Overall, the results suggest that for intermediate and low operative risk patients, periprocedural and short-term (one-year) mortality rates do not differ significantly between TAVI and open aortic valve repair. However, like the high- and prohibitive-risk populations, TAVI is associated with higher rates of major vascular complications, paravalvular regurgitation, and need for permanent pacemakers, but lower rates of major bleeding.

RANDOMIZED CONTROLLED TRIALS

Eight RCTs including patients with severe aortic stenosis who were at low and/or intermediate risk for open surgery have been published. The RCTs are summarized in Tables 4 and 5 and the following paragraphs.

Table 4. Characteristics of RCTs Comparing TAVI With SAVR in Patients at Low and Intermediate Surgical Risk

					Interventions		
Study and Trial	Countries	Sites	Dates	Participants	TAVR	SAVR	Sponsor
Nielsen	Denmark	2	Nov	Mean age, 81	n=34	n=36	Participating

					Interventions		
Study and Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVR**	**SAVR**	**Sponsor**
(2012)[67] STACCATO			2008-May 2011	years No significant coronary artery disease Any surgical risk (mean STS PROM, 3.3)	Edwards Sapien THV	Conventional open-heart surgery with CPB	hospitals and Danish Heart Foundation
Thyregod (2015)[66] Søndergaard (2016)[72] Thyregod (2019)[73] Søndergaard (2019)[74] NOTION (NCT01057173)	Denmark, Sweden	3	Dec 2009-Apr 2013	Mean age, 79 years No significant coronary artery disease Any surgical risk (mean STS PROM, 3.0; 82% low-risk)	n=145 Core-Valve	n=135 Conventional open-heart surgery with CPB	Danish Heart Foundation
Reardon (2016)[75] CoreValve U.S. Pivotal (NCT01240902)	U.S.	45	Feb 2011-Sep 2012	Mean age, 81 years STS score <7[a] (median, 5.3) Symptomatic (NYHA class ≥II)	n=202 Core-Valve	n=181 Conventional open-heart surgery with CPB	Manufacturer
Leon (2016)[68] PARTNER 2A (NCT01314313)	U.S., Canada	57	Dec 2011-Nov 2013	Mean age, 82 years Symptomatic (NYHA class ≥II) STS PROM ≥4 and ≤8 or STS PROM <4 with coexisting conditions (mean, 5.8)	n=1,011 SAPIEN XT	n=1,021 Conventional surgery	Manufacturer
Reardon (2017)[76] SURTAVI (NCT01586910)	U.S., Spain, Netherlands, Germany, UK, Canada, Switzerland, Sweden	87	NR	Mean age, 80 years STS PROM ≥4 and <15 (mean, 4.5) Symptomatic (NYHA class ≥II)	n=879 Core-Valve	n=867 Conventional surgery with coronary re-vascularization if needed	Manufacturer
Popma (2019)[77] Forrest (2022)[78] Evolut Low Risk Trial	Australia, Canada, France, Japan, Netherlands, New	86	Mar 2016 - Nov 2018	Mean age, 74 years STS PROM≤ 3 (mean, 1.9) 90% NYHA class ≥II (symptomatic);	n=734 CoreValve, Evolut R, or Evolut PRO	n=734 Conventional surgery	Manufacturer

					Interventions		
Study and Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVR**	**SAVR**	**Sponsor**
(NCT02701283)	Zealand, U.S.			10% NYHA class I (asymptomatic)			
Mack (2019)[79] Leon (2021)[80] PARTNER 3, (NCT02675114)	U.S., Canada, Australia, New Zealand, Japan	71	Mar 2016 - Oct 2017	Mean age, 73 years STS PROM <4 (mean, 1.9) 28% NYHA III or IV	n=503 SAPIEN 3	n=497 Conventional surgery	Manufacturer
Toff (2022)[81] UK TAVI (ISRCTN57819173)	UK	34	April 2014-April 2018	Mean age, 81 years Median STS PROM, 2.7[b] 43% NYHA III or IV	n=458 SAPIEN 3 (45.1%)	n=455 Conventional surgery	NIHR HTA Programme; University of Leicester

CPB: cardiopulmonary bypass; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVR: transcatheter aortic valve replacement; THV: Transcatheter heart valve

[a] Includes analysis of a subset of originally randomized patients

[b] No specified risk threshold for trial inclusion

TABLE 5. RCTS Comparing TAVI with Surgical Repair in Patients at Low and Intermediate Surgical Risk

Study	**Primary Outcome**	**Results of Primary Outcomes, %**				**All-Cause Mortality (2 years), %**			**New Permanent Pacemaker (2 years), %**		
		TAVI	**Surg**	**TE (95% CI)**	**p**	**TAVI**	**Surg**	**p**	**TAVI**	**Surg**	**p**
Nielsen (2012)[67] STACCATO	Death, stroke, or renal failure at 30 d										
All patients		14.7	2.8	RD (NR)	0.07	NR	NR		NR	NR	
Thyregod (2015)[66] NOTION	Death, stroke, or MI at 1 year										
All patients		13.1	16.3	RD = -3.2	0.43[a]	4.9	7.5	0.38	34.1	1.6	<0.001
Reardon (2016)[75] CoreValve U.S. Pivotal	Death at 2 years										

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 years), %			New Permanent Pacemaker (2 years), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
STS score ≤7		26.3	15.0	HR (NR)	0.01	See previous columns			27.7	10.5	<0.001
Leon (2016)[68] PARTNER 2A	Death or disabling stroke at 2 years										
All patients		19.3	21.1	HR 0.92 (0.75 to 1.08)		16.7	18.0	0.45	11.8	10.9	0.29
Trans-femoral access		16.8	20.4	HR 0.79 (0.62 to 1.00)		14.2	17.2	0.11	11.4	10.8	0.71
Trans-thoracic access		27.7	23.4	HR 1.21 (0.84 to 1.74)		25.2	20.7	0.26	13.1	8.6	0.13
Reardon (2017)[76]	Death or disabling stroke at 2 years										
All patients		12.6	14.0	RD = -1.4 (-5.2 to 2.3)[b]		11.4	11.6	-3.8 to 3.3[b]	25.9	6.6	15.9 to 22.7[b]
Popma (2019)[77] Forrest (2022)[78] Evolut Low Risk Trial	Death or disabling stroke at 2 years										
All patients		5.3	6.7	RD = -1.4 (−4.9 to 2.1)[b]		4.3	6.3	NR	23.8	7.0	NR

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 years), %			New Permanent Pacemaker (2 years), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
Mack (2019)[79] Leon (2021)[80] PARTNER 3	Death, stroke, or rehospital-ization at 1 year										
All patients		8.5	15.1	RD = -6.6 (−10.8 to −2.5)[b]		11.5	17.4		NR		
Study	**Primary Outcome**	**Results of Primary Outcomes, %**				**All-Cause Mortality (2 years), %**			**New Permanent Pacemaker (1 year), %**		
		TAVI	**Surg**	**TE (95% CI)**	**p**	**TAVI**	**Surg**	**p**	**TAVI**	**Surg**	**p**
Toff (2022)[81] UK TAVI	Death at 1 year										
All patients		4.6	6.6	RD = -2.0 (-∞ to 1.2)[c]	<0.001	NR			14.2	7.3	<0.001

CI: confidence interval; HR: hazard ratio; RD: risk difference; MI: myocardial infarction; NR: not reported; STS: Society of Thoracic Surgeons; Surg: surgical repair; TAVI: transcatheter aortic valve implantation; TE: treatment effect.
[a] Superiority
[b] Bayesian credible interval
[c] Noninferiority with 97.5% confidence interval

Mixed Risk Populations Including Intermediate- and Low-Risk Patients

A previous RCT, the STACCATO trial, was designed to compare transapical TAVI using the SAPIEN valve with surgical aortic valve repair in operable patients with isolated aortic stenosis, without selection based on the predicted risk of death after surgery. However, the trial was prematurely terminated due to an increase in adverse events in the TAVI arm. The available results were reported by Nielsen (2012).[67] The trial was limited by a design that assumed a low event rate (2.5%). Also, operators' experience with the device and implantation techniques at the time of the trial might not be representative of current practice.

Reardon (2016) reported on an analysis of patients from the U.S. Pivotal High Risk Trial who had STS score less than 7.0% at baseline.[75] The trial was described in a previous section on high surgical risk. Of the 750 total patients in the trial, 383 (202 TAVR, 181 SAVR) had an STS PROM score of 7% or less, with a median STS PROM score of 5.3%. All-cause mortality at

two years for TAVR versus SAVR in the subgroup with STS score less than 7.0 was 15% (95% CI 9% to 20%) vs. 26% (95% CI 20% to 33%, p=0.01). The rates of stroke at two years for TAVR versus SAVR were 11% versus 15% (p=0.50).

Thyregod (2015) reported on the results of the NOTION RCT, which compared TAVI with surgical repair in 280 patients with severe aortic stenosis who were 70 years or older, regardless of the predicted risk of death after surgery.[66] Patients randomized to TAVI underwent implantation of the CoreValve self-expanding prosthesis by the femoral (preferred) or subclavian route. The trial was powered to detect an absolute risk reduction of 10% or a RR reduction of 66.7% in the primary outcome at one year. At baseline, 81.8% of the study population was considered to be at low risk (STS Risk Score <4). Some of the main findings from NOTION are summarized in Table 5. In addition, TAVI-treated patients had lower rates of major or life-threatening bleeding (11.3% vs. 20.9%, p=0.03), cardiogenic shock (4.2% vs. 10.4%, p=0.05), stage 2 or 3 AKI (0.7% vs. 6.7%, p=0.01), and new-onset or worsening atrial fibrillation (16.9% vs. 57.8%, p<0.001) than surgical repair patients, all respectively. Both groups showed improvements in NYHA functional class. However, more TAVI-treated patients were in NYHA functional class II at one-year follow-up (29.5% vs. 15.0%, p=0.01).

In a two-year follow-up of the NOTION trial, Søndergaard (2016) reported slight improvements in the TAVI-treated group (n=142) compared with the surgical repair group (n=134), although between-group differences were almost exclusively not statistically significant.[72] For the composite rate of death at two years, the between-group difference was also statistically insignificant (18.8% of surgical repair patients vs. 15.8% of TAVI-treated patients, p=0.43). A similar difference was observed for all-cause mortality (8.0% of patients treated with TAVI experienced all-cause mortality vs. 9.8% of the surgical repair patients, p=0.54). Cardiovascular mortality rates, stroke rates, and MI were likewise marginally improved in the TAVI-treated patients, although the only significant difference was found for atrial fibrillation and permanent pacemaker implantation. For the former outcome, there were 60.0% of surgical patients, compared with 22.7% of TAVI patients (p<0.001); for the latter, only 4.2% of surgical patients received implantation versus 41.3% of the TAVI group (p<0.001). As a secondary outcome, moderate aortic regurgitation was improved at two years for the TAVI group (15.4%) compared with the surgical group (0.9%, p<0.001). The authors noted that the variety of risk levels observed in the patients limited their results, as did the exclusion of patients with coronary artery disease. Further, the trial was limited by its lack of power for subgroup analyses, and its inability to reveal any significant differences between groups with certainty. Overall, the results showed that TAVI-treated patients had comparable, if not improved, outcomes when treated alongside patients who received SAVR.

Results after five years of follow-up were reported by Thyregod (2019).[73] There were no significant differences between TAVR and SAVR in the incidence of the composite primary outcome (38.0% vs. 36.3%, p=0.86) or any of the components of the composite. The incidence of moderate/severe total aortic regurgitation (8.2% vs. 0.0%, p<0.001) and a new pacemaker (43.7% vs. 8.7%, p<0.001) were both higher in the TAVR group. Four patients had prosthetic re-intervention. Søndergaard (2019) compared the durability of TAVR versus SAVR after six years of follow-up from NOTION. At six years, the rates of all-cause mortality were similar for TAVR (42.5%) and SAVR (37.7%) patients. The rate of moderate to severe structural valve deterioration was higher for SAVR than TAVR (24.0% vs. 4.8%, p < 0.001) and there were no differences in nonstructural valve deterioration (57.8% vs. 54.0%), bioprosthetic valve failure (6.7% vs. 7.5%) or endocarditis (5.9% vs. 5.8%).[74] At eight years of follow-up, Jørgensen

(2021) found no significant difference between TAVI and SAVR in the composite outcome of mortality, stroke, or MI.[82]

Toff (2022) published one-year results from an investigator-initiated, publicly funded, pragmatic RCT in the United Kingdom (UK TAVI) that compared clinical outcomes for 913 patients aged ≥80 years, or aged ≥70 years with low-to-intermediate surgical risk, with severe, symptomatic aortic stenosis randomized to TAVI or SAVR.[81] For the primary outcome (all-cause mortality at one year), TAVI was noninferior to SAVR (4.6% vs. 6.6%, adjusted absolute risk difference, -2.0%, one-sided 97.5% CI -∞ to 1.2%, p<0.001) based on a prespecified margin of 5%. The adjusted hazard ratio for death from any cause was 0.69 (95% CI 0.38 to 1.26, p=0.23). No significant differences in cardiovascular deaths or strokes (fatal or nonfatal) were found between groups. While TAVI was associated with significantly shorter hospital stay and fewer major bleeding events, it was also associated with more vascular complications (p<0.001), conduction disturbances requiring pacemaker implantation (p=0.01), and mild or moderate aortic regurgitation (p<0.001). Trial follow-up is planned for five years.

Including Intermediate-Risk Only

Reardon (2017) published two-year results from an RCT (SURTAVI trial) that compared clinical outcomes for 1,746 patients at intermediate surgical risk randomized to TAVR or SAVR.[76] For the primary outcome (composite death at two years), an improvement was observed in the TAVR-treated group, compared with surgery (12.6% of TAVR patients vs. 14.0% of SAVR patients [95% credible interval -5.2% to 2.3%], posterior probability >0.999). Rates of death, MI, and disabling stroke were comparable between groups, as were secondary outcomes that included echocardiographic measurement of aortic valve gradient and paravalvular regurgitation (data reported in the supplemental material). More patients were assigned to the CoreValve bioprosthesis (n=724) than received Evolut R bioprosthesis (n=137), which might have affected the results; also, a considerable number of patients withdrew consent before surgery, resulting in an as-treated population of 1660. Finally, the authors acknowledged a gap in knowledge of how baseline characteristics of patients who received surgery differed from those who did not. The authors noted the low 30-day surgical mortality ratio (0.38, observed-to-expected) and the similarity of this rate between groups (2.2% of the TAVR patients vs. 1.7% of surgical patients).

Leon (2016) reported on results of a multicenter noninferiority RCT (PARTNER 2A) comparing TAVI with the Edwards SAPIEN XT valve system in patients with severe aortic stenosis who were at intermediate risk for open surgery, stratified by access route (transfemoral or transthoracic).[68] Eligible patients had degenerative aortic valve stenosis, with NYHA functional class II or higher, and were in STS PROM score of 4 or greater (or <4 if determined by a heart team to have an “intermediate-risk patient profile with important comorbidities not represented in the STS Risk Calculator algorithm.”) The trial used a noninferiority design, with a primary composite endpoint of death from any cause or disabling stroke (score of ≥2 on the modified Rankin Scale) at two years and a noninferiority margin of 1.2 (i.e., noninferiority was considered met if upper bound of two-sided CI for the RR for the primary outcome was <1.2). A total of 2032 patients were randomized to TAVI (n=1,011) or surgical repair (n=1,021), with 1,550 considered suitable for transfemoral placement (76.3%) and 482 (23.7%) requiring transthoracic access. At baseline, the mean STS Risk Score was 5.8%; 81.3% had a score between 4% and 8%. The primary outcome results and select additional results of the trial are summarized in Table 5. Also, similar to other TAVI trials, the frequency and severity of paravalvular regurgitation was higher after TAVI than in surgical repair. The presence of

paravalvular regurgitation was associated with all-cause mortality during follow-up (HR for moderate or severe paravalvular regurgitation vs. none or trace 2.85, 95% CI 1.57 to 5.21, p<0.001). The five-year outcomes from the PARTNER 2A study revealed no significant difference in the incidence of death from any cause or disabling stroke between the TAVI and surgical repair groups (47.9% vs. 43.4%, HR 1.09, 95% CI 0.95 to 1.25, p=0.21).[83] Overall, more patients in the TAVI group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%), experienced repeat hospitalizations (33.3% vs. 25.2%), and underwent aortic valve reinterventions (3.2% vs. 0.8%). Improvement in health status at five years was similar between the groups.

Including Low-Risk Only

Popma (2019) reported results of prespecified, interim analyses of the multinational Evolut Low Risk Trial, a noninferiority trial conducted from 2016 to 2018 comparing TAVR (n=734) to SAVR (n=734) in patients who had severe aortic stenosis and were at low surgical risk (STS-PROM ≤3%).[77] Patients with bicuspid aortic valves were excluded. Patients assigned to TAVR were treated with one of three Medtronic self-expanding, supra-annular bioprostheses (CoreValve, Evolut R, or Evolut PRO). Preliminary analyses were performed when 850 patients had reached 12-month follow-up. Long-term follow-up is scheduled to continue for 10 years. The primary outcome was a composite of death or disabling stroke at 24 months performed using Bayesian methods. At the time of the preliminary analysis, 149 patients had reached the 24 months visit. The 24-month estimated incidence of the primary outcome was 5.3% in the TAVR group and 6.7% in the SAVR group (risk difference -1.4%, 95% Bayesian credible interval −4.9 to 2.1, posterior probability of noninferiority >0.999). Several 30-day outcomes were also reported. The incidence at 30 days of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), AKI (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) were lower in TAVR compared to SAVR. The incidence at 30 days of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%) was higher in TAVR compared to SAVR. There was not a statistically significant difference in the KCCQ overall summary score at 30 days (88.7±14.2 in the TAVR group vs. 78.6±18.9 in the SAVR group). Forrest (2022) published two-year outcomes.[78] Follow-up data was available for 97.7% in the TAVI group and 92.3% in the SAVR group. The Kaplan-Meier estimate of all-cause mortality or disabling stroke at two years was 4.3% and 6.3% in the TAVI and SAVR groups, respectively (p=0.084). The number of patients requiring new permanent pacemaker implantation was significantly higher with TAVI (23.8% vs. 7.0%). Similar results were found at three years follow-up.

Mack (2019) reported results of the multinational PARTNER 3 trial randomizing patients with severe aortic stenosis and low surgical risk to either TAVR with the SAPIEN (n=503) or SAVR (n=497) in 2016 to 2017.[79] Patients bicuspid aortic valves were excluded. The primary outcome was a composite of death, stroke, or rehospitalization at one year. Follow-up is designed to continue for at least 10 years. Primary analyses were performed and reported in the as-treated population (n=496 in the TAVR, n=454 in SAVR) but sensitivity analyses of the primary outcome performed in the intention-to-treat population with multiple imputations for missing data were reportedly consistent with the primary analysis. The number of participants that did not receive the assigned treatment was higher in the SAVR group (7 vs. 43). The most common reported reason was refusal to undergo surgery or the choosing to undergo surgery at a non-trial site. The estimated incidence of the primary outcome at one year was significantly lower in TAVR versus SAVR (8.5% vs. 15.1%, risk difference -6.6%, 95% CI −10.8 to −2.5, p<0.001 for noninferiority). All components of the composite (death, stroke, and

hospitalization) individually favored TAVR at 30 days and one year. At 30 days, the rate of stroke (0.6% vs. 2.4%, HR 0.25 (95% CI 0.07 to 0.88), p=0.02) and new-onset atrial fibrillation (5.0% vs. 39.5%, HR 0.10 (95% CI 0.06 to 0.16) p<0.001) was lower in TAVR than SAVR and index hospitalization time was shorter (three days vs. seven days, p<0.001). There were no significant differences at 30 days in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. The incidence of mild paravalvular regurgitation at one year was higher with TAVR (29.4% vs. 2.1%). In an analysis specific to the echocardiographic findings of the PARTNER 3 trial, Pibarot (2020) reported that the percentage of moderate or severe aortic regurgitation was low and not statistically different between the TAVR and SAVR groups at 30 days (0.8% vs. 0.2%, p=0.38); mild aortic regurgitation occurred more frequently after TAVR than SAVR (28.8% vs. 4.2%, p<0.001).[84] Mean transvalvular gradient (13.7 ±5.6 vs. 11.6 ±5.0 mmHg, p=0.12) and aortic valve area (1.72 ±0.37 vs. 1.76 ±0.42 cm^2, p=0.12) were similar between groups at one year. In another analysis specific to atrial fibrillation (n=781), Shahim (2021) found lower early postoperative atrial fibrillation in patients following TAVI compared with SAVR (19.5% vs. 36.6%, p<0.0001).[85] At two-year follow-up, Leon (2021) reported continued improvement of the composite primary endpoint with TAVI versus SAVR (11.5% vs. 17.4%, HR 0.63, 95% CI 0.45 to 0.88, p=0.007); however, there was no significant difference in death or stroke between TAVI and SAVR.[80]

Study limitations

The purpose of the study limitation tables (see Tables 6 and 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following the tables and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Nielsen (2012) STACATTO	4: Included patients with any surgical risk, not limited to patients requiring alternative access	4: Transapical TAVI, multidetector computed tomography was not performed before procedure			1, 2: Terminated early
Thyregod (2015) NOTION	4: Included patients with any surgical risk				
Reardon (2016) CoreValve U.S. Pivotal	4: Subgroup analysis included patients at low/intermediate risk by STS-PROM but deemed at high surgical risk based on screening committee				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
	assessment despite their STS scores				
Leon (2016) PARTNER 2A	4: 12% of the study population had an STS risk score > 8				
Reardon (2017)[76] SURTAVI					
Popma (2019)[77] Evolut Low Risk Trial					
Mack (2019)[79] PARTNER 3				4: Rehospital-ization was included in composite primary outcome	
Toff (2022)[81] UK TAVI	1. Proportion of patients with low vs. intermediate risk unclear; median STS risk score 2.7				

STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVI: transcatheter aortic valve implantation. The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Nielsen (2012)[67] STACCATO		1: Patients and study staff not blinded		1: Study terminated early with only 70 participants		
Thyregod (2015)[66]		1: Patients and study				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
NOTION		staff not blinded 2,3: Unclear if outcome adjudication was blinded				
Reardon (2016)[75] CoreValve U.S. Pivotal		1: Patients and study staff not blinded			2: Post-hoc analysis of RCT: not powered to detect differences in the low/ intermediate risk population	
Leon (2016)[68] PARTNER 2A		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Reardon (2017)[76] SURTAVI		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Popma (2019)[77] Evolut Low Risk Trial		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		3: Incomplete reporting of confidence intervals and/or p-values
Mack (2019)[79] PARTNER 3		1: Patients and study staff not blinded 2,3: Outcome		1: High frequency of withdrawals in patients assigned to undergo surgery		

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		adjudication not blinded				
Toff (2022)[81] UK TAVI		1: Patients and study staff not blinded				

RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: TAVI Outcomes in Patients at Intermediate- or Low-Risk for Open Surgery

Intermediate-Risk

Most participants in five RCTs were intermediate risk, and two RCTs included only intermediate surgical risk patients. The primary outcomes were generally a composite of death and stroke; most RCTs were noninferiority studies. The rates of the primary outcome were noninferior for TAVI compared with SAVR and numerically lower, although not statistically significantly lower in three of the five RCTs including the two RCTs exclusively enrolling intermediate risk patients. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and AKI higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon RCT suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Two-year follow-up results were published for NOTION, PARTNER 2A, CoreValve U.S. Pivotal, and SURTAVI trials, but reported outcomes did not include rates of reoperation. A number of recently completed meta-analyses evaluated mortality for TAVR versus SAVR at the 30-day mark. Mortality rates were found to be comparable between the two procedures.

Low-Risk

The NOTION and UK TAVI trials were predominantly low surgical risk patients; the Evolut Low Risk Trial and PARTNER 3 were only low-risk patients. The STACCATO trial also included some patients at low surgical risk. In the NOTION trial, the risk of the composite outcome of death from any cause, stroke, or MI at one year was numerically but not statistically significantly lower in the TAVR group compared to SAVR and after five years of follow-up,

there were still no significant differences between TAVR and SAVR in the incidence of the composite outcome (38.0% vs. 36.3%, p=0.86) or any of the components of the composite. Six-year follow-up from NOTION showed less structural valve deterioration in TAVR than SAVR. In the publicly sponsored UK TAVI trial, TAVI was noninferior to SAVR with respect to all-cause mortality at one year. In the Evolut Low Risk Trial, TAVR was noninferior to SAVR with respect to the composite outcome of death or disabling stroke at 24 months. At 30 days, TAVR was associated with a lower incidence of disabling stroke, acute kidney injury, bleeding events, and atrial fibrillation but with a higher incidence of aortic regurgitation and permanent pacemaker use. In the PARTNER 3 trial, the rate of the composite of death, stroke, or rehospitalization at one year was significantly lower with TAVR than SAVR. At 30 days, TAVR was associated with a lower rate of stroke, death or stroke composite, new-onset atrial fibrillation, and shorter index hospitalization. There were no significant between-group differences in major vascular complications or new permanent pacemaker insertions at 30 days. The age of participants in the low-risk RCTs was markedly lower than that in previous TAVR trials and therefore life expectancy is longer. Extended follow-up will be needed to address the long-term advantages and disadvantages of TAVR versus SAVR and valve durability. Both of the low-risk RCTs have planned follow-up of 10 years and both excluded patients with bicuspid aortic valves.

The ongoing NOTION 2 Trial (NCT02825134) includes only patients ≤75-years-old and does not exclude patients with bicuspid aortic valves. Data collection of the primary outcome was scheduled for completion in 2021.

TAVI OUTCOMES FOR "VALVE-IN-VALVE" APPROACH

Clinical Context and Therapy Purpose

The purpose of transcatheter aortic "valve-in-valve" implantation is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical aortic valve repair and medical management, in patients with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair.

Systematic Reviews

Aedma (2022) conducted an umbrella or meta-meta-analysis evaluating the efficacy and safety of valve-in-valve (ViV) TAVI compared to redo-surgical aortic valve replacement (redo-SAVR).[86] Nine analyses were included for review. ViV TAVI was associated with a significantly lower risk of 30-day mortality (OR 0.60, 95% CI 0.53 to 0.68, p<0.00001) and procedural mortality (OR 0.52, 95% CI 0.27 to 0.98, p=0.04). No significant differences in one-year mortality or hospital readmissions were identified. ViV TAVI was also associated with a lower risk several complications, including stroke (OR 0.71, 95% CI 0.59 to 0.84, p<0.001), major bleeding (OR 0.44, 95% CI 0.35 to 0.57, p<0.000001), acute kidney injury (OR 0.57, 95% CI 0.43 to 0.75, p<0.0001), and pacemaker implantation (OR 0.67, 95% CI 0.52 to 0.86, p<0.002). No association of acute myocardial infarction with ViV TAVI and redo-SAVR was found (OR 1.15, 95% CI 0.84 to 1.59, p=0.38); however, ViV TAVI was associated with a higher risk of vascular complications (OR 2.70, 95% CI 1.58 to 4.62, p<0.0003).

Raschpichler (2022) published a meta-analysis of nonrandomized studies comparing ViV TAVI with redo-SAVR.[87] A total of 15 studies with 8,881 patients were identified for analysis, which included 4,458 patients (50.2%) treated with ViV TAVI and 4,423 patients (49.8%) treated with redo-SAVR. Short-term mortality (<30 days) was 2.8% in patients undergoing ViV TAVI

compared with 5.0% in patients undergoing redo-SAVR (RR 0.55, 95% CI 0.34 to 0.91). Midterm mortality (up to five years) was not significantly different between groups (HR 1.27, 95% CI 0.72 to 2.25). The rate of acute kidney failure was lower following ViV (RR 0.54, 95% CI 0.33 to 0.88); however, prosthetic aortic valve regurgitation (RR 4.18, 95% CI 1.88 to 9.3, p=0.003) and severe patient-prosthesis mismatch (RR 3.12, 95% CI 2.35 to 4.1, p<0.001) were significantly more frequent. Additionally, the transvalvular gradient was significantly higher following ViV procedures (standard mean difference 0.44, 95% CI 0.15 to 0.72, p=0.008). There were no significant differences between groups with respect to stroke, myocardial infarction, or pacemaker implantation. The authors concluded that the early safety advantages of ViV should be weighed against a potential midterm benefit of redo-SAVR. The authors also noted that given the likely selection bias in individual studies, an adequately powered multicenter randomized trial with sufficiently long follow-up in patients with low-to-intermediate surgical risk is warranted.

A subsequent time-to-event analysis of all-cause mortality in ViV TAVI versus redo-SAVR in 10 studies conducted by Sá (2023) similarly found a short-term protective effect with ViV TAVI in the first 44 days (HR 0.67, 95% CI 0.49 to 0.93, p=0.017).[88] A HR reversal was observed after 197 days favoring redo-SAVR (HR 1.53, 95% CI 1.22 to 1.93, p<0.001). Additionally, a statistically significant association of patient-prosthesis mismatch with all-cause mortality during follow-up for ViV TAVI was identified via Cox regression modeling (p<0.001).

In 2019, the National Institute for Health and Care Excellence prepared an interventional procedure overview on safety and efficacy of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction based on a rapid review of medical literature including publications through August 2018 and specialist opinion.[89] The review included three systematic reviews and meta-analysis[90-92] and eight case series (registries) totaling 4,256 patients, although the authors note that there may be some overlap of patients in the global valve-in-valve register and other registries. There are no RCTs comparing valve-in-valve TAVI with redo SAVR. The available evidence is from observational studies and registry data with follow-up ranging from one month to one year. Two systematic reviews and meta-analysis compare valve-in-valve TAVI with redo SAVR and reported similar favorable outcomes. One of the included systematic reviews of 15 studies (861 patients) reported a pooled technical success rate of 95% (95% CI 94% to 97%). Another included systematic review of six observational studies reported no statistically significant difference between valve-in-valve TAVI and redo SAVR in perioperative mortality (5% vs. 6%, RR 0.78, 95% CI 0.33 to 1.84), late mortality (median one-year follow-up, incident rate ratio 0.93, 95% CI 0.74 to 1.16), or perioperative stroke (2% vs. 3%, RR 0.73, 95% CI 0.18 to 3.02), whereas, the rate of permanent pacemaker insertion was statistically significantly lower in the valve-in-valve TAVI group (8% vs. 15%, RR 0.57, 95% CI 0.32 to 1.0) and the rate of mild or greater paravalvular regurgitation was statistically significantly higher in the valve-in-valve TAVI group (21% vs. 6%, RR 3.83, 95% CI 1.2 to 12.22). In two registries (including 365 and 227 patients), the rate of conversion to surgery or surgical reintervention within 30 days was less than 1%.

Registries

Registries not included in the systematic reviews described above will be briefly summarized if they include longer follow-up than those already summarized.

Following the National Institute for Health and Care Excellence review, three-year results from the PARTNER 2 valve-in-valve registry were published by Webb (2019).[89] The registry

included 365 patients who had valve-in-valve[91 92] procedures with a mean age of 79 (± 10) years and mean STS-PROM score of 9.1% (±4.7). The estimated incidence of all-cause mortality at three years was 32.7%. Aortic valve re-replacement was performed in 1.9% by three years. From baseline to year three, NYHA functional class improved; 90.4% of patients were in class III or IV at baseline and 14.1% were in class III or IV at three years (p<0.0001). QoL as measured by the KCCQ overall score also increased from baseline to three years (43.1 to 73.1, p < 0.`

PRACTICE GUIDELINE SUMMARY

American College of Cardiology and American Heart Association

In 2014, the American College of Cardiology and the American Heart Association published joint guidelines on the management of valvular heart disease.[93] Both groups issued a joint focused update in 2017.[94] In 2020, a new full guideline was published that replaces the 2014 revision and 2017 focused update.[95] These guidelines made the following recommendations on the timing of intervention and choice of surgical or transcatheter intervention for treatment of aortic stenosis (see Table 8).

Additionally, the guidelines state the following:

- "Treatment of severe aortic stenosis with either a transcatheter or surgical valve prosthesis should be based primarily on symptoms or reduced ventricular systolic function. Earlier intervention may be considered if indicated by results of exercise testing, biomarkers, rapid progression, or the presence of very severe stenosis."
- "Indications for TAVI are expanding as a result of multiple randomized trials of TAVI versus surgical aortic valve replacement. The choice of type of intervention for a patient with severe aortic stenosis should be a shared decision-making process that considers the lifetime risks and benefits associated with type of valve (mechanical versus bioprosthetic) and type of approach (transcatheter versus surgical)."

Table 8. Recommendations on Surgical or Transcatheter Intervention for Aortic Stenosis

Recommendation	COR	LOE
Timing of Intervention		
“In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, heart failure, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated."	I	A
“In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% (Stage C2), AVR is indicated."	I	B
“In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D2), AVR is recommended."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D3), AVR is recommended if AS is the most likely cause of symptoms."	I	B
“In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mmHg from baseline to peak exercise."	IIa	B

Recommendation	COR	LOE
“In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable."	IIa	B
“In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide level is >3 times normal."	IIa	B
"In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year."	IIa	B
"In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in left ventricular ejection fraction on at least 3 serial imaging studies to <60%, AVR may be considered.	IIb	B
"In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.	IIb	C
Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR is Appropriate		
"For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended."	I	A
"For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability."	I	A
"For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy of <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR."	I	A
"In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in the 3 recommendations above."	I	B
"For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated B-type natriuretic peptide, SAVR is recommended in preference to TAVI."	I	B
"For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve or vascular anatomy or other factors are not suitable for transfemoral TAVI, SAVR is recommended."	I	A
"For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life."	I	A
"For symptomatic patients with severe AS for whom predicted post-TAVI or post-SAVR survival is <12 months or for whom minimal improvement in quality of life is expected, palliative care is recommended after shared decision-making, including discussion of patient preferences and values."	I	C
"In critically ill patients with severe AS, percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVI."	IIb	C
Intervention for Prosthetic Valve Stenosis		
"In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless surgical risk is prohibitive."	I	B
"For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable."	IIa	B

Recommendation	COR	LOE
Prosthetic Valve Regurgitation		
"In patients with intractable hemolysis or HF attributable to prosthetic transvalvular or paravalvular leak, surgery is recommended unless surgical risk is high or prohibitive."	I	B
"In asymptomatic patients with severe prosthetic regurgitation and low operative risk, surgery is reasonable."	IIa	B
"In patients with prosthetic paravalvular regurgitation with the following: 1) either intractable hemolysis or NYHA class III or IV symptoms and 2) who are at high or prohibitive surgical risk and 3) have anatomic features suitable for catheter-based therapy, percutaneous repair of paravalvular leak is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with severe HF symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B

AS: aortic stenosis; AVR: aortic valve replacement; COR: class of recommendation; LOE: level of evidence; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

SUMMARY

TAVI

There is enough research to show that transcatheter aortic valve implantation (TAVI) can improve health outcomes for individuals with heart failure who have severe symptomatic aortic stenosis. For patients who are not surgical candidates due to excessive surgical risk, trial results have shown decreased mortality for the TAVI patients at one year compared with medical care, but an increased risk of stroke and vascular complications. For patients who are surgical candidates, trials have shown similar or better outcomes for TAVI compared to open surgical procedures. Therefore, TAVI may be considered medically necessary for patients that meet the policy criteria.

TAVR

There is not enough research to show that transcatheter aortic valve replacement (TAVR) can improve health outcomes for individuals with bioprosthetic valves who have valve dysfunction and aortic stenosis or regurgitation compared with open repair. Studies comparing TAVR to surgical repair and have reported similar mortality, stroke, and survival rates for the two procedures, however there is a lack of high-quality trial data. Therefore, TAVR may be considered medically necessary for high- or prohibitive-risk surgical patients but is otherwise considered investigational.

Bicuspid Aortic Valves

There is not enough research to show that transcatheter aortic valve implantation or replacement can improve health outcomes for patients for patients with bicuspid valves. Individuals with bicuspid aortic valves were excluded from the large trials that evaluated transcatheter aortic valve implantation (TAVI) and transcatheter aortic valve replacement (TAVR), due to an increased risk of complications. Further study is needed to evaluate the long-term health outcomes and identify which patients may benefit from these procedures.

Therefore, TAVI and TAVR are considered investigational for patients with bicuspid aortic valves.

Other Indications and Devices

There is not enough research to show that transcatheter aortic valve implantation or replacement can improve health outcomes for patients without heart failure symptoms and severe aortic stenosis. There is also a lack of evidence regarding non-FDA-approved devices. Therefore, these are considered investigational.

REFERENCES

1. Freeman RV,Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation.* 2005;111:3316-26. PMID: 15967862
2. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation.* 2006;114:e84-231. PMID: 16880336
3. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J.* 2005;26:2714-20. PMID: 16141261
4. Lieberman EB, Bashore TM, Hermiller JB, et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *Journal of the American College of Cardiology.* 1995;26:1522-8. PMID: 7594080
5. Food and Drug Administration. Boston Scientific announces LOTUS Edge aortic valve system voluntary recall and product discontinuation. January 11, 2021. Secondary Food and Drug Administration. Boston Scientific announces LOTUS Edge aortic valve system voluntary recall and product discontinuation. January 11, 2021 [cited 5/2/2023]. 'Available from:' https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/boston-scientific-announces-lotus-edgetm-aortic-valve-system-voluntary-recall-and-product?utm_medium=email&utm_source=govdelivery.
6. Coeytaux RR, Williams JW, Jr., Gray RN, et al. Percutaneous heart valve replacement for aortic stenosis: state of the evidence. *Ann Intern Med.* 2010;153:314-24. PMID: 20679543
7. Figulla L, Neumann A, Figulla HR, et al. Transcatheter aortic valve implantation: evidence on safety and efficacy compared with medical therapy. A systematic review of current literature. *Clinical research in cardiology : official journal of the German Cardiac Society.* 2011;100(4):265-76. PMID: 21165626
8. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *The New England journal of medicine.* 2010;363(17):1597-607. PMID: 20961243
9. Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation.* 2011;124:1964-72. PMID: 21969017

10. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *The New England journal of medicine.* 2012;366(18):1696-704. PMID: 22443478
11. Svensson LG, Blackstone EH, Rajeswaran J, et al. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. *Journal of the American College of Cardiology.* 2014;64(2):158-68. PMID: 25011720
12. Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. *Circulation.* 2014;130:1483-92. PMID: 25205802
13. Webb JG, Doshi D, Mack MJ, et al. A Randomized Evaluation of the SAPIEN XT Transcatheter Heart Valve System in Patients With Aortic Stenosis Who Are Not Candidates for Surgery. *JACC Cardiovascular interventions.* 2015;8(14):1797-806. PMID: 26718510
14. Kapadia SR, Huded CP, Kodali SK, et al. Stroke After Surgical Versus Transfemoral Transcatheter Aortic Valve Replacement in the PARTNER Trial. *Journal of the American College of Cardiology.* 2018;72(20):2415-26. PMID: 30442284
15. Huded CP, Arnold SV, Chhatriwalla AK, et al. Rehospitalization Events After Aortic Valve Replacement: Insights From the PARTNER Trial. *Circulation Cardiovascular interventions.* 2022;15(12):e012195. PMID: 36538580
16. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *Journal of the American College of Cardiology.* 2014;63(19):1972-81. PMID: 24657695
17. Yakubov SJ, Adams DH, Watson DR, et al. 2-Year Outcomes After Iliofemoral Self-Expanding Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis Deemed Extreme Risk for Surgery. *Journal of the American College of Cardiology.* 2015;66(12):1327-34. PMID: 26383718
18. Baron SJ, Arnold SV, Reynolds MR, et al. Durability of quality of life benefits of transcatheter aortic valve replacement: Long-term results from the CoreValve US extreme risk trial. *American heart journal.* 2017;194:39-48. PMID: 29223434
19. Arnold SV, Petrossian G, Reardon MJ, et al. Five-Year Clinical and Quality of Life Outcomes From the CoreValve US Pivotal Extreme Risk Trial. *Circulation Cardiovascular interventions.* 2021;14(6):e010258. PMID: 34092091
20. Osnabrugge RL, Arnold SV, Reynolds MR, et al. Health status after transcatheter aortic valve replacement in patients at extreme surgical risk: results from the CoreValve U.S. trial. *JACC Cardiovascular interventions.* 2015;8(2):315-23. PMID: 25700755
21. Reardon MJ, Adams DH, Coselli JS, et al. Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery. *The Journal of thoracic and cardiovascular surgery.* 2014;148(6):2869-76 e1-7. PMID: 25152474
22. Mack MJ, Brennan JM, Brindis R, et al. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA.* 2013;310:2069-77. PMID: 24240934
23. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J.* 2014;35:2672-84. PMID: 24682842
24. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention : journal of EuroPCR in collaboration with*

the Working Group on Interventional Cardiology of the European Society of Cardiology. 2008;4(2):242-9. PMID: 19110790
25. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *Journal of the American College of Cardiology.* 2010;55:1080-90. PMID: 20096533
26. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J.* 2011;32:198-204. PMID: 20864486
27. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation.* 2011;123:299-308. PMID: 21220731
28. Panoulas VF, Francis DP, Ruparelia N, et al. Female-specific survival advantage from transcatheter aortic valve implantation over surgical aortic valve replacement: Meta-analysis of the gender subgroups of randomised controlled trials including 3758 patients. *International journal of cardiology.* 2018;250:66-72. PMID: 29169764
29. Dagan M, Yeung T, Stehli J, et al. Transcatheter Versus Surgical Aortic Valve Replacement: An Updated Systematic Review and Meta-Analysis With a Focus on Outcomes by Sex. *Heart, lung & circulation.* 2021;30(1):86-99. PMID: 32732125
30. Villablanca PA, Mathew V, Thourani VH, et al. A meta-analysis and meta-regression of long-term outcomes of transcatheter versus surgical aortic valve replacement for severe aortic stenosis. *International journal of cardiology.* 2016;225:234-43. PMID: 27732927
31. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet.* 2015;385(9986):2477-84. PMID: 25788234
32. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology.* 2015;66(2):113-21. PMID: 26055947
33. Panchal HB, Ladia V, Desai S, et al. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events following transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. *The American journal of cardiology.* 2013;112(6):850-60. PMID: 23756547
34. Takagi H, Niwa M, Mizuno Y, et al. A meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement. *The Annals of thoracic surgery.* 2013;96(2):513-9. PMID: 23816417
35. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *The New England journal of medicine.* 2011;364(23):2187-98. PMID: 21639811
36. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). *Journal of the American College of Cardiology.* 2012;60:548-58. PMID: 22818074
37. Genereux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I Trial (Placement of Aortic Transcatheter Valve). *Journal of the American College of Cardiology.* 2014;63(11):1100-9. PMID: 24291283

38. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *The New England journal of medicine.* 2014;370(19):1790-8. PMID: 24678937
39. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology.* 2016;67(22):2565-74. PMID: 27050187
40. Zorn GL, 3rd, Little SH, Tadros P, et al. Prosthesis-patient mismatch in high-risk patients with severe aortic stenosis: A randomized trial of a self-expanding prosthesis. *The Journal of thoracic and cardiovascular surgery.* 2016;151(4):1014-22, 23 e1-3. PMID: 26614412
41. Arnold SV, Chinnakondepalli KM, Magnuson EA, et al. Five-Year Health Status After Self-expanding Transcatheter or Surgical Aortic Valve Replacement in High-risk Patients With Severe Aortic Stenosis. *JAMA cardiology.* 2021;6(1):97-101. PMID: 32997095
42. Conte JV, Hermiller J, Jr., Resar JR, et al. Complications After Self-expanding Transcatheter or Surgical Aortic Valve Replacement. *Seminars in thoracic and cardiovascular surgery.* 2017;29(3):321-30. PMID: 29195573
43. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. *Journal of the American College of Cardiology.* 2018;72(22):2687-96. PMID: 30249462
44. Food and Drug Administration. Summary of Safety And Effectiveness Data (SSED): LOTUS Edge™ Valve System. Secondary Food and Drug Administration. Summary of Safety And Effectiveness Data (SSED): LOTUS Edge™ Valve System. [cited 5/2/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180029B.pdf.
45. Reardon MJ, Feldman TE, Meduri CU, et al. Two-Year Outcomes After Transcatheter Aortic Valve Replacement With Mechanical vs Self-expanding Valves: The REPRISE III Randomized Clinical Trial. *JAMA cardiology.* 2019;4:223-29. PMID: 30810703
46. Makkar RR, Cheng W, Waksman R, et al. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. *Lancet.* 2020;396(10252):669-83. PMID: 32593323
47. Muneretto C, Bisleri G, Moggi A, et al. Treating the patients in the 'grey-zone' with aortic valve disease: a comparison among conventional surgery, sutureless valves and transcatheter aortic valve replacement. *Interact Cardiovasc Thorac Surg.* 2015;20:90-5. PMID: 25320140
48. Minutello RM, Wong SC, Swaminathan RV, et al. Costs and in-hospital outcomes of transcatheter aortic valve implantation versus surgical aortic valve replacement in commercial cases using a propensity score matched model. *The American journal of cardiology.* 2015;115(10):1443-7. PMID: 25784513
49. Sedaghat A, Al-Rashid F, Sinning JM, et al. Outcome in TAVI patients with symptomatic aortic stenosis not fulfilling PARTNER study inclusion criteria. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2015;86(6):1097-104. PMID: 26032437
50. Arora S, Strassle PD, Ramm CJ, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Lower Surgical Risk Scores: A Systematic Review and Meta-Analysis of Early Outcomes. *Heart, lung & circulation.* 2017;26(8):840-45. PMID: 28169084
51. Arora S, Vaidya SR, Strassle PD, et al. Meta-analysis of transfemoral TAVR versus surgical aortic valve replacement. *Catheterization and cardiovascular interventions :*

official journal of the Society for Cardiac Angiography & Interventions. 2018;91(4):806-12. PMID: 29068166
52. Garg A, Rao SV, Visveswaran G, et al. Transcatheter Aortic Valve Replacement Versus Surgical Valve Replacement in Low-Intermediate Surgical Risk Patients: A Systematic Review and Meta-Analysis. *The Journal of invasive cardiology.* 2017;29(6):209-16. PMID: 28570236
53. Singh K, Carson K, Rashid MK, et al. Transcatheter Aortic Valve Implantation in Intermediate Surgical Risk Patients With Severe Aortic Stenosis: A Systematic Review and Meta-Analysis. *Heart, lung & circulation.* 2018;27(2):227-34. PMID: 28473216
54. Ando T, Takagi H,Grines CL. Transfemoral, transapical and transcatheter aortic valve implantation and surgical aortic valve replacement: a meta-analysis of direct and adjusted indirect comparisons of early and mid-term deaths. *Interact Cardiovasc Thorac Surg.* 2017;25:484-92. PMID: 28549125
55. Gozdek M, Raffa GM, Suwalski P, et al. Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve bioprostheses: systematic review and meta-analysis. *Eur J Cardiothorac Surg.* 2018;53:495-504. PMID: 29029105
56. Khan SU, Lone AN, Saleem MA, et al. Transcatheter vs surgical aortic-valve replacement in low- to intermediate-surgical-risk candidates: A meta-analysis and systematic review. *Clinical cardiology.* 2017;40(11):974-81. PMID: 29168984
57. Tam DY, Vo TX, Wijeysundera HC, et al. Transcatheter vs Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Intermediate Risk Patients: A Meta-analysis. *The Canadian journal of cardiology.* 2017;33(9):1171-79. PMID: 28843328
58. Witberg G, Lador A, Yahav D, et al. Transcatheter versus surgical aortic valve replacement in patients at low surgical risk: A meta-analysis of randomized trials and propensity score matched observational studies. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2018;92(2):408-16. PMID: 29388308
59. Ueshima D, Fovino LN, D'Amico G, et al. Transcatheter versus surgical aortic valve replacement in low- and intermediate-risk patients: an updated systematic review and meta-analysis. *Cardiovasc Interv Ther.* 2019;34:216-25. PMID: 30232711
60. Levett JY, Windle SB, Filion KB, et al. Meta-Analysis of Transcatheter Versus Surgical Aortic Valve Replacement in Low Surgical Risk Patients. *The American journal of cardiology.* 2020;125(8):1230-38. PMID: 32089249
61. Vipparthy SC, Ravi V, Avula S, et al. Meta-Analysis of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Low Surgical Risk. *The American journal of cardiology.* 2020;125(3):459-68. PMID: 31784051
62. Anantha-Narayanan M, Kandasamy VV, Reddy YN, et al. Low-Risk Transcatheter Versus Surgical Aortic Valve Replacement - An Updated Meta-Analysis of Randomized Controlled Trials. *Cardiovasc Revasc Med.* 2020;21(4):441-52. PMID: 31678116
63. Kundu A, Sardar P, Malhotra R, et al. Cardiovascular Outcomes with Transcatheter vs. Surgical Aortic Valve Replacement in Low-Risk Patients: An Updated Meta-Analysis of Randomized Controlled Trials. *Cardiovasc Revasc Med.* 2020;21(4):453-60. PMID: 31669113
64. Kolkailah AA, Doukky R, Pelletier MP, et al. Cochrane corner: transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis in people with low surgical risk. *Heart (British Cardiac Society).* 2020;106(14):1043-45. PMID: 32482670

65. Zhou Y, Wang Y, Wu Y, et al. Transcatheter versus surgical aortic valve replacement in low to intermediate risk patients: A meta-analysis of randomized and observational studies. *International journal of cardiology.* 2017;228:723-28. PMID: 27886617
66. Thyregod HG, Steinbruchel DA, Ihlemann N, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *Journal of the American College of Cardiology.* 2015;65(20):2184-94. PMID: 25787196
67. Nielsen HH, Klaaborg KE, Nissen H, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 2012;8(3):383-9. PMID: 22581299
68. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *The New England journal of medicine.* 2016;374(17):1609-20. PMID: 27040324
69. Kondur A, Briasoulis A, Palla M, et al. Meta-Analysis of Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis. *The American journal of cardiology.* 2016;117(2):252-7. PMID: 26639040
70. Tamburino C, Barbanti M, D'Errigo P, et al. 1-Year Outcomes After Transfemoral Transcatheter or Surgical Aortic Valve Replacement: Results From the Italian OBSERVANT Study. *Journal of the American College of Cardiology.* 2015;66(7):804-12. PMID: 26271063
71. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ.* 2016;354:i5130. PMID: 27683246
72. Sondergaard L, Steinbruchel DA, Ihlemann N, et al. Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement: The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial. *Circulation Cardiovascular interventions.* 2016;9(6). PMID: 27296202
73. Thyregod HGH, Ihlemann N, Jorgensen TH, et al. Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients. *Circulation.* 2019. PMID: 30704298
74. Sondergaard L, Ihlemann N, Capodanno D, et al. Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients at Lower Surgical Risk. *Journal of the American College of Cardiology.* 2019;73(5):546-53. PMID: 30732707
75. Reardon MJ, Kleiman NS, Adams DH, et al. Outcomes in the Randomized CoreValve US Pivotal High Risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of 7% or Less. *JAMA cardiology.* 2016;1:945-49. PMID: 27541162
76. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *The New England journal of medicine.* 2017;376(14):1321-31. PMID: 28304219
77. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *The New England journal of medicine.* 2019;380(18):1706-15. PMID: 30883053
78. Forrest JK, Deeb GM, Yakubov SJ, et al. 2-Year Outcomes After Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. *Journal of the American College of Cardiology.* 2022;79(9):882-96. PMID: 35241222

79. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *The New England journal of medicine.* 2019;380(18):1695-705. PMID: 30883058
80. Leon MB, Mack MJ, Hahn RT, et al. Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk. *Journal of the American College of Cardiology.* 2021;77(9):1149-61. PMID: 33663731
81. Toff WD, Hildick-Smith D, Kovac J, et al. Effect of Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement on All-Cause Mortality in Patients With Aortic Stenosis: A Randomized Clinical Trial. *Jama.* 2022;327(19):1875-87. PMID: 35579641
82. Jørgensen TH, Thyregod HGH, Ihlemann N, et al. Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. *Eur Heart J.* 2021;42(30):2912-19. PMID: 34179981
83. Makkar RR, Thourani VH, Mack MJ, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. *The New England journal of medicine.* 2020;382(9):799-809. PMID: 31995682
84. Pibarot P, Salaun E, Dahou A, et al. Echocardiographic Results of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients: The PARTNER 3 Trial. *Circulation.* 2020;141(19):1527-37. PMID: 32272848
85. Shahim B, Malaisrie SC, George I, et al. Postoperative Atrial Fibrillation or Flutter Following Transcatheter or Surgical Aortic Valve Replacement: PARTNER 3 Trial. *JACC Cardiovascular interventions.* 2021;14(14):1565-74. PMID: 34294398
86. Aedma SK, Khan N, Altamimi A, et al. Umbrella Meta-analysis Evaluating the Effectiveness of ViV-TAVI vs Redo SAVR. *SN Comprehensive Clinical Medicine.* 2022;4(1):63. PMID:
87. Raschpichler M, de Waha S, Holzhey D, et al. Valve-in-Valve Transcatheter Aortic Valve Replacement Versus Redo Surgical Aortic Valve Replacement for Failed Surgical Aortic Bioprostheses: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2022;11(24):e7965. PMID: 36533610
88. Sá MP, Van den Eynde J, Simonato M, et al. Late outcomes of valve-in-valve transcatheter aortic valve implantation versus re-replacement: Meta-analysis of reconstructed time-to-event data. *International journal of cardiology.* 2023;370:112-21. PMID: 36370873
89. National Institute For Health And Care Excellence. Interventional procedure overview of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction (IP 1013/2 [IPG653]). June 2019. Secondary National Institute For Health And Care Excellence. Interventional procedure overview of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction (IP 1013/2 [IPG653]). June 2019 [cited 5/2/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg653/evidence/overview-final-pdf-6834685357.
90. Phan K, Zhao DF, Wang N, et al. Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. *J Thorac Dis.* 2016;8:E83-93. PMID: 26904259
91. Chen HL,Liu K. Clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction: A meta-analysis. *International journal of cardiology.* 2016;212:138-41. PMID: 27038719
92. Tam DY, Vo TX, Wijeysundera HC, et al. Transcatheter valve-in-valve versus redo surgical aortic valve replacement for the treatment of degenerated bioprosthetic aortic valve: A systematic review and meta-analysis. *Catheterization and cardiovascular*

interventions : official journal of the Society for Cardiac Angiography & Interventions. 2018;92(7):1404-11. PMID: 30024102
93. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2014;63(22):2438-88. PMID: 24603192
94. Nishimura RA, O'Gara PT,Bonow RO. Guidelines Update on Indications for Transcatheter Aortic Valve Replacement. *JAMA cardiology.* 2017;2:1036-37. PMID: 28768333
95. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology.* 2021;77(4):e25-e197. PMID: 33342586

CODES

Codes	Number	Description
CPT	33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
	33362	;open femoral artery approach
	33363	;open axillary artery approach
	33364	;open iliac artery approach
	33365	;transaortic approach (eg, median sternotomy, mediastinotomy)
	33366	;transapical exposure (eg, left thoracotomy)
	33367	;cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)
	33368	;cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
	33369	;cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)
HCPCS	None	

Date of Origin: *December 2018*

Regence

Medical Policy Manual Surgery, Policy No. 204

Ablation of Primary and Metastatic Liver Tumors

Effective: March 1, 2024

Next Review: November 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ablation is a method of locoregional therapy used to treat cancerous lesions, including hepatocellular carcinoma and hepatic metastases from other primary cancers.

MEDICAL POLICY CRITERIA

Note: This policy addresses locoregional therapies, specifically, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation for primary and metastatic liver tumors. Please see Cross References for other ablative techniques and indications.

I. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave local ablative techniques may be considered **medically necessary** for treatment of liver tumors when either of the following (A. or B.) are met:

   A. In patients *not* currently awaiting liver transplantation, and one or more of the following criteria are met:

      1. Unresectable primary liver tumors [hepatocellular carcinoma] when **all** of the following criteria (a.-c.) are met:

         a. The tumor(s) is 5 cm or less in diameter; and

b. There are no more than 3 hepatic lesions; and

c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection).

2. Hepatic metastases from colorectal tumors, including but not limited to adenocarcinoma when **all** of the following criteria (a.-d.) are met

a. The metastatic tumor(s) is 5 cm or less in diameter; and

b. There are no more than 5 hepatic lesions; and

c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities, or an estimate of inadequate liver volume following resection); and

d. No extrahepatic metastatic disease is present.

3. Hepatic metastases from neuroendocrine tumors when **all** of the following criteria (a.-c.) are met:

a. The disease is symptomatic; and

b. Systemic therapy has failed to control symptoms; and

c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection)

B. As a bridge to liver transplantation when the intent is to prevent tumor progression or decrease tumor size to achieve or maintain a patient's candidacy for liver transplant.

II. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered **investigational** as a treatment for all other benign or malignant liver tumors that do not meet the medical necessity criteria above, including but not limited to the following:

A. More than 3 hepatocellular carcinoma tumors; more than 5 metastatic colorectal tumors in the liver; or metastatic or primary liver tumors larger than 5 cm in diameter

B. Metastases to the liver from organ tumors other than colorectal, asymptomatic neuroendocrine tumors, or neuroendocrine tumors with symptoms controlled by systemic therapy

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

NEUROENDOCRINE TUMORS

Neuroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body.[1] Neuroendocrine tumors include the following:

- Carcinoid Tumors

- Islet Cell Tumors (also known as Pancreatic Endocrine Tumors)
- Neuroendocrine Unknown Primary
- Adrenal Gland Tumors
- Pheochromocytoma/paraganglioma
- Poorly Differentiated (High Grade or Anaplastic)/Small Cell
- Multiple Endocrine Neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple Endocrine Neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Neuroendocrine tumors may also be referred to by their location (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors).

Some appendiceal carcinoids, also called adenocarcinoids, goblet cell carcinoids, or crypt cell carcinoids, have mixed histology, including elements of adenocarcinoma. While these biphasic tumors have both neuroendocrine and adenocarcinoma components, the National Comprehensive Cancer Network (NCCN) recommends they be managed according to colon cancer guidelines.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Specific description of the tumor(s) targeted for treatment including the following:
    - Tumor type (primary vs. metastatic; primary tumor type)
    - The location of tumor(s)
    - The number and size(s) of lesion(s) being treated
2. Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
3. Whether the goal of treatment is curative or palliative
4. Comorbidities and any contraindicated treatments (e.g., surgery; radiation therapy)
5. Prior treatments, if any, and tumor response
6. Documentation of whether this treatment is to preserve organ function
7. Include documentation of the presence or absence of extra-hepatic disease

CROSS REFERENCES

1. Radioembolization, Transarterial Embolization (TAE), and Transarterial Chemoembolization (TACE), Medicine, Policy No. 140
2. Radiofrequency Ablation (RFA) of Tumors Other than Liver, Surgery, Policy No. 92
3. Cryosurgical Ablation of Miscellaneous Solid Tumors, Surgery, Policy No. 132
4. Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation, Surgery, Policy No. 139
5. Microwave Tumor Ablation, Surgery, Policy No. 189
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214

BACKGROUND

ABLATIVE TECHNIQUES

THERMAL ABLATION

Radiofrequency Ablation

Radiofrequency ablation (RFA) is one of a number of locoregional thermal ablation therapies to treat various benign or malignant tumors. RFA kills cells (cancerous and normal) by applying a heat-generating rapidly alternating radiofrequency current through probes inserted into the tumor. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edge of this scar tissue and, in some cases, may be retreated. RFA can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or computed tomography (CT) guidance. The goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain cancerous tumors.

Reports have been published on use of RFA to treat renal cell carcinomas, breast cancer, pulmonary (including primary and metastatic lung tumors), bone, and other tumors including those that are non-cancerous (benign). Well-established local or systemic treatment alternatives are available for each of these tumor types.

Radiofrequency ablation (RFA) has been investigated as a treatment for unresectable hepatic tumors, both as primary treatment and as a bridge to liver transplant. In the latter setting, RFA is being tested to determine whether it can reduce the incidence of tumor progression in patients awaiting transplantation and thus maintain patients' candidacy for liver ablation, transhepatic arterial chemoembolization, microwave coagulation, percutaneous ethanol injection, and radioembolization (yttrium-90 microspheres).

Microwave Ablation

Microwave ablation (MWA) is a technique in which the use of microwave energy induces an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field which causes water molecule rotation and the creation of heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, approximately 2 to 3 cm elliptical area (5 x 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2 to 3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within one minute after a pulse of energy, and multiple pulses may be delivered within a treatment session depending on the size of the tumor. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edges. Treatment may be repeated as needed. MWA may be used to: 1) control local tumor growth and prevent recurrence; 2) palliate symptoms; and 3) extend survival duration.

Complications from MWA are usually considered mild and may include pain and fever. Other potential complications associated with MWA include those caused by heat damage to

normal tissue adjacent to the tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant patients since potential risks to the patient and/or fetus have not been established and in patients with implanted electronic devices such as implantable pacemakers that may be adversely affected by microwave power output.

MWA is an ablative technique similar to radiofrequency or cryosurgical ablation; however, MWA may have some advantages. In MWA, the heating process is active, which produces higher temperatures than the passive heating of radiofrequency ablation and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (over 100° C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating, and therefore, does not have electrical current flow through patients and does not require grounding pads be used during the procedure to prevent skin burns. Unlike radiofrequency ablation, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference. Finally, MWA can be completed in less time than radiofrequency ablation since multiple antennas can be used simultaneously.

Regulatory Status

There are several devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (a subsidiary of Tyco Healthcare) Evident Microwave Ablation System has 510(k) clearance for soft tissue ablation, including partial or complete ablation of non-resectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical Corporation’s MicroThermX® Microwave Ablation System (MTX-180);
- MicroSurgeon Microwave Soft Tissue Ablation Device;
- Angiodynamics’ Solero Microwave Tissue Ablation System;
- Surgnova Healthcare Technologies’ Microwave Ablation System;
- Microsulis Medical’s Acculis Accu2i; and
- Johnson & Johnson’s NEUWAVE Microwave Ablation System

FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

CRYOSURGICAL ABLATION

Cryosurgical ablation (also called cryosurgery, cryotherapy, or cryoablation) kills cells (cancerous and normal) by freezing target tissues, most often by inserting a probe into the tumor through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The goals of cryosurgery may include the following:

- Destruction or shrinkage of tumor tissue
- Controlling local tumor growth and preventing recurrence
- Palliating symptoms

- Extending survival duration for patients with certain tumors.

Potential complications associated with cryosurgery in any organ include the following:

- Hypothermic damage to normal tissue adjacent to the tumor (e.g., nerve damage)
- Structural damage along the probe track
- Secondary tumors if cancerous cells are seeded during probe removal.

Regulatory Status

There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear, nose and throat. Examples include:

- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical;
- IceRod® CX, IcePearl® 2.1 CX and IceFORCE® 2.1 CX Cryoablation Needles by Galil Medical;
- SeedNet™ System by Galil Medical;
- Visica® System by Sanarus Medical;
- Visual-ICE® Cryoablation System by Galil;
- ERBECRYO 2® Cryosurgical Unit, ERBE USA Incorporated

PERCUTANEOUS ETHANOL INJECTION

Using a needle, percutaneous ethanol injection (PEI) delivers an injection of 95 percent ethanol directly into a tumor. Multiple treatment sessions may be performed in order to achieve tumor destruction. Prior to RFA, PEI was the most widely accepted, minimally invasive method to treat hepatocellular carcinoma. Like other local ablative techniques, PEI is most successful in small HCC tumors when resection is not an option.

LIVER (HEPATIC) TUMORS

Hepatic tumors can arise either as primary liver cancer (such as hepatocellular carcinoma, HCC) or by metastasis to the liver from other primary cancer sites. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential. Partial liver resection, hepatectomy, is considered the gold standard. However, the majority of hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Locoregional therapies are proposed as a treatment for unresectable hepatic tumors, both as primary treatment, palliative treatment, and as a bridge to liver transplant. In the case of liver transplants, it is hoped that locoregional ablative techniques will reduce the incidence of tumor progression while awaiting transplantation and thus maintain a patient's candidacy for liver transplant during the wait time for a donor organ.

EVIDENCE SUMMARY

MULTIPLE ABLATIVE TECHNIQUES

Systematic Reviews

Lu (2022) performed a systematic review of ten studies, including 854 patients with histologically proven HCC who received a combination of RFA and PEI or RFA alone.[2] The results demonstrated that patients who received RFA-PEI had slight improvements in 1-year overall survival (OS) [risk ratio (RR): 1.11; 95% CI: 1.03, 1.19] 2-year OS (RR: 1.25; 95% CI: 1.12, 1.40), 3-year OS (RR: 1.42; 95% CI: 1.11, 1.83), 1-year local recurrence-free (LRF) proportion (RR: 1.2; 95% CI: 1.01, 1.42), and complete tumor necrosis (CTN) (RR: 1.32; 95% CI: 1.14, 1.53). Common complications, such as fever, were found to be significant (RR: 1.78, 95% CI: 1.13, 2.80). Despite RFA-PEI appearing to be superior for HCC patients with a compensated liver in terms of OS, current evidence contained moderate to significant heterogeneity, and it was difficult to draw a definite conclusion regarding the therapeutic management in terms of LRF and CTN.

Yu (2021) performed a meta-analysis of RCTs comparing RFA with microwave ablation for the treatment of localized, very early- or early-stage HCC.[3] Five RCTs comparing RFA (n=413) and microwave ablation (n=431) were identified. The OS between microwave ablation and RFA was not significantly different at one year (OR=0.705; 95% CI 0.382 to 1.301) or three years (OR=0.972; 95% CI 0.615 to 1.538). Similarly, there was no difference observed in recurrence-free survival between microwave ablation and RFA at one year (OR=1.167; 95% CI: 0.568 to 2.396) and three years (OR=0.981; 95% CI 0.616 to 1.562). Among the procedure-related complications evaluated, there were no statistically significant differences between the two groups.

A similar analysis was published by Gupta in 2021 that compared outcomes for very early and early HCC following RFA, MWA, or cryoablation.[4] A total of 19 studies (six RCTs and 13 observational studies) met inclusion criteria. No statistically significant differences between groups were identified for OS or local recurrence (LR).

Shin (2021) compared the efficacy of surgical resection with local ablative therapies for HCC meeting Milan criteria.[5] The analysis included seven RCTs and 18 non-randomized trials (n=5,629) that compared surgical resection with either RFA, microwave ablation, or RFA plus TACE. Four of the RCTs were judged to be at high risk of bias overall, due to either lack of reported randomization method or missing data. All non-randomized trials were classified as having a high risk for bias due to the missing data. There was no significant difference between surgical resection and RFA alone when the RCTs were analyzed; the three- and five-year OS favored surgical resection in the analysis of the non-randomized trials. A multiple treatment meta-analysis using a frequentist framework random effect model found that 5-year recurrence free survival was highest with surgical resection (hazard ratio [HR]=0.64, 95% CI 0.56 to 0.74 vs RFA), followed by RFA plus TACE (HR=0.70, 95% CI 0.53 to 0.92 vs RFA); no difference was found between microwave ablation and RFA (HR=0.93, 95% CI 0.63 to 1.37). However, the latter comparisons were limited by the number of trials evaluating RFA plus TACE (five studies) and microwave ablation (two studies).

Cui (2020) conducted a systematic review and meta-analysis of MWA compared to various treatment modalities for the treatment of hepatocellular carcinoma.[6] The analysis included four RCTs, with three comparing MWA to RFA and one comparing MWA to TACE. The

remaining 11 studies were nonrandomized trials comparing MWA to RFA (eight studies), resection (two studies), or ethanol ablation (one study). Meta-analyses were not performed for MWA versus TACE or ethanol ablation, because these comparisons were only examined in one study each. Meta-analyses of studies comparing MWA to RFA found no difference in three-year OS, five-year OS, local tumor progression at one year, progression-free survival at three years, or major complications. A meta-analysis of two nonrandomized studies comparing MWA to resection found no difference in three-year OS between treatments; however, this comparison is limited by the small number of studies included and the lack of RCTs included. The reviewers concluded that MWA showed similar safety and efficacy compared with RFA, but higher quality clinical studies are needed to validate the superiority of MWA.

Gui (2020) reported a systematic review and meta-analysis of trans-arterial chemoembolization plus RFA compared to surgical resection for hepatocellular carcinoma.[7] One RCT and eight retrospective studies met inclusion criteria. According to the unadjusted pooled analysis, there was no significant difference in one-, three-, and five-year OS and one-year disease-free survival between TACE+RFA and surgical resection. There were statistically significant differences favoring surgical resection in three-year disease-free survival (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.62 to 0.98, p=0.03) and five-year disease-free survival (OR 0.74, 95% CI 0.58 to 0.95, p=0.02) compared to TACE+RFA. In the propensity matched analysis, the difference in three- and five-year disease-free survival was not significant.

Han (2020) reported a systematic review comparing MWA and RFA for early stage hepatocellular carcinoma.[8] Five RCTs, one prospective cohort studies and 20 retrospective cohort studies were included, for a total of 4,396 patients. Four of the RCTs were rated as high quality and one as low quality. Of the remaining studies, 16 were rated as high quality and five as low quality. According to the meta-analysis, there were no statistically significant differences between MWA and RFA for disease progression (OR=0.877, 95% CI 0.710 to 1.084, I^2=0%, p =0.225), or survival, either overall or disease-free (hazard ratio [HR]=0.891 and 1.014, p=0.222 and 0.852, respectively). Only six studies reported the OS rates, with five reporting one-year, five reporting three-year, and three reporting five-year OS. The one-, three-, and five-year OS estimates were 88.00% (95% CI 72.30% to 100%), 47.00% (95% CI 23.50 to 70.50%), and 17.00% (95% CI 0 to 34.60%) for LITT; 95.10% (95% CI 91.20 to 99.00%), 76.83% (95% CI 67.00 to 86.60%), and 27.00% (95% CI 11.00 to 51.00%) for RFA; not reported, 66.67% (95% CI 29.40 to 103.90%), and 33.33% (95% CI 0 to 70.60%) for MWA; and 91.49% (95% CI 83.70 to 99.30%), 79.3% (95% CI 59.70 to 98.90%), and not reported for PC.

Xiang (2020) published a systematic review and pooled analysis of multiple types of magnetic resonance-guided ablation techniques for the treatment of liver tumors.[9] Thirty studies (14 on RFA, one on MWA and RFA, eight on LITT, two on percutaneous cryoablation, and one on percutaneous ethanol injection) met inclusion criteria. No quality assessment was reported. The rates of complete ablation were 95.60%, 98.86%, 77.78%, 47.92%, and 85.71% in patients who underwent RFA, MWA, LITT, PC, and PEI, respectively.

Glassberg (2019) performed a systematic review and meta-analysis comparing MWA and RFA for the treatment of liver cancer.[10] A total of 28 RCTs and observational studies met inclusion criteria. The overall quality of the studies was rated as acceptable and most studies had low or unclear risk of bias across most domains. The meta-analysis indicated that local tumor progression was significantly reduced in patients treated with MWA as compared to RFA,

whether the analysis included all studies (30% reduction, risk ratio [RR]=0.70, p=0.02) or RCTs only (45% reduction, RR=0.55, p=0.007). No other efficacy or safety outcomes were found to be significantly different between groups.

Di Martino (2019) compared local ablative therapies for resectable colorectal liver metastases in a systematic review and meta-analysis.[11] Therapies evaluated included RFA, MWA, cryoablation and electroporation. A total of 20 studies with 860 patients met inclusion criteria. Surgical resection was superior to local ablative therapies with respect to disease-free survival, tumor progression, and overall survival. Compared to surgical resection, RFA reduced one-year disease-free survival (RR 0.83, 95% CI 0.71 to 0.98), three-year disease-free survival (RR 0.5, 95% CI 0.33 to 0.76), five-year DFS (RR 0.53, 95% CI 0.28 to 0.98) and five-year OS (RR 0.76, 95% CI 0.58 to 0.98).

A meta-analysis by Meijerink (2018) compared RFA and MWA to systemic chemotherapy and to partial hepatectomy (PH) for the treatment of colorectal liver metastases.[12] Forty-eight articles were identified, most of which were observational studies and case series, although two RCTs and eight systematic reviews were included. The authors found 18 observational studies of very low quality that looked at RFA alone compared to PH alone or PH plus RFA. For OS, their analysis concluded that PH alone was superior to RFA alone (HR=1.78; 95% CI 1.35 to 2.33). The meta-analysis for 30-day mortality comparing RFA alone to PH alone showed no difference between the two interventions (RR=0.64; 95% CI 0.21 to 1.95). DFS was higher for PH alone over RFA alone (HR=1.49; 95% CI 1.23 to 1.81), as well as for local progression-free survival (HR=5.36; 95% CI 1.64 to 17.52). However, complication rates were lower for RFA alone than for PH alone (risk ratio=0.47; 95% CI 0.28 to 0.78). One limitation of this review is that the included observational studies were all confounded by indication because RFA was only performed on unresectable lesions. Observational studies are also at increased risk for publication bias.

Majumdar (2017) published a Cochrane review and network meta-analysis of the management of early and very early-stage HCC.[13] Reviewers included 14 RCTs (total n=2533 patients) of nonsurgical treatments compared with each other, sham, or no intervention in patients with unresectable HCC. The quality of the evidence was rated as low or very low for all outcomes. Follow-up ranged from 6 to 37 months. Compared with RFA, mortality was higher for percutaneous acetic acid injection (HR=1.8; 95% CI 1.1 to 2.8; one trial; n=125) and PEI (HR=1.49; 95% CI 1.2 to 1.9; five trials; n=882). No trials reported health-related quality of life.

In 2016, Lan published a network meta-analysis comparing different interventional treatments for early stage HCC.[14] A total of 21 RCTs were included that compared transhepatic arterial chemoembolization (TACE), RFA, percutaneous ethanol injection (PEI), and hepatic resection, or combinations of treatments. These studies were all rated at a low-to-moderate risk of bias, with lack of blinding being the most substantial limitation. The primary outcome measures were overall survival (OS) at one, three, and five years posttreatment. The treatments and combinations of treatments were rank-ordered by results on OS. At each time point, the combination of RFA plus TACE was the number one ranked treatment. The combination of RFA plus TACE ranked second highest at one and three years, and was third highest at five years, with hepatic resection ranked second at five years. RFA alone was ranked as the fourth highest treatment at one year and the fifth highest treatment at three and five years.

In 2016, Facciorusso reported results from a systematic review and meta-analysis of one RCT and six retrospective studies (n=774) comparing RFA and MWA for the treatment of

unresectable hepatocellular carcinoma (HCC).[15] The authors found a non-significant trend of higher complete response rates in the patients treated with MWA (OR=1.12, 95% CI 0.67 to1.88, p = 0.67). Overall local recurrence was similar between the two treatment groups (OR 1.01, 95% CI 0.53 to 1.87, p=0.98) but MWA outperformed RFA in cases of larger nodules (OR 0.46, 95% CI 0.24 to 0.89, p=0.02). Three-year survival was higher after RFA without statistically significant difference (OR 0.95, 95% CI 0.58 to 1.57, p=0.85). Major complications were more frequent, although not significantly, in MWA patients (OR 1.63, 95% CI 0.88 to 3.03, p=0.12).

In a 2013 Cochrane review, Weis reviewed studies on RFA for HCC versus other interventions.[16] Moderate-quality evidence demonstrated hepatic resection had superior survival outcomes compared with RFA; however, resection might have greater rates of complications and longer hospital stays. Other systematic reviews and meta-analyses have also found superior survival with hepatic resection but higher rates of complications than RFA.[17-20] This finding reinforces the use of RFA only for unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over PEI.[16] Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.[16]

RADIOFREQUENCY ABLATION

RFA AS A PRIMARY TREATMENT OF HEPATOCELLULAR CANCER

Systematic Reviews

Jia (2021) performed a meta-analysis to compare clinical efficacy between RFA and surgical resection in patients with HCC meeting Milan criteria.[21] The analysis only included RCTs, accounting for eight trials (n=1,177). There were no significant differences found between RFA and surgical resection in OS and disease-free survival (DFS) rates. In a subgroup analysis stratifying by tumor size, there was still no significant differences between the two therapies for both tumors ≤4 cm and >4 cm. Limitations of the analysis include inclusion of clinical trials with small sample sizes and a lack of double blinding as it is not feasible.

Pan (2020) reported a systematic review comparing stereotactic body radiotherapy and RFA for hepatocellular carcinoma.[22] No RCTs and 10 retrospective studies (n=2,732 patients) met inclusion criteria. Over half of the studies were giving a medium score for quality because of inconsistent comparability. According to the meta-analysis, SBRT had significantly higher one- and three-year local control (OR 0.42, 95% CI 0.24 to 0.74, p=0.003; and OR 0.54, 95% CI 0.37 to 0.80, p=0.002, respectively) and significantly shorter one- and two-year OS (OR 1.52, 95% CI 1.21 to 1.90, p=0.0003; and OR 1.66, 95% CI 1.38 to 2.01, p<0.00001, respectively). When used as a bridge to treatment, no significant differences were identified between groups in transplant rate or post-transplant pathological necrosis rate (OR 0.57, 95% CI 0.32 to 1.03, p=0.060; and OR 0.49, 95% CI 0.13 to 1.82, p=0.290, respectively).

Jin (2020) performed a systematic review of RCTs comparing laparoscopic hepatectomy and RFA for HCC.[23] Seven RCTs met inclusion criteria. The studies were at unclear risk of bias for allocation concealment and blinding (participants, personnel, and outcome assessment) and low risk of reporting and attrition bias. Pooling of the five studies that reported duration of surgery showed that the RFA group had significantly shorter duration than the hepatectomy group (MD=−99.04; 95% CI −131.26 to −66.82; p<0.001; I^2=95%). Four studies reported the incidence of cancer recurrence, and pooled data from these RCTs indicated a higher rate of

recurrence in the RFA group (OR=2.68; 95% CI 1.72 to 4.18; p<0.001; I^2=23%). The pooled data from the four RCTs that reported on estimated bleeding volume during surgery and duration of hospital stay showed that the RFA group had significantly lower volume (MD=−241.97; 95% CI −386.93 to −97.02; p< 0.001; I^2=97%) and shorter duration (MD=−3.4; 95% CI −5.22 to −1.57; p<0.001; I^2=94%) than the hepatectomy group. Pooling of the three studies that reported the incidence of blood transfusion during surgery indicated significantly lower incidence in the RFA group (OR=0.08; 95% CI 0.02 to 0.37; p=0.001; I^2=0%).

Li (2019) performed a systematic review and meta-analysis to compare the effectiveness of laparoscopic hepatectomy and RFA.[24] A total of 10 studies met inclusion criteria. This included 1,570 HCC patients treated with laparoscopic hepatectomy or RFA. The pooled five-year OS rate was significantly higher in the hepatectomy group (OR=0.53, 95% CI=0.40, 0.69, p<0.001) analyzed as a whole and in a subgroup analysis of small HCCs (OR=0.47, 95% CI=0.33, 0.66, p<0.001). The hepatectomy group also had better one- and three-year disease-free survival rate and a lower recurrence rate, but additionally a higher complication rate (OR=0.64, 95% CI 0.46 to 0.89, p=0.008).

Si (2019) reported results of a systematic review and meta-analysis of minimally invasive liver surgery compared to RFA for the treatment of small HCC nodules.[25] A total of six studies met inclusion criteria, including 313 RFA-treated and 284 surgically treated patients. Three-year OS rates were significantly higher in the surgically treated patients (OR 0.55; 95% CI 0.36 to 0.84), as were three-year disease-free survival rates (OR 0.63; 95% CI 0.41 to 0.98). RFA-treated patients experienced significantly higher rates of local intrahepatic recurrence (OR 2.24; 95% CI 1.47 to 3.42), lower incidence of postoperative complications (OR 0.34; 95% CI 0.22 to 0.53), and shorter operation (OR - 145.31, 95% CI - 200.24 to - 90.38) and hospitalization (OR - 4.02,95% CI - 4.94 to - 3.10) durations.

Another systematic review comparing surgery to RFA, this one of early HCC, was reported by Tan (2019).[26] A total of 11 studies met inclusion criteria. These included 1,691 patients undergoing hepatic resection or RFA. The hepatic resection group had statistically significantly higher three- and five-year OS, as well as three-year disease-free survival. This group also had a lower local recurrence rate that did not reach statistical significance. Patients undergoing laparoscopic radiofrequency ablation had higher three- and five-year OS than other minimally invasive ablation techniques.

In 2012, Xu reported on a meta-analysis of 13 studies that compared RFA with surgical resection for early HCC.[27] Only two studies were RCTs. Surgical resection was done in 1233 patients and RFA was used in 1302 patients. Surgical resection patients had significantly longer OS rates at one, three, and five years than RFA patients (OR 0.60; 95% CI 0.42 to 0.86, OR=0.49; 95% CI 0.36 to 0.65; OR=0.60; 95% CI 0.43 to 0.84), respectively. When only HCC tumors of 3 cm or less were analyzed, resection still had significantly better OS than RFA at one, three, and five years. Recurrence rates were also significantly lower in the surgical resection group at one, three, and five years than in the RFA group (OR=1.48; 95% CI 1.05 to 2.08; OR=1.76; 95% CI 1.49 to 2.08; OR=1.68; 95% CI 1.21 to 2.34; all respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than with RFA (OR=6.25; 95% CI 3.12 to 12.52; p=0.000), but, in a subanalysis of HCC 3 cm or less, complication rates were significantly lower with resection than RFA.

Randomized Controlled Trials

No randomized trials published after the above systematic reviews were identified.

Nonrandomized Studies

A large body of case series, meta-analyses, and retrospective evidence has been published on RFA as a treatment of unresectable primary liver tumors.[28-34] These articles reported disease-free survival rates consistent with those reported in the randomized controlled trials.

RFA AS A PRIMARY TREATMENT OF INTRAHEPATIC CHOLANGIOCARCINOMAS

Cholangiocarcinomas are tumors that originate in the bile duct epithelium; 90% are adenocarcinomas. Intrahepatic cholangiocarcinomas (ICC) are located within the hepatic parenchyma. They may also be referred to as peripheral cholangiocarcinomas. Extrahepatic cholangiocarcinomas (ECC) are more common than intrahepatic cholangiocarcinoma and are located within the extrahepatic bile duct. Complete resection with negative margin is potential curative, though recurrence is common and most cases are unresectable due to advanced disease when diagnosed. For unresectable or metastatic cholangiocarcinomas at any location, the primary treatment may include chemotherapy, treatment within a clinical trial, or best supportive care. RFA and other locoregional therapies may be an option. Biliary drainage with biliary stenting may be warranted for unresectable or metastatic extrahepatic disease. Liver transplantation is potentially curative in carefully selected patients with lymph node negative, nondisseminated locally advanced hilar cholangiocarcinomas and otherwise normal biliary and hepatic function or underlying liver disease precluding surgery.

A number of small (n<20) retrospective analyses and case series have been published for ablation of ICC.[35-43] These studies consistently reported high technical effectiveness with early tumor necrosis, and a low rate of major adverse effects.

RFA AS A PRIMARY TREATMENT OF LIVER METASTASES OF COLORECTAL AND NEUROENDOCRINE ORIGIN

Colon Cancer

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis.[44] A median survival of 21 months has been observed in patients with a single CRC liver metastasis; those with several unilobar lesions have median survival of 15 months; and those with disseminated metastases have median survival of less than one year. A number of first-line systemic chemotherapy regimens have been used to treat metastatic CRC, with a two-year survival rate of 25% for those treated with 5-fluorouracil (5-FU) or 5-FU plus leucovorin.[44] With the introduction of newer agents (e.g., irinotecan, oxaliplatin) and targeted drugs (e.g., cetuximab, bevacizumab), two-year survival rates have increased to between 30% and 39%, with marked improvement in OS. Because the liver is often the only site of metastases from CRC, however, locoregional therapies have been investigated. Surgical resection is considered the criterion standard for treatment of CRC liver metastases, with five-year actuarial survival rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without widely disseminated disease.[45, 46] However, only 10% to 25% of patients with CRC metastases are eligible for surgical resection because of the extent and location of the lesions within the liver or because of the presence of comorbid conditions or disseminated disease. Unresectable cases or those for whom surgery is contraindicated typically are treated with systemic chemotherapy, with poor results and considerable adverse effects.

Alternatively, RFA has been proposed to treat metastatic CRC in the liver. Early clinical experience with RFA comprised case series to establish feasibility, safety, tolerability, and local therapeutic efficacy in short-term follow-up. A 2006 literature review encompassing six case series (total n=446 patients) showed that RFA of unresectable CRC metastases was associated with one-, two-, and three-year survival rates that ranged from 87% to 99%, 69% to 77%, and 37% to 58%, respectively.[45] While these results suggested RFA may have clinical benefit in this setting, a primary caveat is the definition of the term “unresectable” in the different series and that different surgeons may have different opinions on this issue. Further, differences in lesion size, number, distribution, prior treatments, RFA technology, and physician experience may affect results, making it difficult to compare results of different studies.

Systematic Reviews

Hao (2020) reported a systematic review and meta-analysis of RFA versus liver resection for solitary colorectal liver metastases.[47] A total of 10 studies met inclusion criteria. Study quality was not assessed. Significant interstudy heterogeneity was identified. Statistically significant differences were identified in the meta-analysis for one-year PFS (RR 0.77 95% CI 0.630 to 0.940, p=0.009), three-year OS (RR 0.860, 95% CI 0.760 to 0.980, p=0.021, and five-year OS (RR 0.66, 95% CI 0.52 to 0.85, p=0.001), with superior outcomes in the resection group. There was significantly lower incidence of postoperative complication in the RFA group (RR 0.340, 95% CI 0.230 to 0.510, p=0.000). The subgroup analysis identified the following variables as contributing to the heterogeneity: publication year, geographic location, tumor size, adjuvant chemotherapy, and synchronous metastases.

A 2017 systematic review with meta-analyses by van Amerongen compared the RFA to surgery as a curative treatment for patients with colorectal liver metastases.[48] Authors found that all studies included had risk of patient selection bias.

A 2012 systematic review by Cirocchi analyzed 17 nonrandomized studies and a meeting abstract of an RCT on RFA for CRC liver metastases.[49] The RCT reported PFS was significantly higher in 60 patients receiving RFA plus chemotherapy than in 59 patients receiving only chemotherapy. The RCT did not report OS. This Cochrane review found different types of vulnerability in all reviewed studies. Of main concern was the imbalance in patient characteristics across studies reviewed, as well as heterogeneity in the interventions, comparisons, and outcomes. Therefore, the reviewers concluded the evidence was insufficient to recommend RFA for CRC liver metastasis. In a 2014 Health Technology Assessment, Loveman also found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.[50]

In 2012, Weng reported a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases.[51] One prospective study and 12 retrospective studies were included in the analysis. OS at three and five years was significantly longer in liver resection than in RFA (relative risk [RR], 1.377; 95% CI 1.246 to 1.522; RR=1.474; 95% CI 1.284 to 1.692, respectively). DFS was also significantly longer in liver resection than RFA at three and five years (RR=1.735; 95% CI 1.483 to 2.029; RR=2.227; 95% CI 1.823 to 2.720, respectively). While postoperative morbidity with liver resection was significantly higher than with RFA (RR=2.495; 95% CI 1.881 to 3.308), mortality did not differ significantly between treatments. Liver resection also performed significantly better than RFA when data were analyzed in three subgroups: tumors less than 3 cm, solitary tumor, and open or laparoscopic approach.

However, hospital stays were significantly shorter (9.2 days vs 3.9 days, p<0.01) and rates of complications lower (18.3% vs 3.9%, p<0.01) with RFA than liver resection. Interpretation of the meta-analysis is limited by the retrospective nature of most studies.

Randomized Controlled Trials

In 2012 and 2017, Ruers published the results of a multicenter RCT that compared RFA plus systemic treatment with systemic treatment alone for unresectable colorectal liver metastases.[52, 53] This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual (n=119 patients). To be included in the trial, patients had to have nonresectable liver metastases with fewer than 10 nodes and without extrahepatic disease. In the experimental arm, RFA, with or without additional resection, was given in combination with systemic therapy. The primary end point was a 30-month survival higher than 38% in the experimental arm with intention-to-treat analysis. At three years, OS did not differ significantly between groups. However, there was a significant improvement in progression-free survival (HR=0.74; 95% CI 0.42 to 0.95; p=0.025), which corresponded to a difference in progression-free survival at three years from 10.6% in the systemic therapy arm to 27.6% in the combined treatment arm. At a median follow-up of 9.7 years, 39 (65%) of 60 patients in the combined treatment arm had died compared with 53 (89.8%) of 59 in the systemic treatment arm (HR=0.58; 95% CI 0.38 to 0.88; p=0.01).

Nonrandomized Studies

Nonrandomized studies in which RFA was compared to resection or systemic chemotherapy in patients with localized CRC metastases and no evidence of additional metastatic disease have been conducted. Tago reported a retrospective analysis in 2021 of CRC patients with liver metastases who underwent RFA (n=26), resection (n=92), or chemotherapy (n=29).[54] Median OS was 44.9, 49.5, and 11.6 months in the RFA, resection, and chemotherapy groups, respectively, with statistically significant differences between RFA and resection (p=0.027), and RFA and chemotherapy (p=0.003). Five-year OS was not significantly different between RFA and resection (p=0.508).

In 2016, Hof compared outcomes from RFA or hepatic resection in patients with hepatic metastases from CRC.[55] There were 431 patients included from an institutional database. All patients underwent locoregional treatment for hepatic metastases from CRC. Initial treatment was either hepatic resection (n=261), open RFA (n=26), percutaneous RFA (n=75), or a combination of resection plus RFA (n=69). Mean follow-up was 38.6 months. The overall recurrence rate was 83.5% (152/182) in patients treated with RFA compared to 66.6% (201/302) in patients treated with hepatic resection (p<0.001). The five-year OS estimate by Kaplan-Meier analysis was 51.9% for RFA and 53.0% for hepatic resection (p=0.98).

Abdalla examined recurrence and survival rates for clinically similar patients treated with hepatic resection only (n=190), resection plus RFA (n=101), RFA only (n=57, open laparotomy by hepatobiliary surgeon), and systemic chemotherapy alone (n=70).[56] In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with nonresectable CRC metastases (median, one lesion per patient; range, 1 to 8; median tumor size, 2.5 cm), OS at four years was 22% in the RFA group and 10% in the chemotherapy group (p=0.005). Median survival was estimated at 25 months in the RFA group and 17 months in the chemotherapy group (p not reported). Recurrence at a median follow-up of 21 months was 44% in the RFA group and 11% in the resection-only group (p<0.001), although the proportion

of patients with distant recurrence as a component of failure was similar (41% resection vs 40% RFA, p=*NS*).

In a second trial, a consecutive series of well-defined, previously untreated patients (n=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach.[57] Three groups were identified: those amenable to hepatic resection (n=117); those for whom resection plus local ablation were indicated (RFA, n=27; cryoablation, n=18); and those deemed unresectable and unsuitable for local ablation (n=39) who received systemic chemotherapy. Median OS was 61 months (95% CI 41 to 81 months) in resected patients (median, one tumor per patient; range, 1 to 9; median diameter, 3.8 cm), 31 months (95% CI 20 to 42 months) in locally ablated patients (median, four tumors per patient; range, 1-19; median diameter, 3 cm per lesion), and 26 months (95% CI 17 to 35 months) in the chemotherapy patients (median, four tumors per patient; range, 1 to 17; median diameter, 4 cm per lesion; p=*NS*, ablated vs chemotherapy). Results from two validated quality-of-life instruments (EuroQol-5D, EORTC QLQ C-30) showed that patients treated by local ablation returned to baseline values within three months, whereas those treated with chemotherapy remained significantly lower (ie, worse quality of life) than baseline over 12 months posttreatment ($p<0.05$).

In 2011, Van Tilborg reported long-term results in 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions).[58] Lesion size ranged from 0.2 to 8.3 cm (mean 2.4 cm). Mean follow-up time was 29 months (range, 6-93 months). Major complications (including abscess, hemorrhage, grounding pad burns, and diaphragm perforation) occurred in eight patients. Factors that determined the success of the procedure included lesion size and the number and location of the lesions. Local tumor site recurrence was 5.6% for tumors less than 3 cm, 19.5% for tumors 3 to 5 cm, and 41.2% for those greater than 5 cm. Centrally located lesions recurred more often than peripheral, at 21.4% versus 6.5%, respectively (p=0.009). Mean survival time from the time of RFA was 56 months (95% CI 45 to 67 months).

Neuroendocrine Cancer

Unlike the above liver tumors, the treatment benefit for RFA of neuroendocrine metastases in the liver is related to symptom control rather than survival or local recurrence. Therefore, patient selection and outcome measures in related studies focused on the level of symptoms rather than lesion size, number, and location. The primary treatment of symptomatic neuroendocrine tumor (NET) metastases is chemotherapy.

Systematic Reviews

Most reports of RFA treatment for neuroendocrine liver metastases include small numbers of patients or subsets of patients in reports of more than one ablative method or very small subsets of larger case series of patients with various diagnoses. A systematic review of RFA as treatment for unresectable metastases from neuroendocrine tumors was published in 2015.[59] Seven unique studies (total n=301 patients) included in the review, all were retrospective case series from a single institution. The most common tumor type was carcinoid (59%), followed by nonfunctional pancreatic tumors (21%) and functional pancreatic tumors (13%). There were two periprocedural deaths (rate, 0.7%), and the overall rate of complications was 10% (including hemorrhage, abscess, viscus perforation, bile leak, biliopleural fistula, transient liver insufficiency, pneumothorax, grounding pad burn, urinary retention, pneumonia, pleural effusion). Improvement in symptoms was reported in 92%

(117/127) of symptomatic patients, with a median duration of symptom relief ranging from 14 to 27 months. There was a high degree of variability in the length of follow-up and surveillance used for follow-up, and a wide range of local recurrence rates, from less than 5% to 50%. The reported five-year survival rates ranged from 57% to 80%.

Randomized Controlled Trials

No randomized controlled trials of RFA as a treatment for neuroendocrine metastases in the liver were identified.

Nonrandomized Studies

Fairweather (2017) compared OS in patients with neuroendocrine liver metastases (N=649) from a large prospective database.[60] Primary treatment modalities included: systemic therapy (n=316), chemoembolization (n=130), observation (n=117), surgical resection (n=58), and RFA (n=28). The most favorable 10-year OS estimates were achieved with surgical resection (70%), followed by RFA (55%), systemic therapy (31%), chemoembolization (28%), and observation (20%).

Berber (2008) analyzed a large series of liver tumors treated with RFA.[61] Of 1,032 tumors in the study, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range, 1 to 16) and mean lesion size was 2.3 cm (range, 0.5 to 10.0 cm). Local recurrence rates were lower in patients with neuroendocrine tumors than in patients with other tumor types: neuroendocrine tumors (19/295 [6%]), colorectal metastases (161/480 [24%]), non–colorectal, non–neuroendocrine metastases (28/126 [22%]), and HCC (23/131 [18%]). In patients with neuroendocrine tumors, 58% of the recurrences were evident at one year and 100% at two years versus 83% at one year and 97% at two years for colorectal metastases. Eight neuroendocrine tumors were eligible for repeat RFA; seven were retreated, and one was not. Symptom control and survival were not reported.

Mazzaglia reported on a series gathered over 10 years for 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA.[62] Tumor types were 36 carcinoid, 18 pancreatic islet cell, and nine medullary thyroid cancer. Indications for study enrollment were liver metastases from neuroendocrine tumors, enlarging liver lesions, worsening of symptoms, and/or failure to respond to other treatment modalities and predominance of disease in the liver; patients with additional minor extrahepatic disease were not excluded. RFA was performed 1.6 years (range, 0.1 to 7.8 years) after diagnosis of liver metastases. Fourteen patients had repeat sessions for disease progression. The mean number of lesions treated at the first RFA session was six and the mean tumor size was 2.3 cm. One week after surgery, 92% of patients had at least partial symptom relief and 70% had complete relief. Symptom control lasted 11 months. Median survival times were 11 years postdiagnosis of the primary tumor, 5.5 years postdiagnosis of the neuroendocrine hepatic metastases, and 3.9 years after the first RFA treatment.

Elias reported on 16 patients who underwent a one-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors.[63] A mean of 15 liver tumors per patient were surgically removed, and a mean of 12 were ablated using RFA. Three-year survival and DFS rates were similar to those observed in the authors' preliminary series of 47 patients who had hepatectomy with a median of seven liver tumors per patient. Venkatesan reported on six patients treated for pheochromocytoma metastases.[64]

Complete ablation was achieved in six of seven metastases. Mean follow-up was 12.3 months (range, 2.5 to 28 months).

RFA AS A PRIMARY TREATMENT OF UNRESECTABLE LIVER METASTASES OF OTHER ORIGIN

Breast Cancer

A number of case series have reported on use of RFA to treat breast cancer liver metastases. In 2014, Veltri analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).[65] Complete ablation was seen on initial follow-up in 90% of tumors, but tumor recurrence occurred in 19.7% within eight months. RFA did not impact OS, which at one year was 90% and at three years was 44%.

In a retrospective review, Meloni assessed local control and intermediate- and long-term survival in 52 patients.[66] Inclusion criteria were fewer than five tumors, maximum tumor diameter of 5 cm, and disease confined to the liver or stable with medical therapy. Complete tumor necrosis was achieved in 97% of tumors. Median time to follow-up from diagnosis of liver metastasis and from RFA was 37.2 and 19.1 months, respectively. Local tumor progression occurred in 25% of patients, and new intrahepatic metastases developed in 53%. Median OS, from the time of first liver metastasis diagnosis, was 42 months, and five-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had worse prognoses than those with smaller tumors. The authors concluded that these survival rates were comparable to those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, technical success (tumor ablation) was achieved in 107 (96%) metastases.[67] During follow-up, local tumor progression was observed in 15 metastases. Estimated median OS was 58.6 months. Survival was significantly lower among patients with extrahepatic disease, with the exception of skeletal metastases.

A series of 19 patients was reported by Lawes.[68] Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of the report, seven patients, with disease confined to the liver at presentation, were alive, as were six with extrahepatic disease; median follow-up after RFA was 15 months (range, 0 to 77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in three patients.

Sarcoma

Jones evaluated RFA in a series of patients with sarcoma.[69] Thirteen gastrointestinal stromal tumor (GIST) patients and 12 with other histologic subtypes received RFA for metastatic disease in the liver: 12 responded to the first RFA procedure and one achieved stable disease. Two GIST patients received RFA on two occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, seven underwent RFA to liver lesions, five of whom responded to RFA, one progressed, and one was not assessable at the time of analysis. RFA was well-tolerated in this series of sarcoma patients. RFA may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere. The authors advised conducting further larger studies to better define the role of this technique in this patient population.

A case series of 66 patients who underwent hepatic resection (n=35), resection and RFA (n=18), or RFA alone (n=13) was reported by Pawlik.[70] After a median follow-up of 35.8 months, 44 patients had recurrence (intrahepatic only, n=16; extrahepatic only, n=11; both,

n=17). The one-, three-, and five-year OS rates were 91.5%, 65.4%, and 27.1%, respectively. The authors recommended that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

RFA AS A TREATMENT OF UNRESECTABLE HCC TUMORS IN THE TRANSPLANT SETTING

The goal of RFA prior to transplantation is to maintain a patient's eligibility for liver transplant by either downsizing a large tumor or by preventing progression of a smaller tumor. The literature related to locoregional therapy for HCC in the transplant setting can be divided into three objectives:

- Prevention of tumor progression while on the waiting list
- Downgrading HCC prior to transplantation
- To reduce risk of post-transplantation tumor recurrence in patients with T3 tumors

Assessment of the effects of pre-transplantation RFA on these objectives would, ideally, include clinical trials that compare the recurrence-free survival of patients who received pretransplant locoregional therapies with those who did not and to study recurrence-free survival in patients who received locoregional therapies to downsize larger tumor(s) or to prevent progression of smaller tumor(s) in order to meet transplant waiting list criteria.

The current published evidence is limited to case series and retrospective reviews which are considered unreliable due to methodologic limitations such as lack of randomization and lack of a control group for comparison.[71-80] In addition to these limitations, current studies targeted only a subset of candidates for liver transplant to treat HCC. Because only patients with adequate liver reserves were offered treatment, it cannot be determined whether any reported increase in recurrence-free survival was related to the pretransplant locoregional therapy or liver reserve status. It is unknown whether patients with adequate liver reserves have improved outcomes regardless of pretransplant management.

United Network for Organ Sharing policy

The United Network for Organ Sharing (UNOS) recognizes pretransplant locoregional therapies including RFA as a component of patient management during the waiting period for a donor liver.[81] In allocating donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. For HCC, part of this balance included tumor size and number of nodules as follows:

T1: 1 nodule 1.9 cm or smaller
T2: 1 nodule between 2.0–5.0 cm, or 2 or 3 nodules each smaller than 3.0 cm
T3: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 cm

Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions were considered at high risk of post-transplant recurrence. Patients with T2 tumors were considered to have an increased risk of dying while on the waiting list compared with T1 lesions, and an acceptable risk of post-transplant tumor recurrence. Therefore, the UNOS criteria prioritized T2 HCC. In addition, patients could be removed from the waiting list if they were determined to be unsuitable for transplantation based on progression of HCC. Thus these criteria provide incentives to use locoregional therapies to maintain T2 classification.

The UNOS allocation system provides incentives to use locoregional therapies in two different settings:

To downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points; or to prevent progress of T2 tumors while on the waiting list to maintain the UNOS allocation points.

These two indications are discussed further here. It should be noted that the UNOS policy addresses the role of locoregional therapy in the pretransplant setting as follows:

> Organ Procurement and Transplant Network (OPTN) Class 5T (Treated) nodules are defined as any OPTN Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone loco-regional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:
>
> - Past loco-regional treatment for HCC (OPTN class 5 lesion or biopsy proven prior to ablation).
> - Evidence of persistent/recurrent HCC such as nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.

OPTN guidelines also indicate “candidates whose tumors have been ablated after previously meeting the criteria for additional MELD/PELD points (OPTN Class 5T) will continue to receive additional MELD/PELD points (equivalent to a 10-percentage point increase in candidate mortality) every 3 months without RRB review, even if the estimated size of residual viable tumor falls below stage T2 criteria.”

Candidates with HCC not meeting transplant criteria, “including those with downsized tumors whose original or presenting tumor was greater than a stage T2, must be referred to the applicable RRB [Regional Review Board] for prospective review in order to receive additional priority.”[81]

ADVERSE EVENTS

Complication rates for RFA of liver tumors are reported in approximately 7% of patients, as compared with that of open liver resection which may be as high as 22%.[82]

Specific complications reported in the literature to date include the following:[58, 61, 82-85]

1. Hemorrhage
2. Liver Abscess
3. Liver infarction
4. Liver failure
5. Cutaneous burn
6. Diaphragm perforation
7. Bowel perforation
8. Seeding of the needle tract with cancer cells
9. Hydrothorax or hemothorax requiring drainage
10. Bile duct injury
11. Death

MWA AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

Systematic Reviews

Dou (2022) conducted a systematic review and meta-analysis that compared the safety and efficacy of MWA compared to RFA in patients with HCC.[86] The analysis included 28 cohort studies and 5 RCTs. Overall, there was no significant difference in disease-free survival, OS, or major complications between the two groups. In the cohort studies, MWA had a lower local tumor progression rate than RFA (OR, 0.78; 95% CI, 0.64 to 0.96; p=.02). The authors concluded that there were various differences in the included studies (e.g., equipment used, operator experience) and that more high-quality RCTs are needed to draw a definitive conclusion on MWA and RFA in this patient population.

Glassberg (2019) conducted a systematic review of MWA compared to resection in patients with HCC or metastatic liver cancer. One RCT (Xu 2015)[87] was included; the other studies (n=15) were observational (2 prospective, 13 retrospective).[88] Patients who received MWA had significantly higher risk of LTR compared to those who received resection (RR=3.04; p<0.001). At one year, overall survival did not differ between MWA and resection, but three- and five-year overall survival was significantly higher in patients who had received resection. Overall complications and major complications were lower with MWA compared to resection. Additionally, operative time, intraoperative blood loss, and hospital length of stay were significantly lower with MWA. Some studies included patients that were nonresectable in the MWA treatment arm, but due to limited reporting and patient preference affecting which treatment was performed, the reviewers were not able to calculate the number of patients who were nonresectable or to conduct subgroup analyses by resectable vs unresectable tumors. Microwave ablation was typically selected for patients with smaller and/or deeper tumors, more comorbidities, and a preference for a less invasive procedure. The reviewers concluded that MWA can be an effective and safe alternative to HR in patients or tumors that are not amenable to resection, but more studies are needed to determine the target population that would benefit most from MWA.

In 2017, Zhang reported results from a systematic review and meta-analysis comparing hepatic resection with microwave ablation as a treatment of hepatocellular carcinoma.[89] Nine studies with follow-up time of three years or greater were included overall, totalling 1,480 participants. For overall survival (seven reports), studies were not found to have statistical bias, and overall heterogeneity amongst studies was not significant (I^2 =0.0%, p=0.749), however, heterogeneity amongst studies included for meta-analysis of disease-free survival (five reports) was significant (I^2 =71.1%, p=0.008). No difference was found comparing MWA to resection for OS and DFS (HR =0.98, 95% CI 0.76 to 1.26, p=0.878, and HR =1.16, 95% CI 0.79 to 1.71, p=0.442, respectively). Meta-analysis demonstrated that MWA was associated with shorter operation time (standardized mean difference [SMD] −1.37, 95% CI −1.92 to −0.81, p=0.000), less amount of blood loss in operation (SWD −1.19, 95% CI −1.76 to −0.61, p=0.000), and less complications (OR 0.22, 95% CI 0.12 to 0.40, p=0.000) than resection. The authors concluded that MWA may be superior given there were no differences identified in OS and DFS, but demonstrated fewer complications and improved intraoperative outcomes.

In 2011, Bertot conducted a systematic review evaluating mortality and complication rates of ablation techniques for primary and secondary liver tumors.[90] This review included two studies using MWA totaling 1,185 patients.[91, 92] The pooled mortality rate for MWA was 0.23% (95%

CI 0.0 to 0.58%). Major complication rates were 4.6% for MWA (calculated by using a random effects model since there was significant heterogeneity). The authors concluded that percutaneous ablation techniques, including MWA, are safe and have acceptable complication rates for the treatment of liver tumors.

In 2009, Ong conducted a systematic review of studies on MWA for primary and secondary liver tumors.[93] Based on the results from 25 clinical studies, the authors concluded that MWA was an effective and safe technique for liver tumor ablation with low complication rates and survival rates comparable to hepatic resection. However, rates of local recurrence after MWA were noted to be higher than hepatic resection. In most studies of MWA, hepatocellular carcinoma recurrence rates were approximately 10% but were also noted to be as high as 50%, which the authors indicated could be addressed with further ablation. Survival rates in the studies on MWA for hepatocellular carcinoma were as high as 92% at three years and 72% at five years, which was noted to be comparable to radiofrequency ablation (RFA) and percutaneous ethanol injections. Pain and fever were the most frequently reported complications, but complications increased when there were more tumors, larger tumors, and more microwave antennas used. The authors concluded that MWA may be a promising option for the treatment of HCC tumors but should be reserved for patients not amenable to hepatic resection. The authors also noted further randomized clinical trials are warranted to compare MWA to other ablation procedures.

Randomized Controlled Trials

Zaitoun (2021) compared the safety and efficacy of combination therapy with TACE and MWA (n=89) compared to TACE (n=84) or MWA (n=92) only in patients with solitary HCC lesions measuring between 3 to 5 cm.[94] TACE was performed first, followed by MWA after 15 days. Mean tumor size was 3.6 cm, 3.9 cm, and 3.7 cm in the TACE, MWA, and combination groups, respectively (p=0.053). Complete response at one month was achieved by 86.5% of patients who received combination therapy compared with 54.8% of patients treated with TACE and 56.5% of patients treated with MWA. Patients treated with combination therapy had a significantly lower recurrence rate at 12 months (p=0.0001) and a significantly higher OS rate at three years (69.6%; p=0.02). Post-procedural minor adverse events (e.g., nausea, vomiting, abdominal pain, and low-grade fever) were reported in 24.7%, 47.6%, and 38% of patients in the combined, TACE, and MWA groups, respectively. Severe hepatic dysfunction was observed in one patient in the combined group and three patients in the TACE group. Tumor seeding was reported in two patients in the MWA group. A decrease in alpha-fetoprotein (AFP) concentration was observed in 75%, 63%, and 48% of patients who underwent combined therapy, MWA, or TACE, respectively.

Chong (2020) conducted an RCT comparing MWA to RFA in 93 patients with HCC (up to 3 lesions of 5 cm or smaller).[95] Mean tumor size was 3.1 cm in the MWA group and 2.8 cm in the RFA group. The primary outcome of this study was the rate of complete ablation at one month, which did not differ significantly for MWA (95.7%) versus RFA (97.8%; p>0.99). Rates of OS up to five years and rates of disease-free survival up to three years were similar between groups. However, the sample size calculations were based on rates of complete ablation at one month, so the study may not have been adequately powered to detect differences in OS or disease-free survival.

Fang (2019) randomized hepatic carcinoma patients to receive conventional surgical excision (n=47) or ultrasound-guided microwave ablation (n=47).[96] Statistically significant differences

(p<0.05) between groups were reported for duration of operation (shorter for MWA), quantities of intraoperative bleeding and blood transfusions (lower for surgical excision), effective rate of treatment (higher for MWA), occurrence rate of complications (lower for MWA). In addition significantly higher albumin and total bilirubin and lower alanine aminotransferase and aspartate transaminase were reported for the MWA group (p<0.05).

Older RCTs are included in the SRs above.

Nonrandomized Studies

In addition to the studies noted above, a number of nonrandomized studies have been published on the use of MWA in patients with hepatocellular carcinoma. Several examples are cited, below. The results of these studies should be interpreted with caution due to the following limitations:

- Results from small sample sizes (n<100), limit the ability to rule out the role of chance as an explanation of study findings.[97-104]
- Results from studies with short-term follow-up (<one year) are not adequate to determine the durability of the treatment effect.[97, 105, 106]
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.[91, 92, 103-112]

Given the limitations noted above, nonrandomized studies do not provide reliable data to demonstrate the efficacy of MWA treatment in patients with HCC.

MWA AS A TREATMENT OF HEPATIC METASTASIS

Systematic Reviews

Mimmo (2022) conducted a systematic review of MWA for colorectal liver metastases.[113] Twelve studies (N=741) were included, and 395 patients were treated with MWA versus conventional surgical procedure (n=346). The mean follow-up duration was 20.5 months. Pooled data analysis showed mean recurrence free rates for MWA at one, three, and five years were 65.1%, 44.6%, and 34.3%, respectively. Mean OS rates for MWA at one, three, and five years were 86.7%, 59.6%, and 44.8%, respectively. Mean local recurrence rates for MWA at 3, 6, and 12 months were 96.3%, 89.6%, and 83.7%, respectively.

A 2014 Health Technology Assessment[50] and a 2013 Cochrane review[114] also identified only one RCT on ablation for liver metastasis, Shibata.[115] The reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection.

In 2013, Vogl reviewed evidence regarding RFA, laser-induced thermotherapy (LITT) and MWA treatment of breast cancer liver metastasis.[116] Local tumor response, progression and survival rates were evaluated. Authors reported positive response rates of 63 % to 97 % in RF-ablated lesions, 98.2 % in LITT-treated lesions and 34.5-62.5 % in MWA lesions. Median survival was 10.9-60 months with RFA, 51-54 months with LITT and 41.8 months with MWA. Five-year survival rates were 27-30 %, 35 % and 29 %, respectively. Local tumour progression ranged from 13.5 % to 58 % using RFA, 2.9 % with LITT and 9.6 % with MWA. The authors called for additional, large RCTs to further explore the benefits of ablation therapies.

In the Ong review described above[93], local recurrence rates for liver metastases after treatment with MWA averaged approximately 15% but varied between 0 and 50% in the seven studies reviewed that addressed liver metastases. As noted above, Ong concluded MWA may be a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection.

In 2011, Pathak also conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA, totaling 406 patients with a minimum of 1-year follow-up.[117] Mean survival rates were 73%, 30% and 16% and ranged from 40–91.4%, 0–57% and 14–32% at one-, three-, and five-years' follow-up, all respectively. Minor and major complication rates were considered acceptable and ranged from 6.7–90.5% and 0–19%, respectively. Local recurrence rates ranged from 2-14%. The authors acknowledged limitations in the available studies but concluded survival rates for MWA are more favorable than for palliative chemotherapy alone.

Randomized Controlled Trials

Only one RCT comparing the use of MWA for hepatic metastases to the gold standard of surgical resection was identified. In 2000, Shibata reported on a trial of 30 patients with hepatic metastases from colorectal cancer randomly assigned without stratification to treatment with either MWA after laparotomy (n=14) or hepatectomy (n=16).[115] The study began with 40 patients, but 10 patients were excluded because the researchers discovered intraoperatively that these patients did not meet study criteria due to having extensive metastasis or equal to or greater than 10 tumors. The treatment groups of MWA vs. hepatectomy were not significantly different in age (mean age 61 in both groups) number of tumors (mean 4.1 vs. 3.0, respectively) or tumor size (mean 27 mm vs. 34 mm, respectively). The authors reported no significant differences in survival rates following MWA or hepatectomy (27 months vs. 25 months, respectively) and mean disease-free survival (11.3 vs. 13.3 months, respectively). However, intraoperative blood loss was significantly lower and no blood transfusions were required in the MWA group whereas six patients in the hepatectomy group required blood transfusions. Complications in the microwave group consisted of one hepatic abscess and one bile duct fistula. In the hepatectomy group, complications were one intestinal obstruction, one bile duct fistula and one wound infection.

Nonrandomized Studies

Several nonrandomized trials regarding MWA treatment in patients with liver metastases were identified; however, these studies were limited by a lack of comparison group,[118-120] short-term follow-up[118, 119] and small sample size.[118, 120].

CRYOSURGICAL ABLATION

CRYOSURGICAL ABLATION AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

The evidence regarding cryoablation as a treatment for hepatocellular carcinoma (HCC) remains controversial. However, use of cryotherapy for HCC became a standard of care and published research increased through the late 1990's and early 2000's. Awad published a systematic Cochrane Review in 2009, noting that the literature consisted of two prospective cohort studies and two retrospective cohort studies.[121] Overall, the Review concluded that the evidence is not sufficient to evaluate potential harms and benefits; large well-designed

randomized clinical trials (RCTs) are feasible and necessary to define the role of cryotherapy in the treatment of HCC.

A 2023 meta-analysis by Kim compared the benefits and harms of locoregional treatments for HCC in patients who had early HCCs of <4 cm with no extrahepatic spread of portal invasion [122]. While this study included 19 trials, the only cryoablation study included was the one included below by Wang (2015). Overall, cryoablation had similar overall survival, progression-free survival, and local progression-free survival scores as radiofrequency ablation. Further research is needed with additional participants to examine the effect of cryoablation on patient health outcomes compared to standard care.

Since the 2009 Cochrane Systematic Review, Wang (2015) reported results from one RCT comparing the safety and efficacy of cryotherapy vs RFA.[1] One hundred eighty participants were randomized to each group, with no significant differences found at baseline between the arms, with the exception of number of tumors – 10.56% of the cryo group participants had two tumors at enrollment, compared to 5% in the RFA group. Participants were followed for five years, and there were no differences in local recurrence, new recurrence, overall survival, or tumor-free survival. At the end of follow-up, 52 patients (28.9%) in the CRYO group and 55 patients (30.6%) in the RFA group died. The causes of death included HCC progression in 44 (24.4%), hepatic failure in five (2.8%), and variceal bleeding in three (1.7%) in the CRYO group, and HCC progression in 47 (26.1%), hepatic failure in four (2.2%), variceal bleeding in two (1.1%), and refractory ascites-induced renal failure in two (1.1%) in the RFA group. Overall, the authors concluded that patients with Child-Pugh class A-B cirrhosis and HCC lesions less than or equal to 4cm and no more than two lesions in total, percutaneous cryoablation and RFA are equally safe and effective ablation treatments. For HCC 3.1 to 4.0 cm, cryoablation was associated with a lower rate of local tumor progression than RFA.

CRYOSURGICAL ABLATION AS A TREATMENT OF LIVER METASTASES

A 2019 Cochrane SR was published by Bala evaluation the use of cryotherapy for the treatment of liver metastases.[123] The selection criteria included RCTs assessing effects of cryotherapy and its comparators for liver metastases. One RCT was identified. It compared cryotherapy with conventional surgery for patients with liver metastases from the following primary sites: colon and rectum (66.6%), stomach (7.3%), breast (6.5%), skin (4.9%), ovaries (4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The SR authors were not able to calculate the risk of bias of the randomization process, allocation concealment, presence of blinding, incomplete outcome data, or selective outcome reporting bias due to insufficient reporting by the RCT authors. Follow-up was five months to 10 years. The trial reported mortality at 10 years (81% vs. 92% for cryotherapy vs. conventional therapy) and the SR authors calculated the relative risk (RR=0.88, 95% CI 0.77 to 1.02). The evidence regarding mortality was rated as low-certainty. The SR authors also calculated chance of recurrence in the liver, which was 86% in the cryotherapy group and 95% in the conventional surgery group (RR 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). The SR authors concluded that the evidence is limited and they cannot determine whether cryotherapy is beneficial or harmful compared to conventional surgery.

PERCUTANEOUS ETHANOL INJECTION

Like RFA, percutaneous ethanol injection (PEI) is most often considered a treatment option for patients with small HCC lesions who are not resection candidates. RFA and PEI are the most commonly performed ablation therapies.

Weis (2015) published a Cochrane Systematic Review that evaluated the harms and benefits of percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI) in adults with early HCC defined by Milam criteria, i.e., one cancer nodule up to 5 cm in diameter or up to three cancer nodules up to 3 cm in diameter compared with no intervention, sham intervention, each other, other percutaneous interventions, or surgery.[124] One randomized trial compared PEI versus surgery; we included 76 participants in the analyses. There was no significant difference in the overall survival (HR 1.57; 95% CI 0.53 to 4.61) and recurrence-free survival (HR 1.35; 95% CI 0.69 to 2.63). No serious adverse events were reported in the PEI group while three postoperative deaths occurred in the surgery group. Given the data on PEI were available for only one RCT, the authors concluded there is insufficient evidence to determine whether PEI versus surgery was more effective for early HCC.

In a number of RCT's, the safety and efficacy of RFA and PEI have been investigated in the treatment of Child-Pugh class A patients with early stage HCC tumors.[125-131] Complication rates were relatively low for both methods.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines for hepatocellular carcinoma cancers (v.2.2023) recommend ablation be considered in patients who are not candidates for transplant, surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies (category 2A).[132] In addition, they state that "ablation alone may be curative in treating tumors ≤ 3 cm. In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as the tumor is accessible for ablation. Unresectable/inoperable lesions greater than 5 cm should be considered for treatment using arterially directed therapy, systemic therapy, or RT. (category 2A).

The NCCN guidelines for rectal (v.6.2023) and colon (v.2.2022) cancer metastatic to the liver state that "Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection."[133, 134] (category 2A).

The NCCN guidelines for neuroendocrine and adrenal tumors (v.1.2023) recommend ablation be considered as a primary therapy in locally advanced/metastatic disease. The recommendations state that "percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to 4 lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement [category 2B]."[135]

AMERICAN COLLEGE OF RADIOLOGY (ACR)

The 2014 ACR Appropriateness Criteria® for metastatic rectal cancer states that RFA "yields excellent local control of small (<3 cm) CRC liver metastases."[136]

The 2011 ACR Appropriateness Criteria® considered RFA by percutaneous, open, or laparoscopic methods effective for treatment of small (≤5 cm) HCC tumors.[137] While ablative

therapy is most effective for these small HCCs, moderate success has also been described with tumors ≤7 cm. With larger tumor number and/or size, “the operator may want to focus on arterial-based therapies and adjuvant or neoadjuvant therapy.” The 2016 guidelines were consistent with the previous recommendations.[138]

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

The American Association for the Study of Liver Diseases (2018) published a guideline on the treatment of hepatocellular carcinoma.[139] For adults with Child-Pugh class cirrhosis and resectable T1 or T2 hepatocellular carcinoma (HCC), the guideline suggests using resection over radiofrequency ablation (RFA; moderate quality/certainty of evidence; conditional strength of recommendation). Technical remarks in the guideline note that "Stage T1 and T2 HCC include a wide range of tumor sizes from <1 cm to 5 cm, and the effectiveness of available therapies depend in large part on the size, number, and location of the tumors. Whereas smaller, single tumors (<2.5 cm) that are favorably located may be equally well treated by either resection or ablation, tumors larger than 2.5-3 cm, multifocal, or near major vascular or biliary structures may have limited ablative options." Additionally, the guideline highlighted that "randomized trials performed to date comparing RFA to resection have been performed primarily in East Asian patients, in whom there is a higher etiologic prevalence of HBV [hepatitis B virus] (including noncirrhotic HBV–associated HCC) and a lower prevalence of other liver diseases such as NAFLD [non-alcoholic fatty liver disease] or HCV [hepatitis C virus] compared with Western patients. The impact of these demographic differences on oncologic outcomes of different therapies is unknown."

SUMMARY

For primary tumors of the liver, and hepatic metastases from colorectal tumors or neuroendocrine tumors, there is limited research regarding locoregional ablative therapies; however, treatment options are limited in this population. Clinical practice guidelines based on research recommend ablative therapies in carefully selected patients. Therefore, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation may be considered medically necessary when policy criteria are met.

Due to a lack of research and clinical practice guidelines, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered investigational when the policy criteria are not met.

REFERENCES

1. Wang C, Wang H, Yang W, et al. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology.* 2015;61(5):1579-90. PMID: 25284802
2. Lu DE, Cheng SW, Lin YS, et al. Combination of radiofrequency ablation and percutaneous ethanol injection versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis. *Ann Hepatol.* 2022;27(5):100729. PMID: 35700935

3. Yu Q, Liu C, Navuluri R, et al. Percutaneous microwave ablation versus radiofrequency ablation of hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *Abdom Radiol (NY).* 2021;46(9):4467-75. PMID: 33870454
4. Gupta P, Maralakunte M, Kumar MP, et al. Overall survival and local recurrence following RFA, MWA, and cryoablation of very early and early HCC: a systematic review and Bayesian network meta-analysis. *Eur Radiol.* 2021;31(7):5400-08. PMID: 33439319
5. Shin SW, Ahn KS, Kim SW, et al. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. *Ann Surg.* 2021;273(4):656-66. PMID: 33074898
6. Cui R, Yu J, Kuang M, et al. Microwave ablation versus other interventions for hepatocellular carcinoma: A systematic review and meta-analysis. *Journal of cancer research and therapeutics.* 2020;16(2):379-86. PMID: 32474527
7. Gui CH, Baey S, D'Cruz R T, et al. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. *Eur J Surg Oncol.* 2020;46(5):763-71. PMID: 31937433
8. Han J, Fan YC, Wang K. Radiofrequency ablation versus microwave ablation for early stage hepatocellular carcinoma: A PRISMA-compliant systematic review and meta-analysis. *Medicine.* 2020;99(43):e22703. PMID: 33120763
9. Xiang J, Liu M, Lu R, et al. Magnetic resonance-guided ablation of liver tumors: A systematic review and pooled analysis. *Journal of cancer research and therapeutics.* 2020;16(5):1093-99. PMID: 33004753
10. Glassberg MB, Ghosh S, Clymer JW, et al. Microwave ablation compared with radiofrequency ablation for treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis. *OncoTargets and therapy.* 2019;12:6407-38. PMID: 31496742
11. Di Martino M, Rompianesi G, Mora-Guzmán I, et al. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2019:S0748-7983(19)31496-9. PMID: 31862133
12. Meijerink MR, Puijk RS, van Tilborg A, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. *Cardiovasc Intervent Radiol.* 2018;41(8):1189-204. PMID: 29666906
13. Majumdar A, Roccarina D, Thorburn D, et al. Management of people with early- or very early-stage hepatocellular carcinoma: an attempted network meta-analysis. *The Cochrane database of systematic reviews.* 2017;3:Cd011650. PMID: 28351116
14. Lan T, Chang L, Mn R, et al. Comparative Efficacy of Interventional Therapies for Early-stage Hepatocellular Carcinoma: A PRISMA-compliant Systematic Review and Network Meta-analysis. *Medicine.* 2016;95(15):e3185. PMID: 27082558
15. Facciorusso A, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2016;32(3):339-44. PMID: 26794414
16. Weis S, Franke A, Mossner J, et al. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. *The Cochrane database of systematic reviews.* 2013;12:CD003046. PMID: 24357457

17. Feng Q, Chi Y, Liu Y, et al. Efficacy and safety of percutaneous radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis of 23 studies. *Journal of cancer research and clinical oncology.* 2015;141(1):1-9. PMID: 24889505
18. Wang Y, Luo Q, Li Y, et al. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. *PLoS One.* 2014;9:e84484. PMID: 24404166
19. Qi X, Tang Y, An D, et al. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *Journal of clinical gastroenterology.* 2014;48(5):450-7. PMID: 24172183
20. Duan C, Liu M, Zhang Z, et al. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. *World J Surg Oncol.* 2013;11:190. PMID: 23941614
21. Jia Z, Zhang H, Li N. Evaluation of clinical outcomes of radiofrequency ablation and surgical resection for hepatocellular carcinoma conforming to the Milan criteria: A systematic review and meta-analysis of recent randomized controlled trials. *Journal of gastroenterology and hepatology.* 2021;36(7):1769-77. PMID: 33569810
22. Pan YX, Fu YZ, Hu DD, et al. Stereotactic Body Radiotherapy vs. Radiofrequency Ablation in the Treatment of Hepatocellular Carcinoma: A Meta-Analysis. *Front Oncol.* 2020;10:1639. PMID: 33194569
23. Jin S, Tan S, Peng W, et al. Radiofrequency ablation versus laparoscopic hepatectomy for treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *World journal of surgical oncology.* 2020;18(1):199-99. PMID: 32787883
24. Li X, Wu Y-S, Chen D, et al. Laparoscopic hepatectomy versus radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. *Cancer Manag Res.* 2019;11:5711-24. PMID: 31417314
25. Si M-B, Yan P-J, Hao X-Y, et al. Efficacy and safety of radiofrequency ablation versus minimally invasive liver surgery for small hepatocellular carcinoma: a systematic review and meta-analysis. *Surgical endoscopy.* 2019;33(8):2419-29. PMID: 30989373
26. Tan H-Y, Gong J-F, Yu F, et al. Long-Term Efficacy of Laparoscopic Radiofrequency Ablation in Early Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. *J Laparoendosc Adv Surg Tech A.* 2019;29(6):770-79. PMID: 30801203
27. Xu G, Qi FZ, Zhang JH, et al. Meta-analysis of surgical resection and radiofrequency ablation for early hepatocellular carcinoma. *World J Surg Oncol.* 2012;10:163. PMID: 22897815
28. Bouza C, Lopez-Cuadrado T, Alcazar R, et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol.* 2009;9:31. PMID: 19432967
29. Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *The Cochrane database of systematic reviews.* 2004(2):CD003046. PMID: 15106188
30. Hsieh CB, Chang HM, Chen TW, et al. Comparison of transcatheter arterial chemoembolization, laparoscopic radiofrequency ablation, and conservative treatment for decompensated cirrhotic patients with hepatocellular carcinoma. *World J Gastroenterol.* 2004;10(4):505-8. PMID: 14966906
31. Iezzi R, Pompili M, La Torre MF, et al. Radiofrequency ablation plus drug-eluting beads transcatheter arterial chemoembolization for the treatment of single large hepatocellular carcinoma. *Digestive and liver disease : official journal of the Italian Society of*

Gastroenterology and the Italian Association for the Study of the Liver. 2015;47(3):242-8. PMID: 25577299
32. Morimoto M, Numata K, Sugimori K, et al. Successful initial ablation therapy contributes to survival in patients with hepatocellular carcinoma. *World J Gastroenterol.* 2007;13(7):1003-9. PMID: 17373733
33. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg.* 2005;242(2):158-71. PMID: 16041205
34. Park MJ, Kim TH, Lee KM, et al. Radiofrequency Ablation of Metastatic Liver Masses: Recurrence Patterns and Prognostic Factors based on Radiologic Features. *Hepato-gastroenterology.* 2012;60(123). PMID: 23108077
35. Fu Y, Yang W, Wu W, et al. Radiofrequency ablation in the management of unresectable intrahepatic cholangiocarcinoma. *J Vasc Interv Radiol.* 2012;23:642-9. PMID: 22525022
36. Giorgio A, Calisti G, G DES, et al. Radiofrequency ablation for intrahepatic cholangiocarcinoma: retrospective analysis of a single centre experience. *Anticancer research.* 2011;31:4575-80. PMID: 22199333
37. Kim JH, Won HJ, Shin YM, et al. Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. *AJR Am J Roentgenol.* 2011;196:W205-9. PMID: 21257864
38. Carrafiello G, Lagana D, Cotta E, et al. Radiofrequency ablation of intrahepatic cholangiocarcinoma: preliminary experience. *Cardiovasc Intervent Radiol.* 2010;33(4):835-9. PMID: 20411389
39. Kamphues C, Seehofer D, Eisele RM, et al. Recurrent intrahepatic cholangiocarcinoma: single-center experience using repeated hepatectomy and radiofrequency ablation. *Journal of hepato-biliary-pancreatic sciences.* 2010;17(4):509-15. PMID: 20714840
40. Chiou YY, Hwang JI, Chou YH, et al. Percutaneous ultrasound-guided radiofrequency ablation of intrahepatic cholangiocarcinoma. *Kaohsiung J Med Sci.* 2005;21:304-9. PMID: 16089307
41. Xu HX, Wang Y, Lu MD, et al. Percutaneous ultrasound-guided thermal ablation for intrahepatic cholangiocarcinoma. *Br J Radiol.* 2012;85:1078-84. PMID: 22374282
42. Haidu M, Dobrozemsky G, Schullian P, et al. Stereotactic radiofrequency ablation of unresectable intrahepatic cholangiocarcinomas: a retrospective study. *Cardiovasc Intervent Radiol.* 2012;35(5):1074-82. PMID: 22006031
43. Butros SR, Shenoy-Bhangle A, Mueller PR, et al. Radiofrequency ablation of intrahepatic cholangiocarcinoma: feasability, local tumor control, and long-term outcome. *Clinical imaging.* 2014;38(4):490-4. PMID: 24637151
44. Kemeny N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park).* 2006;20(10):1161-76, 79; discussion 79-80, 85-6. PMID: 17024869
45. McKay A, Dixon E, Taylor M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. *The British journal of surgery.* 2006;93(10):1192-201. PMID: 16983740
46. Lencioni R, Crocetti L, Cioni D, et al. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. *Invest Radiol.* 2004;39(11):689-97. PMID: 15486530
47. Hao W, Binbin J, Wei Y, et al. Can Radiofrequency Ablation Replace Liver Resection for Solitary Colorectal Liver Metastasis? A Systemic Review and Meta-Analysis. *Front Oncol.* 2020;10:561669. PMID: 33312946

48. van Amerongen MJ, Jenniskens SFM, van den Boezem PB, et al. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2017;19(9):749-56. PMID: 28687147
49. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. *The Cochrane database of systematic reviews.* 2012;6:CD006317. PMID: 22696357
50. Loveman E, Jones J, Clegg AJ, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. *Health Technol Assess.* 2014;18(7):vii-viii, 1-283. PMID: 24484609
51. Weng M, Zhang Y, Zhou D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. *PLoS One.* 2012;7(9):e45493. PMID: 23029051
52. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Annals of oncology : official journal of the European Society for Medical Oncology.* 2012;23(10):2619-26. PMID: 22431703
53. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *Journal of the National Cancer Institute.* 2017;109(9). PMID: 28376151
54. Tago T, Katsumata K, Udou R, et al. Significance of Radiofrequency Ablation for Unresectable Colorectal Cancer With Liver Metastases. *Anticancer research.* 2021;41(11):5539-47. PMID: 34732424
55. Hof J, Wertenbroek MW, Peeters PM, et al. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. *The British journal of surgery.* 2016;103(8):1055-62. PMID: 27193207
56. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg.* 2004;239(6):818-25; discussion 25-7. PMID: 15166961
57. Ruers TJ, Joosten JJ, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol.* 2007;14(3):1161-9. PMID: 17195903
58. Van Tilborg AA, Meijerink MR, Sietses C, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. *Br J Radiol.* 2011;84(1002):556-65. PMID: 21159807
59. Mohan H, Nicholson P, Winter DC, et al. Radiofrequency Ablation for Neuroendocrine Liver Metastases: A Systematic Review. *J Vasc Interv Radiol.* 2015;26(7):935-42 e1. PMID: 25840836
60. Fairweather M, Swanson R, Wang J, et al. Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database. *Ann Surg Oncol.* 2017;24(8):2319-25. PMID: 28303430
61. Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol.* 2008;15(10):2757-64. PMID: 18618182
62. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery.* 2007;142(1):10-9. PMID: 17629995

63. Elias D, Goere D, Leroux G, et al. Combined liver surgery and RFA for patients with gastroenteropancreatic endocrine tumors presenting with more than 15 metastases to the liver. *Eur J Surg Oncol.* 2009;35(10):1092-7. PMID: 19464140
64. Venkatesan AM, Locklin J, Lai EW, et al. Radiofrequency ablation of metastatic pheochromocytoma. *J Vasc Interv Radiol.* 2009;20(11):1483-90. PMID: 19875067
65. Veltri A, Gazzera C, Barrera M, et al. Radiofrequency thermal ablation (RFA) of hepatic metastases (METS) from breast cancer (BC): an adjunctive tool in the multimodal treatment of advanced disease. *La Radiologia medica.* 2014;119(5):327-33. PMID: 24297589
66. Meloni MF, Andreano A, Laeseke PF, et al. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. *Radiology.* 2009;253(3):861-9. PMID: 19709994
67. Jakobs TF, Hoffmann RT, Schrader A, et al. CT-guided radiofrequency ablation in patients with hepatic metastases from breast cancer. *Cardiovasc Intervent Radiol.* 2009;32(1):38-46. PMID: 18575933
68. Lawes D, Chopada A, Gillams A, et al. Radiofrequency ablation (RFA) as a cytoreductive strategy for hepatic metastasis from breast cancer. *Annals of the Royal College of Surgeons of England.* 2006;88(7):639-42. PMID: 17132311
69. Jones RL, McCall J, Adam A, et al. Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur J Surg Oncol.* 2010;36(5):477-82. PMID: 20060679
70. Pawlik TM, Vauthey JN, Abdalla EK, et al. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg.* 2006;141(6):537-43; discussion 43-4. PMID: 16785353
71. Heckman JT, Devera MB, Marsh JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol.* 2008;15(11):3169-77. PMID: 18696158
72. Fisher RA, Maluf D, Cotterell AH, et al. Non-resective ablation therapy for hepatocellular carcinoma: effectiveness measured by intention-to-treat and dropout from liver transplant waiting list. *Clin Transplant.* 2004;18(5):502-12. PMID: 15344951
73. Yamashiki N, Tateishi R, Yoshida H, et al. Ablation therapy in containing extension of hepatocellular carcinoma: a simulative analysis of dropout from the waiting list for liver transplantation. *Liver Transpl.* 2005;11(5):508-14. PMID: 15838878
74. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg.* 2004;240(5):900-9. PMID: 15492574
75. Lu DS, Yu NC, Raman SS, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology.* 2005;41(5):1130-7. PMID: 15841454
76. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl.* 2005;11(12):1505-14. PMID: 16315294
77. Sauer P, Kraus TW, Schemmer P, et al. Liver transplantation for hepatocellular carcinoma: is there evidence for expanding the selection criteria? *Transplantation.* 2005;80(1 Suppl):S105-8. PMID: 16286885
78. Merli M, Nicolini G, Gentili F, et al. Predictive factors of outcome after liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Transplant Proc.* 2005;37(6):2535-40. PMID: 16182736

79. Yao FY, Kinkhabwala M, LaBerge JM, et al. The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. *Am J Transplant.* 2005;5(4 Pt 1):795-804. PMID: 15760404
80. Lee MW, Raman SS, Asvadi NH, et al. Radiofrequency ablation of hepatocellular carcinoma as bridge therapy to liver transplantation: A 10-year intention-to-treat analysis. *Hepatology.* 2017;65(6):1979-90. PMID: 28170115
81. Organ Procurement and Transplantation Network (OPTN). Policies. Policy 9: Allocation of LIvers and Liver-Intestines. Updated 12/6/2020. [cited 1/16/2024]. 'Available from:' https://optn.transplant.hrsa.gov/governance/policies/.
82. Gervais DA, Goldberg SN, Brown DB, et al. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. *J Vasc Interv Radiol.* 2009;20(1):3-8. PMID: 18948025
83. Kong WT, Zhang WW, Qiu YD, et al. Major complications after radiofrequency ablation for liver tumors: analysis of 255 patients. *World J Gastroenterol.* 2009;15(21):2651-6. PMID: 19496197
84. Snoeren N, Jansen MC, Rijken AM, et al. Assessment of viable tumour tissue attached to needle applicators after local ablation of liver tumours. *Dig Surg.* 2009;26(1):56-62. PMID: 19169031
85. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(3):493-508. PMID: 19841322
86. Dou Z, Lu F, Ren L, et al. Efficacy and safety of microwave ablation and radiofrequency ablation in the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. *Medicine.* 2022;101(30):e29321. PMID: 35905207
87. Xu J, Zhao Y. Comparison of percutaneous microwave ablation and laparoscopic resection in the prognosis of liver cancer. *Int J Clin Exp Pathol.* 2015;8(9):11665-69. PMID: 26617907
88. Glassberg MB, Ghosh S, Clymer JW, et al. Microwave ablation compared with hepatic resection for the treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis. *World journal of surgical oncology.* 2019;17(1):98-98. PMID: 31182102
89. Zhang M, Ma H, Zhang J, et al. Comparison of microwave ablation and hepatic resection for hepatocellular carcinoma: a meta-analysis. *OncoTargets and therapy.* 2017;10:4829-39. PMID: 29042794
90. Bertot LC, Sato M, Tateishi R, et al. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol.* 2011;21(12):2584-96. PMID: 21858539
91. Lu MD, Xu HX, Xie XY, et al. Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. *Journal of gastroenterology.* 2005;40(11):1054-60. PMID: 16322950
92. Liang P, Wang Y, Yu X, et al. Malignant liver tumors: treatment with percutaneous microwave ablation--complications among cohort of 1136 patients. *Radiology.* 2009;251(3):933-40. PMID: 19304921
93. Ong SL, Gravante G, Metcalfe MS, et al. Efficacy and safety of microwave ablation for primary and secondary liver malignancies: a systematic review. *European journal of gastroenterology & hepatology.* 2009;21(6):599-605. PMID: 19282763
94. Zaitoun MMA, Elsayed SB, Zaitoun NA, et al. Combined therapy with conventional trans-arterial chemoembolization (cTACE) and microwave ablation (MWA) for

hepatocellular carcinoma >3-<5 cm. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2021;38(1):248-56. PMID: 33615957
95. Chong CCN, Lee KF, Cheung SYS, et al. Prospective double-blinded randomized controlled trial of Microwave versus RadioFrequency Ablation for hepatocellular carcinoma (McRFA trial). *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2020;22(8):1121-27. PMID: 32044268
96. Fang L, Meng X, Luo W, et al. Treatment of primary hepatic carcinoma through ultrasound-guided microwave ablation. *Niger J Clin Pract.* 2019;22(10):1408-11. PMID: 31607731
97. Simo KA, Sereika SE, Newton KN, et al. Laparoscopic-assisted microwave ablation for hepatocellular carcinoma: safety and efficacy in comparison with radiofrequency ablation. *J Surg Oncol.* 2011;104(7):822-9. PMID: 21520094
98. Swan RZ, Sindram D, Martinie JB, et al. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(4):719-29. PMID: 23404173
99. Liu Y, Zheng Y, Li S, et al. Percutaneous microwave ablation of larger hepatocellular carcinoma. *Clinical radiology.* 2013;68(1):21-6. PMID: 22766484
100. Abdelaziz A, Elbaz T, Shousha HI, et al. Efficacy and survival analysis of percutaneous radiofrequency versus microwave ablation for hepatocellular carcinoma: an Egyptian multidisciplinary clinic experience. *Surg Endosc.* 2014;28(12):3429-34. PMID: 24935203
101. Abdelaziz AO, Nabeel MM, Elbaz TM, et al. Microwave ablation versus transarterial chemoembolization in large hepatocellular carcinoma: prospective analysis. *Scandinavian journal of gastroenterology.* 2015;50(4):479-84. PMID: 25592058
102. Vogl TJ, Farshid P, Naguib NN, et al. Ablation therapy of hepatocellular carcinoma: a comparative study between radiofrequency and microwave ablation. *Abdominal imaging.* 2015;40(6):1829-37. PMID: 25601438
103. Chiang J, Cristescu M, Lee MH, et al. Effects of Microwave Ablation on Arterial and Venous Vasculature after Treatment of Hepatocellular Carcinoma. *Radiology.* 2016;281(2):617-24. PMID: 27257951
104. Xu Y, Shen Q, Wang N, et al. Percutaneous microwave ablation of 5-6 cm unresectable hepatocellular carcinoma: local efficacy and long-term outcomes. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2016:1-8. PMID: 27649577
105. Yu J, Liang P, Yu XL, et al. Needle track seeding after percutaneous microwave ablation of malignant liver tumors under ultrasound guidance: analysis of 14-year experience with 1462 patients at a single center. *Eur J Radiol.* 2012;81(10):2495-9. PMID: 22137097
106. Poggi G, Montagna B, P DIC, et al. Microwave ablation of hepatocellular carcinoma using a new percutaneous device: preliminary results. *Anticancer research.* 2013;33:1221-7. PMID: 23482806
107. Zhou P, Liang P, Dong B, et al. Long-term results of a phase II clinical trial of superantigen therapy with staphylococcal enterotoxin C after microwave ablation in hepatocellular carcinoma. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group.* 2011;27(2):132-9. PMID: 21117923

108. Zhou P, Liang P, Yu X, et al. Percutaneous microwave ablation of liver cancer adjacent to the gastrointestinal tract. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2009;13(2):318-24. PMID: 18825464
109. Takami Y, Ryu T, Wada Y, et al. Evaluation of intraoperative microwave coagulo-necrotic therapy (MCN) for hepatocellular carcinoma: a single center experience of 719 consecutive cases. *Journal of hepato-biliary-pancreatic sciences.* 2013;20(3):332-41. PMID: 22710886
110. Xu LF, Sun HL, Chen YT, et al. Large primary hepatocellular carcinoma: transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-percutaneous microwave coagulation therapy. *Journal of gastroenterology and hepatology.* 2013;28(3):456-63. PMID: 23216261
111. Yin T, Li W, Zhao P, et al. Treatment efficacy of CT-guided percutaneous microwave ablation for primary hepatocellular carcinoma. *Clinical radiology.* 2017;72(2):136-40. PMID: 27890422
112. Ma S, Ding M, Li J, et al. Ultrasound-guided percutaneous microwave ablation for hepatocellular carcinoma: clinical outcomes and prognostic factors. *Journal of cancer research and clinical oncology.* 2017;143(1):131-42. PMID: 27650934
113. Mimmo A, Pegoraro F, Rhaiem R, et al. Microwave Ablation for Colorectal Liver Metastases: A Systematic Review and Pooled Oncological Analyses. *Cancers (Basel).* 2022;14(5). PMID: 35267612
114. Bala MM, Riemsma RP, Wolff R, et al. Microwave coagulation for liver metastases. *The Cochrane database of systematic reviews.* 2013;10:CD010163. PMID: 24122576
115. Shibata T, Niinobu T, Ogata N, et al. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. *Cancer.* 2000;89(2):276-84. PMID: 10918156
116. Vogl TJ, Farshid P, Naguib NN, et al. Thermal ablation therapies in patients with breast cancer liver metastases: a review. *Eur Radiol.* 2013;23(3):797-804. PMID: 23064713
117. Pathak S, Jones R, Tang JM, et al. Ablative therapies for colorectal liver metastases: a systematic review. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland.* 2011;13(9):e252-65. PMID: 21689362
118. Lorentzen T, Skjoldbye BO, Nolsoe CP. Microwave ablation of liver metastases guided by contrast-enhanced ultrasound: experience with 125 metastases in 39 patients. *Ultraschall Med.* 2011;32(5):492-6. PMID: 21259183
119. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. *Ann Surg Oncol.* 2010;17(1):171-8. PMID: 19707829
120. Liu Y, Li S, Wan X, et al. Efficacy and safety of thermal ablation in patients with liver metastases. *European journal of gastroenterology & hepatology.* 2013;25:442-6. PMID: 23470267
121. Awad T, Thorlund K, Gluud C. Cryotherapy for hepatocellular carcinoma. *The Cochrane database of systematic reviews.* 2009(4):CD007611. PMID: 19821432
122. Kim HI, An J, Han S, et al. Loco-regional therapies competing with radiofrequency ablation in potential indications for hepatocellular carcinoma: a network meta-analysis. *Clin Mol Hepatol.* 2023;29(4):1013-28. PMID: 37403319
123. Bala MM, Riemsma RP, Wolff R, et al. Cryotherapy for liver metastases. *Cochrane Database of Systematic Reviews.* 2019(7). PMID: CD009058
124. Weis S, Franke A, Berg T, et al. Percutaneous ethanol injection or percutaneous acetic acid injection for early hepatocellular carcinoma. *The Cochrane database of systematic reviews.* 2015;1:CD006745. PMID: 25620061

125. Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scandinavian journal of gastroenterology.* 2008;43(6):727-35. PMID: 18569991
126. Giorgio A, Di Sarno A, De Stefano G, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial. *Anticancer research.* 2011;31(6):2291-5. PMID: 21737654
127. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology.* 2003;228(1):235-40. PMID: 12759473
128. Lin SM, Lin CJ, Lin CC, et al. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology.* 2004;127(6):1714-23. PMID: 15578509
129. Lin SM, Lin CJ, Lin CC, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut.* 2005;54(8):1151-6. PMID: 16009687
130. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology.* 1999;210(3):655-61. PMID: 10207464
131. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology.* 2005;129(1):122-30. PMID: 16012942
132. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Hepatocellular Cancers, Version 2.2023. [cited 1/16/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf.
133. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Rectal Cancer. v.6.2023. [cited 1/16/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
134. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon cancer. v.3.2021. [cited 1/16/2024]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
135. (NCCN) NCCN. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Neuroendocrine and Adrenal Tumors. v.1.2023. [cited 1/16/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
136. Goodman KA, Milgrom SA, Herman JM, et al. ACR Appropriateness Criteria(R) rectal cancer: metastatic disease at presentation. *Oncology (Williston Park).* 2014;28(10):867-71, 76, 78. PMID: 25323613
137. Kouri BE, Funaki BS, Ray CE, Jr., et al. ACR Appropriateness Criteria radiologic management of hepatic malignancy. *Journal of the American College of Radiology : JACR.* 2012;9(12):919-25. PMID: 23206650
138. Kouri BE, Abrams RA, Al-Refaie WB, et al. ACR Appropriateness Criteria Radiologic Management of Hepatic Malignancy. *Journal of the American College of Radiology : JACR.* 2016;13(3):265-73. PMID: 26944037
139. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358-80. PMID: 28130846

CODES

Codes	Number	Description
CPT	47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
	47371	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
	47380	Ablation, open, of one or more liver tumor(s); radiofrequency
	47381	Ablation, open, of 1 or more liver tumor(s); cryosurgical
	47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
	47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
	47399	Unlisted procedure, liver
HCPCS	None	

Date of Origin: *June 2017*

Regence

Medical Policy Manual Surgery, Policy No. 205

Implantable Peripheral Nerve Stimulation and Peripheral Subcutaneous Field Stimulation

Effective: January 1, 2024

Next Review: April 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Implantable peripheral nerve stimulation (PNS) for chronic pain of *peripheral nerve origin* is a type of neuromodulation therapy that involves the subcutaneous implantation of electrodes near or on a peripheral nerve that is *considered to be the origin of pain*. Peripheral subcutaneous field stimulation (PSFS) is a modification of PNS in which electrodes are implanted subcutaneously within the area of maximal pain with the intent of stimulating the nerves, cutaneous afferents, or the dermatomal distribution of the nerves communicating the pain. These procedures differ from other forms of electrical stimulation because the origin of pain is from a peripheral nerve or nerve field and the electrical impulses are delivered to the nerve or nerve field versus surrounding tissues or the spine.

MEDICAL POLICY CRITERIA

Note: This policy only addresses implantable peripheral nerve stimulation (PNS) and peripheral subcutaneous field stimulation (PSFS) (e.g., StimRouter®, SPRINT®) for chronic pain of peripheral nerve origin. Please refer to the Cross References below for other specific neuromodulation or stimulation therapies.

Implantable peripheral nerve stimulation (PNS) and peripheral subcutaneous field

stimulation (PSFS) for pain of peripheral nerve origin is considered **investigational** for all indications, including but not limited to chronic, postoperative, and post-traumatic pain.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Peripheral nerve stimulation (PNS) systems vary from other electrical stimulation therapies.

- Transcutaneous electrical nerve stimulation (TENS) delivers impulses across the skin to alleviate pain. PNS is similar to TENS, except PNS requires electrodes to be inserted under the skin and targets a nerve considered to be the origin of the pain.
- Percutaneous neuromodulation therapy (PNT) is an electrical stimulation therapy in which fine filament electrodes are temporarily placed in the tissues near the area causing pain. PNS is similar to PNT, except PNS requires electrodes to be inserted under the skin and targets a nerve considered to be the origin of the pain.
- Occipital nerve stimulation (ONS) is related to PNS in that a subcutaneous electrode delivers stimulation to the occipital nerve in an attempt to prevent migraines and other headaches in patients who have not responded to medications.

CROSS REFERENCES

1. Percutaneous Neuromodulation Therapy (PNT) and Percutaneous Electrical Nerve Stimulation (PENS), Surgery, Policy No. 44
2. Spinal Cord and Dorsal Root Ganglion Stimulation, Surgery, Policy No. 45
3. Deep Brain Stimulation, Surgery, Policy No. 84
4. Occipital Nerve Stimulation, Surgery, Policy No. 174

BACKGROUND

Implantable peripheral nerve stimulation (PNS) is a type of neuromodulation that delivers electrical impulses *directly to a nerve*.

Implantable PNS therapies have been around since the 1960s.[1] There are several implantable PNS neuromodulation therapies that use electrical stimulation for pain.[2] Examples include, but are not limited to: occipital nerve stimulation (ONS) and spinal cord stimulation (SCS).The StimRouter®, an implantable PNS system, is being marketed specifically for chronic pain *of peripheral nerve origin* i.e. upper/lower limb pain, entrapment syndromes, intercostal neuralgias and other peripheral injuries or diseases.[3] Although SCS addresses pain in the truck and limbs, the electrodes for SCS deliver electrical stimulation to the spine versus directly to the peripheral nerve pain site like the StimRouter®.[4] The SPRINT® Peripheral Nerve Stimulation System (SPR Therapeutics, Inc) has been cleared for marketing for symptomatic relief of chronic pain, post-surgical, and post-traumatic pain of the back and extremities.[5]

PNS systems include a neurostimulator (pulse generator), leads (thin wires with electrodes), a controller (device that allows the patient to control the device), and a programmer that allows a medical professional to make adjustments to the settings of the pulse generator. The leads are subcutaneously positioned and connected to the generator but the electrodes are not permanently implanted as in spinal cord stimulation. For example, the SPRINT® Peripheral

Nerve Stimulation System is indicated for up to 60 days. A trial of PNS is indicated prior to permanent implantation of the generator. If the trial is successful (defined has >50% response rate in pain reduction), the generator is permanently implanted in the chest, abdomen or buttocks.

Peripheral subcutaneous field stimulation (PSFS) is a modification of peripheral nerve stimulation. In peripheral subcutaneous field stimulation, leads are placed subcutaneously within the area of maximal pain. The objective of peripheral subcutaneous field stimulation is to stimulate the region of affected nerves, cutaneous afferents, or the dermatomal distribution of the nerves, which then converge back on the spinal cord. Combination spinal cord stimulation plus peripheral subcutaneous field stimulation is also being evaluated.

REGULATORY STATUS

In July 2018, the SPRINT® Peripheral Nerve Stimulation System (SPR Therapeutics, Inc) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K181422).[5] The SPRINT® PNS System is not intended to treat pain in the craniofacial region. The Bioness StimRouter® Neuromodulation System received FDA 510(k) approval in February 2015,[6] October 2019,[7] and March of 2020.[8] The StimRouter® is not intended to treat pain in the craniofacial region

In March of 2016, the StimQ Peripheral Nerve Stimulator (PNS) System received FDA 510(k) approval.[9] The StimQ PNS System is not intended to treat pain in the craniofacial region.

No device has been approved specifically for peripheral subcutaneous field stimulation (PSFS) by the U.S. Food and Drug Administration (FDA). PSFS is an off-label use of spinal cord stimulation devices or peripheral nerve stimulation devices (e.g. the SPRINT® PNS System) that have been FDA approved for the treatment of pain.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of pain due to any cause may include: relief of pain, improved functional level, and return to work. Relief of pain can be a subjective outcome associated with a placebo effect. Therefore, data from adequately powered, blinded, randomized controlled trials (RCT) are required to control for the placebo effect and determine if an implanted peripheral nerve stimulation (PNS) system f provides a significant advantage over placebo.

Treatment with an implanted PNS system must also be evaluated in general groups of patients against the existing standard of care for the condition being treated. For example, in patients with pain symptoms, treatment with an implanted PNS system should be compared to other forms of conservative therapy such as rest, non-steroidal anti-inflammatory medications, physical therapy, or steroid injection.

IMPLANTED PERIPHERAL NERVE STIMULATION

Systematic Reviews

Ni (2021) published a systematic review with meta-analysis of 13 studies (N=221) in which PNS was evaluated for the treatment of trigeminal neuropathic pain (TNP).[10] Eleven of the 13 studies examined effects of peripheral neuromodulation for TNP. Intractable facial pain of at least six months duration was an inclusion criterion for all included studies, with the exception

of one study which evaluated temporary PNS for the treatment of TNP caused by herpes zoster ophthalmicus. Ten of 13 (76.9%) studies reported response rates (pain reduction over 50%) as the clinical measurement during follow-up and visual analog scale (VAS) scores were available pre- and post-treatment in eight studies (N=110). The overall estimated response rate was 60.2% (95% CI: 41.9–76.1%, I^2 = 70.733%, p < 0.0001) and the mean pain scores were significantly lower at follow-up compared to baseline (standard difference 2.363; 95% CI: 1.408–3.319, I^2 = 85.723%, p < 0.0001). Sub-analysis was conducted to evaluate outcomes by target site of stimulation. In the three studies targeting the Gasserian ganglion as the stimulation target for facial pain, the overall response rate was 29.3% (95% CI: 19.2–41.8%, I^2 = 0, p = 0.635) and in studies using peripheral branch stimulation, 77.6% of patients reported over 50% pain relief (p < 0.0001). Study quality review revealed most studies did not provide sufficient information to evaluate adequate blinding of outcomes assessment, and for none of the included studies was adequate information on sample size justification, power description, or variance and effect estimates provided. Improper location of electrodes, infection, and electrode defects were the most commonly reported complications. The authors conclude that "randomized, controlled, prospective studies are needed to further compare the clinical efficiency of PNS with other conventional treatments for TNP."

Randomized Controlled Trials

Ilfeld (2021) published the results of a randomized controlled pilot study of PNS for the treatment of acute postoperative pain.[11] In this study, an electrical lead was percutaneously implanted preoperatively to target the sciatic nerve for major foot/ankle surgery (e.g., hallux valgus correction), the femoral nerve for anterior cruciate ligament reconstruction, or the brachial plexus for rotator cuff repair, followed by a single injection of long-acting local anesthetic along the same nerve/plexus. Postoperatively, participants were randomized to 14 days of either electrical stimulation (n = 32) or sham stimulation (n = 34). Coprimary outcome measures were cumulative opioid consumption and mean average daily pain scores on a 0 to 10 Numeric Rating Scale within the first seven postoperative days. The authors found opioid use in the active stimulation group was a median (interquartile range) of 5 mg (0 to 30) and 48 mg (25 to 90) in the sham treatment group (ratio of geometric means, 0.20 [97.5% CI, 0.07 to 0.57]; p < 0.001). The average pain intensity in the active stimulation group was (mean ± SD) 1.1 ± 1.1 and 3.1 ± 1.7 in the sham group (difference, −1.8 [97.5% CI, −2.6 to −0.9]; p < 0.001). This pilot study is severely limited by the short follow-up time of seven days, precluding evaluation of mid- or longer-term safety and effectiveness of the intervention. A larger, longer-term randomized controlled trial is anticipated.

In an industry-sponsored randomized controlled trial (RCT) published by Gilmore (2019), 28 lower-extremity amputees with postamputation pain were randomized to PNS or placebo for four weeks.[12] A significantly greater proportion of subjects receiving peripheral nerve stimulation (PNS) (n=7/12, 58%, p=0.037) demonstrated ≥50% reductions in average postamputation pain up to four weeks compared with subjects receiving placebo (n=2/14, 14%). In addition, a significantly greater proportion of PNS subjects reported ≥50% reductions in pain and pain interference after eight weeks of therapy compared with subjects receiving placebo, however the partial crossover design of this study prevents evaluation of placebo effects beyond four weeks. Twelve-month follow-up is ongoing. Overall, the study is limited by a small sample size which limits generalizability.

The results of an RCT of PNS compared to usual care (UC) for hemiplegic shoulder pain was published by Wilson (2016).[13] The study included 25 participants (12 PNS and 12 UC).

Although pain reduction with PNS treatment group was reported as significantly greater than the UC group, the per-protocol analysis of 21 participants showed significant reductions in pain in both groups and no significant slope difference between groups during the study. In addition, no significant group differences were observed for secondary outcome measures including pain interference, physical functioning, and global success rates. The authors concluded that additional RCTs are needed to determine treatment effectiveness.

Deer (2015) published a multicenter, randomized, double-blinded, partial crossover study addressing the safety and efficacy of the StimRouter® neuromodulation system for 94 patients with chronic pain of peripheral nerve origin (upper or lower extremity or trunk).[14] The patients were assigned to the StimRouter® group (n=45) or the control group (n=49). Efficacy was evaluated for three months and safety for one year. Primary outcomes included pain relief and safety. At three months the StimRouter® group reported 27.2% pain reduction vs. the control group 2.3%. Fifty-one percent of patients did not follow-up at one year. No serious adverse events were reported related to the device. A significant limitation of the study is the small sample size and large loss to follow-up.

Nonrandomized Studies

Warner (2020) published a retrospective case series of 72 patients who had undergone PNS implantation for treatment of various indications including occipital neuralgia (47%) and lower-extremity neuropathies (17%).[15] Six-month outcomes were assessed by numerical rating scale pain scores, opioid utilization, and self-reported functioning. Infection and device-related complications were also assessed. PNS implantation was associated with reductions in pain scores ($p<0.001$) and opioid utilization ($p<0.001$). Postoperative surgical site infection was found in ten percent of patients leading to device removal in five patients. No comparison to standard of care was provided.

A retrospective chart review including data from 240 patients implanted with a PNS, 165 of whom were being treated for complex regional pain syndrome, was published by Chmiela in 2020.[16] Median length of follow-up was 74 months. Pain scores at 12-month follow-up were decreased by an estimated 1.87 points (95% CI: [1.29, 2.46], paired t-test $p<0.001$). The percentage of patients on chronic opioid therapy decreased over 12 months from 62% to 41%. Of the 126 patients who reported changes in functional status, 64 (51%) reported improvement, 27 (21%) reported worsening, and 35 (28%) did not report any meaningful change. Excluding end-of-life battery replacements, surgical revision was needed in 56 (34%) of patients. Thirteen patients (8%) underwent implantation of a second PNS due to symptomatic expansion outside of the original region and device explant was performed in 32 (19%) of patients.

A multi-center, prospective case series published by Oswald (2019) evaluated outcomes in 39 patients implanted with the StimRouter™ on various isolated mononeuropathies.[17] The authors report 78% of the participants noted an improvement in pain, 72% noted improvement in activity, and 89% experienced a greater than 50% reduction in opioid consumption. This was not a controlled trial and no information comparing these outcomes to outcomes achieved through standard of care was provided. Future RCTs addressing these limitations are required.

Ilfeld (2017) published a review evaluating the safety of lead types in clinical studies of percutaneous neurostimulation of the peripheral nervous system.[18] Forty-three studies were included and of these both coiled (n = 21) and noncoiled (n = 25) leads were studied. The infection rates were estimated to be 0.03 (95% CI 0.01 to 0.13) infections per 1,000 indwelling

days for coiled leads and 0.83 (95% CI 0.16 to 4.33) infections per 1,000 indwelling days for noncoiled leads. No information is provided in the publication regarding clinical outcomes other than infection rates and no control group is evaluated.

Deer and Rosenfeld (2010) published the results of a single-center open-label study in which eight patients with carpal tunnel syndrome were evaluated for pain relief from the StimRouter™.[19] Pain evaluation occurred before implant, during implant and after explant. The authors concluded the StimRouter™ was effective and safe for pain reduction from carpal tunnel syndrome, but the study had methodological limitations including a small sample size and no mention of follow-up after the StimRouter™ was explanted after five days of treatment.

Numerous additional case series and case studies been published on PNS for the treatment of conditions including complex regional pain syndrome,[20] chronic shoulder pain,[21] chronic low back pain,[22] peripheral neuralgia,[23] oncologic pain,[24] and trigeminal pain.[25] Case studies and small case series generally are not considered in evidence reviews as they do not provide sufficient sample sizes or comparison groups to determine the added benefit of the technology on health outcomes over standard of care for any patient population.

PERIPHERAL SUBCUTANEOUS FIELD STIMULATION

Systematic Review

Sarica (2022) published the results of a systematic review with meta-analysis of studies reporting pain outcomes (visual analogue scale [VAS]) in patients treated with peripheral nerve field stimulation for facial pain, with a focus on trigeminal nerve pain.[26] Data from eleven observational, single-site cohort studies (N=109) were included in the review, five of which were prospective. Nine studies included cohorts of mixed diagnoses, and the most common diagnoses were persistent idiopathic facial pain (PIFP; n = 26) and trigeminal neuropathic pain (TNP; n = 25), followed by postherpetic neuralgia (PHN; n = 19), symptomatic trigeminal neuralgia (STN; n = 14), trigeminal neuralgia type 2 (TN2; n = 12) and type 1 (TN1; n = 8), and trigeminal deafferentation pain (TDP; n = 5). The number of patients included in each study ranged from 7 to 19. Common previously trialed interventions included nerve blocks (56%, 37/66), microvascular decompression (MVD; 25%, 16/65), percutaneous gasserian ganglion procedures (PGPs; 18%, 10/57), and stereotactic radiosurgery (SRS; 7%, 4/57). Nine trials included pre-implantation trial of temporary lead placement, one trial used adhesive electrodes and one used nerve block injections. The mean study follow-up period ranged from one month to 63.7 months. Analysis of individual patient data available for 62 patients from eight studies found mean improvement in VAS pain score at last follow-up to be 6.3 (95% CI 5.5–7.1, paired t-test, $p < 0.001$), with 79% (49/62) having a postoperative pain score < 5. A total of 51 complications occurred across 105 implantation surgeries in 44 patients (49% per procedure). The rate of complications requiring a surgical intervention was 32% per procedure (range 0%–82% across studies). The most frequent complications that required surgical management were skin erosions (n = 13) and infection (n = 10). The risk of bias of the included studies ranged from 4 to 6 out of a possible 6 stars when assessed using the Newcastle-Ottawa Scale and statistical heterogeneity was considerable ($I2 = 79\%$) across all studies. Although evidence of publication bias was not found (Egger's test, $p = 0.20$), significant small-study effects were found; 4 of the 11 studies fell outside of the 95% CI of the effect summary estimate for pain reduction outcome. The considerable heterogeneity across studies with respect to follow-up periods, rating scales used, patient selection/trial methods, stimulation parameters and preoperative conditions, as well as small sample sizes and lack of

controlled/comparator groups are limitations to the available evidence regarding peripheral nerve field stimulation for the treatment of facial pain.

A systematic review (SR) by Hofmeister (2020) evaluating the effectiveness of neurostimulation technologies for the management of chronic pain included one study on peripheral subcutaneous field stimulation (PSFS).[27] This study (Eldabe 2018) is discussed below.[28]

Randomized Controlled Trials

Albright-Trainer (2022) conducted a randomized controlled feasibility trial of PNS for the management of post-amputation pain.[29] Sixteen U.S. veterans undergoing major lower limb amputation at a single center received up to 60 days of PNS with the SPRINT system and standard medical therapy (n=8) or standard medical therapy alone (n=8). Standard medical therapy was defined as routine use of opioid and non-opioid pain medications, injections, physical rehabilitative therapies or complementary and alternative therapies. Responders were defined as participants with a at least a 50% reduction in average residual and phantom limb pain over time as assessed by the Brief Pain Inventory-Short Form (BPI-SF), with greater than 50% improvement considered substantial. At 12 weeks of follow-up, the PNS group experienced a 76% and 100% reduction in average phantom and residual limb pain from baseline compared to 58% and 75% in the control group, respectively. Additionally, only 20% of patients in the PNS group were taking opioids at 12 weeks compared to 38% in the control group. No patients in the PNS group required hospital readmission within 30 days compared to 25% requiring readmission in the control group. Follow up analysis through 12 months is ongoing. No serious study-related adverse events were reported. Follow-up at 12 weeks was missing for three individuals in the PNS group and one individual in the control group. The authors concluded that larger studies are warranted to reproduce the encouraging results of their feasibility study and to elucidate optimal timing of PNS therapy, evaluate surgical indications, and optimize patient selection.

Ilfeld (2021) published the results of a randomized, sham-controlled, pilot study of PNS for the treatment of postoperative pain in individuals receiving foot, ankle, knee, or shoulder surgery. Subjects were randomized to 14 days of electrical PNS stimulation (n=32) or sham stimulation (n=34). The dual primary outcomes were cumulative opioid consumption and mean daily pain scores within the first 7 postoperative days. Both outcomes met superiority thresholds with median opioid consumption of 5 mg versus 48 mg (estimated ratio of geometric means, 0.20; 97.5% CI, 0.07 to 0.57; p<.001) and average pain intensity of 1.1 versus 3.1 (difference in means, -1.8; 97.5% CI, -2.6 to -0.9; p<.001) as assessed by the Brief Pain Inventory-Short Form (BPI-SF) in treatment and sham groups, respectively. Differences in average pain, worst pain, and pain as assessed by the Defense and Veterans Pain Rating Scale were not significantly different between groups following completion of the treatment period on postoperative days 15 and 30.

Van Gorp (2019) published the 12-month follow-up of a multicenter RCT of patients with chronic low back pain in failed back surgery syndrome (FBSS) treated with spinal cord stimulation (SCS) alone and SCS with peripheral subcutaneous nerve field stimulation (PSFS).[28] Although the initial RCT randomized patients to treatment (SCS with PSFS) or control (SCS alone),[30] after the three-month study period, all patients in both groups received optimal SCS with PSFS during the open follow-up for the duration of the subsequent nine months. Thus, for the analysis of the follow-up data, both groups were combined and data from

all patients at 12 months (n=50) were compared to their own baseline values. Back pain, measured on a 100-mm visual analog scale (VAS), significantly decreased by 30.0 mm (95% CI: 237.7/222.4]; p<0.001), and leg pain decreased by 43.7 mm (95% CI: [251.5/236.2]; p<0.001). The authors also reported significant improvements across the 50 participants on secondary outcome measures including physical functioning, disability, pain, social functioning, anxiety, and medication indices. While this prospective, multicenter study provides valuable data on the efficacy of the simultaneous use of SCS and PSFS in a homogeneous, highly selected group of FBSS patients, the data do not permit conclusions regarding the added benefit of PSFS over SCS alone or the added benefit of this technology in other clinical populations. Additional long-term RCTs evaluating the added benefit of PSFS on health outcomes are needed.

Eldabe (2018) published a multi-site (21 sites) RCT comparing the effectiveness of subcutaneous peripheral nerve (field) stimulation (SQS) plus optimized medical management (SQS + OMM arm) compared to optimized medical management alone (OMM arm) in patients with back pain due to failed back surgery syndrome (FBSS).[31] Those in the SQS arm were implanted with a neurostimulator and up to two subcutaneous percutaneous cylindrical leads in the area of pain. Patients were evaluated pre-randomization and at one, three, six, and nine months post-randomization. The primary endpoint was the proportion of subjects with a ≥50% reduction in back pain intensity ("responder") from baseline to nine months. A total of 33.9% (19/56, missing: n = 20 [36%]) of subjects in the SQS + OMM arm and 1.7% (1/60, missing: n = 24 [40%]) in the OMM arm were responders at month nine (p < 0.0001). Although these results suggest that the addition of SQS to OMM is more effective than OMM alone in relieving low back pain at up to nine months in this study population, due to the slow rate of recruitment, the study was terminated early. Additional appropriately powered RCTs with longer-term follow-up are needed.

One small randomized double-blind crossover trial was published by McRoberts in 2013, however, this study did not include a control group or a comparison group of alternative treatment modalities.[32] The aim of this two-phase study was "to obtain preliminary estimates of the safety and efficacy of PSFS therapy using equipment originally designed for spinal cord stimulation." In the first phase of the study, patients (n=32) were initially randomized to one of the four stimulation groups, minimal, subthreshold, low frequency, and standard stimulation. Participants then rotated through all four stimulation groups in four to eight-day intervals. Both the investigator and patient were blinded to the group assigned. Two patients exited the study during phase I due to device/procedure-related adverse effects. "Responders" (n=24), defined as patients in any of the three active stimulation groups reporting $\geq$ 50% pain reduction, progressed to the second phase of permanent system implant (n=23). One responder did not receive permanent implantation due to non-device/procedure-related adverse effects.

Patients were followed for 52 weeks during which time reported mean visual analog scale (VAS), present pain index, and total scores on the Short Form McGill Pain Questionnaire were significantly improved from baseline at all follow-up visits (p<0.001). Excellent or good pain relief was reported in 16 (69.5%) patients at the 52-week follow-up visit. Opioid use decreased in 10 (43%) patients, remained stable in 8 (35%) patients, and increased in 5 (22%) patients. The most common adverse events were diminished or loss of therapy (n=10) and lead migration (n=7). Four patients had their systems explanted prior to completion of the study.

This study had a number of significant limitations that precluded conclusions, including but not limited to the small number of patients and the lack of an appropriate control group. Because

this study did not include a control group, the methodologic strength of these results is similar to that of an uncontrolled study. Further data are needed from well-designed RCTs which include large sample sizes and an appropriate control group for comparison.

NONRANDOMIZED TRIALS

Kloimstein (2014) reported on a prospective study of 118 patients treated with PSFS for chronic low back pain.[33] Before patients were implanted with the permanent PSFS system, a trial of stimulation was given for at least seven days. The permanent stimulation system was implanted in 105 patients. Significant improvements occurred at one, three, and six months' follow-up after implantation in the average pain VAS, Oswestry Disability Questionnaire, Becks Depression Inventory, and the Short Form-12 health survey. Significant reductions in opioid, nonsteroidal anti-inflammatory and anti-convulsant medications also occurred.

Verrills (2014) reported on PSFS for chronic headache conditions.[34] After a trial stimulation period, 60 patients underwent permanent implantation of the PSFS system and were followed for an average of 12.9 ± 9.4 months (range, 3-42 months). Ten patients required revision of the implant system. Significant reductions in pain were reported ($p \leq 0.001$). Additionally, use of analgesics or prophylactic medications was reduced in 83% of patients and disability and depression improved.

Verrills (2011) reported on a series of 100 patients treated PSFS for chronic neuropathic pain. Indications included chronic pain in occipital/craniofacial (n=40), lumbosacral (n=44), thoracic (n=8), groin/pelvis (n=5), or abdominal (n=3) regions.[35] Selection criteria included a clearly defined, discrete focal area of pain with a neuropathic component or combined somatic neuropathic pain component with characteristics of burning and increased sensitivity, and failure to respond to other conservative treatments including medications, psychological therapies, physical therapies, surgery, and pain management programs. Outcomes were assessed at a mean of 8.1 months after implantation (range, 1-23 months) with a combination of numerical pain scores, patient answered questionnaires, and patient medical histories. For the entire cohort, pain decreased from 7.4 at baseline to 4.2 at follow-up. About 34% of patients had at least a 75% improvement in pain scores and 69% improved by at least 50%. Analgesic use decreased in 40% of patients following PSFS. Adverse events were reported in 14% of patients, including unpleasant sensations, lead erosions and lead or battery migration.

Sator-Katzenschlager (2010) reported a retrospective multicenter study of the use of PSFS.[36] A total of 111 patients with chronic pain were treated, including 29 patients with low back pain, 37 with failed back surgery syndrome, 15 with cervical neck pain, and 12 patients with postherpetic neuralgia. The median duration of chronic pain was 13 years and the median number of previous surgeries was 2.7. For permanent implantation of the leads, patients had to have achieved at least 50% improvement in pain on a numerical rating scale during the trial period. After permanent implantation, pain intensity decreased in 102 patients (92%). Mean pain intensity decreased from 8.2 at baseline to 4.0 at follow-up with a reduction in consumption for analgesics and antidepressants. Lead dislocation or fracture occurred in 20 patients (18%).

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF PAIN AND NEUROSCIENCE

In 2022, the American Society of Pain and Neuroscience published consensus clinical guidelines for the use of implantable peripheral nerve stimulation in the treatment of chronic pain based on a review of the literature through March 2021. [37] Recommendations for best practices are listed below:

Head and Neck:

- Stimulation of occipital nerves may be offered to patients with chronic migraine headache when conservative treatment have failed. The average effect size for relief of migraine symptoms is modest to moderate. Level of Evidence (LOE) I. Degree of Recommendation (DOR) B.
- There is presently insufficient evidence to recommend stimulation of supraorbital and infraorbital nerves for neuropathic craniofacial pain LOE: II-3 DOR: C

Upper Extremities:

- PNS may offer modest and short-term pain relief, improved physical function, and better quality of life for chronic hemiplegic shoulder pain. LOE: I DOR: B
- PNS for mononeuropathies of the upper extremity may be offered following a positive diagnostic ultrasound-guided nerve block of the targeted nerve and is associated with modest to moderate pain relief. LOE: II-2 DOR: B

Low Back and Trunk

- Subcutaneous peripheral field stimulation combined with optimal medication management may offer moderate improvement in pain intensity for failed back surgery syndrome compared to optimal medication management alone. LOE: I DOR: B
- There is evidence that peripheral nerve stimulation (PNS) of medial branch nerves may improve pain intensity, physical function, and pain interference in patients with axial, mechanical low back pain. LOE: II-2 DOR: B
- There is limited evidence that PNS alleviates pain in neuropathic pain syndrome involving the trunk and back, including radiculopathy and post-herpetic neuralgia. LOE: III DOR: C

Lower Extremities:

- PNS may be considered for lower extremity neuropathic pain following failure of conservative treatment options and is associated with modest pain relief. LOE: I DOR: B
- PNS may be considered for lower extremity post-amputation pain following failure of conservative treatment options and is associated with modest to moderate pain relief. LOE:I DOR:B

Complex regional pain syndrome (CRPS)

- As a less-invasive modality compared to spinal cord stimulator (SCS) therapy, PNS may be offered to patients with CRPS Type I/II or peripheral causalgia, and may be associated with modest improvement in pain intensity and functional outcomes. However, high-quality evidence is limited and other neuromodulation interventions such as dorsal root ganglion SCS are recommended. LOE: III DOR: C

Other Considerations:

- PNS carries a low-to-intermediate risk for bleeding complications and depends on the proximity of the targeted nerve to critical vessels and invasiveness of PNS implantation. LOE: III DOR: I

The National Institute for Health and Care Excellence issued guidance in 2013 on peripheral subcutaneous field stimulation for chronic low back pain.[38] The guidance stated: “Current evidence on the efficacy of peripheral nerve-field stimulation (PNFS) for chronic low back pain is limited in both quantity and quality, and duration of follow-up is limited. Evidence on safety is also limited and there is a risk of complications from any implanted device. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”

SUMMARY

There is not enough research to show that implantable peripheral nerve stimulation (PNS) or peripheral subcutaneous field stimulation (PSFS) improves health outcomes for any indication, including for the treatment of chronic, postoperative, or post-traumatic pain of peripheral nerve origin. Therefore, the use of an implantable PNS system including peripheral subcutaneous field stimulation (PSFS) for treatment of pain of peripheral nerve origin is considered investigational including but not limited to the treatment of chronic pain, post-operative, or post-traumatic pain.

REFERENCES

1. International Neuromodulation Society: Peripheral Nerve Stimulation. [cited 6/14/2023]. 'Available from:' http://www.neuromodulation.com/PNS.
2. International neuromodulation Society: Neuromodulation Therapies - Patient Information. [cited 6/14/2023]. 'Available from:' http://www.neuromodulation.com/therapies.
3. Bioness. StimRouter. [cited 6/14/2023]. 'Available from:' http://stimrouter.com/.
4. Bioness. Control Your Pain, Live Your Life. [cited 6/14/2023]. 'Available from:' http://www.stimrouter.com/dtcinquiries/?utm_source=PPC&utm_medium=Ads&utm_campaign=WP_StimRouter_Brand&gclid=EAIaIQobChMI5Nf3y_H61gIVwSWBCh0C6A8JEAAYASAAEgLRRfD_BwE.
5. The US Food and Drug Administration: SPRINT Peripheral Nerve Stimulation System (K181422). [cited 6/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181422.pdf.
6. United Stated Food and Drug Administration (FDA): StimRouter Neuromodulation System. [cited 6/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142432.pdf.
7. United Stated Food and Drug Administration (FDA): StimRouter Neuromodulation System. [cited 6/14/2023]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K190047.
8. United Stated Food and Drug Administration (FDA): StimRouter Neuromodulation System. [cited 6/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200482.pdf.

9. United Stated Food and Drug Administration (FDA): StimQ Peripheral Nerve Stimulator (PNS) System. [cited 6/14/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/K152178.pdf.
10. Ni Y, Yang L, Han R, et al. Implantable Peripheral Nerve Stimulation for Trigeminal Neuropathic Pain: A Systematic Review and Meta-Analysis. *Neuromodulation : journal of the International Neuromodulation Society.* 2021. PMID: 34008282
11. Ilfeld BM, Plunkett A, Vijjeswarapu AM, et al. Percutaneous Peripheral Nerve Stimulation (Neuromodulation) for Postoperative Pain: A Randomized, Sham-controlled Pilot Study. *Anesthesiology.* 2021;135(1):95-110. PMID: 33856424
12. Gilmore C, Ilfeld B, Rosenow J, et al. Percutaneous peripheral nerve stimulation for the treatment of chronic neuropathic postamputation pain: a multicenter, randomized, placebo-controlled trial. *Reg Anesth Pain Med.* 2019;44(6):637-45. PMID: 30954936
13. Wilson RD, Gunzler DD, Bennett ME, et al. Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: a randomized controlled trial. *Am J Phys Med Rehabil.* 2014;93(1):17-28. PMID: 24355994
14. Deer T, Pope J, Benyamin R, et al. Prospective, Multicenter, Randomized, Double-Blinded, Partial Crossover Study to Assess the Safety and Efficacy of the Novel Neuromodulation System in the Treatment of Patients With Chronic Pain of Peripheral Nerve Origin. *Neuromodulation : journal of the International Neuromodulation Society.* 2016;19(1):91-100. PMID: 26799373
15. Warner NS, Schaefer KK, Eldrige JS, et al. Peripheral Nerve Stimulation and Clinical Outcomes: A Retrospective Case Series. *Pain Pract.* 2020. PMID: 33222402
16. Chmiela MA, Hendrickson M, Hale J, et al. Direct Peripheral Nerve Stimulation for the Treatment of Complex Regional Pain Syndrome: A 30-Year Review. *Neuromodulation : journal of the International Neuromodulation Society.* 2020. PMID: 33098229
17. Oswald J, Shahi V, Chakravarthy KV. Prospective case series on the use of peripheral nerve stimulation for focal mononeuropathy treatment. *Pain management.* 2019;9(6):551-58. PMID: 31686589
18. Ilfeld BM, Gabriel RA, Saulino MF, et al. Infection Rates of Electrical Leads Used for Percutaneous Neurostimulation of the Peripheral Nervous System. *Pain Pract.* 2017;17(6):753-62. PMID: 27676323
19. Deer TR, Levy RM, Rosenfeld EL. Prospective clinical study of a new implantable peripheral nerve stimulation device to treat chronic pain. *Clin J Pain.* 2010;26(5):359-72. PMID: 20473041
20. Frederico TN, da Silva Freitas T. Peripheral Nerve Stimulation of the Brachial Plexus for Chronic Refractory CRPS Pain of the Upper Limb: Description of a New Technique and Case Series. *Pain Med.* 2020;21(Suppl 1):S18-S26. PMID: 32804227
21. Mansfield JT, Desai MJ. Axillary Peripheral Nerve Stimulation for Chronic Shoulder Pain: A Retrospective Case Series. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(6):812-18. PMID: 31930660
22. Gilmore CA, Kapural L, McGee MJ, et al. Percutaneous Peripheral Nerve Stimulation for Chronic Low Back Pain: Prospective Case Series With 1 Year of Sustained Relief Following Short-Term Implant. *Pain Pract.* 2020;20(3):310-20. PMID: 31693791
23. Abd-Elsayed A. Wireless Peripheral Nerve Stimulation for Treatment of Peripheral Neuralgias. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(6):827-30. PMID: 32128933
24. Mainkar O, Solla CA, Chen G, et al. Pilot Study in Temporary Peripheral Nerve Stimulation in Oncologic Pain. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(6):819-26. PMID: 32185844

25. Bina RW, Palsma RS, Weinand ME, et al. Peripheral Nerve Stimulation for Refractory Trigeminal Pain: Recent Single-Institution Case Series With Long-Term Follow-Up and Review of the Literature. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(6):796-804. PMID: 32141164
26. Sarica C, Iorio-Morin C, Aguirre-Padilla DH, et al. Clinical outcomes and complications of peripheral nerve field stimulation in the management of refractory trigeminal pain: a systematic review and meta-analysis. *J Neurosurg.* 2022:1-9. PMID: 35180702
27. Hofmeister M, Memedovich A, Brown S, et al. Effectiveness of Neurostimulation Technologies for the Management of Chronic Pain: A Systematic Review. *Neuromodulation : journal of the International Neuromodulation Society.* 2020;23(2):150-57. PMID: 31310417
28. van Gorp E, Teernstra O, Aukes HJ, et al. Long-Term Effect of Peripheral Nerve Field Stimulation as Add-On Therapy to Spinal Cord Stimulation to Treat Low Back Pain in Failed Back Surgery Syndrome Patients: A 12-Month Follow-Up of a Randomized Controlled Study. *Neuromodulation : journal of the International Neuromodulation Society.* 2019;22(8):970-77. PMID: 29608807
29. Albright-Trainer B, Phan T, Trainer RJ, et al. Peripheral nerve stimulation for the management of acute and subacute post-amputation pain: a randomized, controlled feasibility trial. *Pain management.* 2022;12(3):357-69. PMID: 34761694
30. van Gorp EJ, Teernstra OP, Gultuna I, et al. Subcutaneous Stimulation as ADD-ON Therapy to Spinal Cord Stimulation Is Effective in Treating Low Back Pain in Patients With Failed Back Surgery Syndrome: A Multicenter Randomized Controlled Trial. *Neuromodulation : journal of the International Neuromodulation Society.* 2016;19(2):171-8. PMID: 26890014
31. Eldabe SS, Taylor RS, Goossens S, et al. A Randomized Controlled Trial of Subcutaneous Nerve Stimulation for Back Pain Due to Failed Back Surgery Syndrome: The SubQStim Study. *Neuromodulation : journal of the International Neuromodulation Society.* 2019;22(5):519-28. PMID: 29704437
32. McRoberts WP, Wolkowitz R, Meyer DJ, et al. Peripheral nerve field stimulation for the management of localized chronic intractable back pain: results from a randomized controlled study. *Neuromodulation : journal of the International Neuromodulation Society.* 2013;16(6):565-74; discussion 74-5. PMID: 23577773
33. Kloimstein H, Likar R, Kern M, et al. Peripheral Nerve Field Stimulation (PNFS) in Chronic Low Back Pain: A Prospective Multicenter Study. *Neuromodulation : journal of the International Neuromodulation Society.* 2014;17(2):180-7. PMID: 24320718
34. Verrills P, Rose R, Mitchell B, et al. Peripheral nerve field stimulation for chronic headache: 60 cases and long-term follow-up. *Neuromodulation : journal of the International Neuromodulation Society.* 2014;17(1):54-9. PMID: 24165152
35. Verrills P, Vivian D, Mitchell B, et al. Peripheral nerve field stimulation for chronic pain: 100 cases and review of the literature. *Pain Med.* 2011;12(9):1395-405. PMID: 21812906
36. Sator-Katzenschlager S, Fiala K, Kress HG, et al. Subcutaneous target stimulation (STS) in chronic noncancer pain: a nationwide retrospective study. *Pain Pract.* 2010;10(4):279-86. PMID: 20230450
37. Strand N, D'Souza RS, Hagedorn JM, et al. Evidence-Based Clinical Guidelines from the American Society of Pain and Neuroscience for the Use of Implantable Peripheral Nerve Stimulation in the Treatment of Chronic Pain. *J Pain Res.* 2022;15:2483-504. PMID: 36039168

38. Peripheral nerve-field stimulation for chronic low back pain: guidance [IPG451]. [cited 6/14/2023]. 'Available from:' https://www.nice.org.uk/guidance/ipg451.

CODES

Codes	Number	Description
CPT	64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64575	Open implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64585	Revision or removal of peripheral neurostimulator electrode array
	64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver
	64595	Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array
	64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array
	64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)
	64598	Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator
	64999	Unlisted procedure, nervous system
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, t programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)
	97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes
HCPCS	C1778	Lead, neurostimulator (implantable)
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8680	Implantable neurostimulator electrode, each
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8679	Implantable neurostimulator, pulse generator, any type

Date of Origin: *January 2018*

Regence

Medical Policy Manual Surgery, Policy No. 206

Balloon Dilation of the Eustachian Tube

Effective: July 1, 2023

Next Review: March 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Balloon dilation of the Eustachian tube is a tuboplasty procedure intended to improve the patency of the cartilaginous Eustachian tube. During the procedure, a saline-filled balloon catheter is introduced into the Eustachian tube through the nose using a minimally invasive transnasal endoscopic method. Pressure is maintained for approximately two minutes after which the balloon is emptied and removed. The procedure is usually performed under general anesthesia.

MEDICAL POLICY CRITERIA

I. Balloon dilation of the eustachian tube for treatment of chronic obstructive eustachian tube dysfunction may be considered **medically necessary** when all of the following Criteria are met (A. – E.):

A. Patient is 18 years and older;

B. Patient has chronic signs and symptoms of obstructive eustachian tube dysfunction that impairs function and meets all of the following Criteria (1. – 4.):

1. The patient does not have patulous eustachian tube dysfunction or another contraindication (See Policy Guidelines); and

2. Symptoms have occurred for at least 12 months including but not limited to aural fullness, aural pressure, otalgia, or hearing loss; and

3. The patient does not have other causes of aural fullness such as temporomandibular joint disorders, extrinsic obstruction of the eustachian tube, superior semicircular canal dehiscence, and endolymphatic hydrops; and

4. Symptoms are continuous rather than episodic (e.g., symptoms occur only in response to baro-challenge such as pressure changes while flying); and

C. The patient has undergone a comprehensive diagnostic assessment documenting all of the following findings:

1. Abnormal tympanogram (Type B or C); and

2. Abnormal tympanic membrane (retracted membrane, effusion, perforation, or any other abnormality identified on exam); and

D. Failure to respond to appropriate medical management of co-occurring conditions, including 4-6 weeks of a nasal steroid spray if indicated. Co-occurring conditions include but are not limited to allergic rhinitis, rhinosinusitis, and laryngopharyngeal reflux; and

E. If the patient had a history of tympanostomy tube placement, symptoms of obstructive eustachian tube dysfunction should have improved while tubes were patent.

II. Balloon dilation of the eustachian tube is considered **not medically necessary** when Criterion I. is not met.

III. Balloon dilation of the eustachian tube is considered **investigational** for repeat balloon dilation of the eustachian tube and all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Contraindications to Balloon Dilation of the Eustachian Tube

The following patients should not be considered for balloon dilation of the eustachian tube:

- Patients with patulous eustachian tube dysfunction
  - A diagnosis of patulous ETD is suggested by symptoms of autophony of voice, audible respirations, pulsatile tinnitus, and/or aural fullness.
- Patients with extrinsic reversible or irreversible causes of eustachian tube dysfunction including but not limited to:
  - craniofacial syndromes, including cleft palate spectrum
  - neoplasms causing extrinsic obstruction of the eustachian tube
  - history of radiation therapy to the nasopharynx
  - enlarged adenoid pads
  - nasopharyngeal mass
  - neuromuscular disorders that lead to hypotonia/ineffective eustachian tube dynamic opening

    - systemic mucosal or autoimmune inflammatory disease affecting the mucosa of the nasopharynx and eustachian tube (e.g. Samter's triad, Wegener's disease, mucosal pemphigus) that is ongoing/active (i.e. not in remission)
- Patients with aural fullness but normal exam and tympanogram
- Patients with chronic and severe atelectatic ears

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes including length of time signs and specific symptoms of obstructive eustachian tube dysfunction have been present and have impaired function.
- Indication for the requested service.
- Documentation patulous eustachian tube dysfunction and other contraindications to the procedure have been ruled out.
- Diagnostic findings documenting abnormal tympanogram and an abnormal tympanic membrane.
- Documentation of failure of medical management for any co-occurring conditions and specify length of time it was trialed.
- If there is a history of tympanostomy tube placement, provide documentation that symptoms of obstructive eustachian tube dysfunction improved while tubes were patent.

CROSS REFERENCES

1. Balloon Ostial Dilation for Treatment of Sinusitis, Surgery, Policy No. 153

BACKGROUND

EUSTACHIAN TUBE FUNCTION

The Eustachian tube (ET) connects the middle ear space to the nasopharynx. It is approximately 36 mm long in adults. The ET ventilates the middle ear space to equalize pressure across the tympanic membrane, clears mucociliary secretions, and protects the middle ear from infection and reflux of nasopharyngeal contents.[1] The tube opens during swallowing or yawning.

Eustachian tube dysfunction (ETD) occurs when the functional valve of the ET fails to open and/or close properly. This failure may be due to inflammation or anatomic abnormalities. ET dilatory dysfunction (ETDD) is most commonly caused by inflammation including rhinosinusitis and allergic rhinitis. ETDD can cause symptoms such as muffled hearing, ear fullness, tinnitus, and vertigo.[2] Chronic ETDD can lead to hearing loss, otitis media, tympanic membrane perforation, and cholesteatomas.

EPIDEMIOLOGY OF ETD

The epidemiology of ETD, including incidence and prevalence of the disorder and associated symptoms in the community, primary care, and referral populations, is not well-characterized.

Data are also lacking to describe the natural history of the disorder and impact on patient functioning.

DIAGNOSIS AND OUTCOME MEASURES

There are no comprehensive guidelines regarding the diagnosis of ETD. Schilder (2015) published a consensus statement from an international group of scientists and physicians with expertise in Eustachian tube disorders, prompted by a Health Technology Assessment from the UK National Institute of Health and Research stating that an important limitation with available evidence for treatments of ETD is a lack of consensus on the definition and diagnosis.[1] The meeting was funded by Acclarent, a manufacturer of a dilation technology. The following summarize relevant 2015 consensus statements from the group.

- There is no universally accepted set of patient-reported symptom scores, functional tests, or scoring systems to diagnose ETD.
- Diagnosis of ETDD should consider patient-reported symptoms along with evidence of negative pressure in the middle ear assessed by clinical assessment.
- Transient ETD is ETD with symptoms and signs lasting less than 3 months while chronic ETD is ETD with symptoms and signs lasting for more than 3 months.
- Future clinical trials should include outcomes related to patient-reported symptoms, otoscopy, tympanometry, and pure-tone audiometry, and outcomes should be assessed at baseline, in the short term (6 weeks to 3 months) and in the long term (6-12 months).
- The 7-item Eustachian Tube Dysfunction Questionnaire (ETDQ-7) is the only patient-reported outcome scale to have undergone initial validation studies.

Tympanometry is a frequently used outcome measure in ETD. Tympanometry measures the mobility of the tympanic membrane and graphically displays results in tympanograms. Tympanograms are classified by the height and location of the tympanometric peak. They are classified into three general patterns: type A indicates normal middle ear and ET function; type B indicates poor tympanic membrane mobility (“flat” tympanogram); and type C indicates the presence of negative middle ear pressure.[3]

The ETDQ-7 is used to assess ETD-related symptoms such as pressure, pain, “clogged” ears, and muffled hearing over the previous month. The 7 items are rated by patients on a 7-level scale from 1 (no problem) to 7 (severe problem). The overall score is reported as a mean item score with a range from 1.0 to 7.0. ETDQ-7 has been shown to be a valid and reliable symptom score for use in adults with ETD with overall score of 2.1 or higher having high accuracy to detect the presence of ETD.[4]

Other important outcomes for evaluating a treatment for ETD are hearing outcomes, otitis media, clearance of middle ear effusion, tympanic membrane retraction, and quality of life. Another important consideration is the need for additional treatment, e.g., additional surgical procedures (including reintervention).

TREATMENT OF ETDD

Medical management of ETDD is directed by the underlying etiology: treatment of viral or bacterial rhinosinusitis; systemic decongestants, antihistamines, or nasal steroid sprays for

allergic rhinitis; behavioral modifications and/or proton pump inhibitors for laryngopharyngeal reflux; and treatment of mass lesions. Although topical nasal steroids are commonly used for ETDD, triamcinolone acetonide failed to show benefit in patients ages six and older presenting with otitis media with effusion and/or negative middle ear pressure in a randomized, placebo-controlled, double-blind trial published in 2011.[5]

Patients who continue to have symptoms following medical management may be treated with surgery. Available surgical management includes myringotomy with placement of tympanostomy tubes or eustachian tuboplasty. There is limited evidence supporting use of these surgical techniques.[6] Norman (2014) reported that eustachian tuboplasty (other than balloon dilation) has been evaluated in seven case series and was associated with improvement in symptoms in 36% to 92% of patients with low rates (13%-36%) of conversion to type A tympanogram (which is normal). Myringotomy and tympanostomy have been evaluated in two case series and were associated with symptom alleviation in a subgroup of patients.[6]

REGULATORY STATUS

In December 2015, the AERA® (Acclarent) was granted a de novo 510(k) classification by the U.S. Food and Drug Administration (FDA) (class II, FDA product code: PNZ).[7] The new classification applies to this device and substantially equivalent devices of this generic type. The device was cleared for marketing by FDA through the 510(k) process (K163509) in January 2018.The AERA® is cleared for dilating the Eustachian tube in patients ages 22 and older with persistent ETD.

In April 2017, the XprESS™ ENT Dilation System (Entellus Medical, Plymouth, MN) was cleared for marketing by FDA through the 510(k) process (K163509).[8] FDA determined that this device was substantially equivalent to existing devices for use in Eustachian tube dysfunction. The predicate devices are XprESS™ Multi-Sinus Dilation System and AERA® Eustachian Tube Balloon Dilation System.

EVIDENCE SUMMARY

SCIENTIFIC EVIDENCE

Evaluating the safety and effectiveness of balloon dilation of the Eustachian tube requires randomized comparisons with standard treatments. These comparisons are necessary to determine whether the benefits of balloon dilation of the Eustachian tube outweigh any risks and whether they offer advantages over conventional methods with respect to increasing quality of life and decreasing long-term morbidity and mortality, or secondary outcomes such as improved Eustachian tube function. The evidence summary below is focused on systematic reviews and randomized controlled trials (RCTs).

Systematic Reviews

Aboueisha (2022) conducted a systematic review of balloon dilation for eustachian tube (BDET) dysfunction in pediatric populations which included seven studies and 408 participants with a mean age of 9.9 years.[9] The primary outcomes of interest were changes in tympanograms and air-bone gap. Type B tympanograms decreased after BDET from 64.2% (95%CI 53.3, 73.8) to 16.1% (95%CI 8.5, 28.4). Air-bone gap (ABG) decreased after BDET from a mean of 25.3 dB (95%CI 18.9, 31.6) to 10.2 dB (95%CI 8.9, 11.5). The pooled estimate

of adverse events after BDET was 5.1% (95%CI 3.2, 8.1), the majority being self-limited epistaxis with no major adverse events reported. This review is limited by the lack of high quality studies including randomized, comparative trials. Additional comparative trials are needed to establish the efficacy of BDET in pediatric populations.

Froehlich (2020) conducted a systematic review and meta-analysis of balloon dilation for eustachian tube dysfunction.[10] Twelve studies were included in the meta-analysis, including three RCTs, five prospective observational studies, and four case series. One RCT (Liang 2016) that compared balloon dilation to tympanic paracentesis reported tympanometry and otoscopy scores but not symptoms. The other two RCTs compared balloon dilation plus medical management to medical management alone and used the ETDQ-7 to measure symptoms. Pooled analyses showed improvements in subjective and objective measures including ETDQ-7 scores, tympanograms, otoscopy exams, and ability to perform a Valsalva maneuver. Improvements appeared to be maintained in studies with longer-term follow up (3-12 months). Case series included in these reviews consistently reported that patients experienced improvement when comparing symptoms before and after balloon dilation. The studies varied in the type of medical management used to treat eustachian tube dysfunction before and after balloon dilation.

The results of two additional systematic reviews and meta-analyses for adults with ETD who were treated with balloon dilation are discussed here. Huisman (2018)[11] provided pooled results for 15 case series (n=1,155) while Hwang (2016)[12] provided qualitative summaries only, for nine case series (n=474). Most selected case series provided follow-up of less than a year. All case series reported that patients experienced improvement when comparing symptoms before and after balloon dilation. The selected studies differed with respect to other treatments for ETD used before and after balloon dilation. In Huisman (2018), revisions due to failure of the first ET balloon dilation procedure were reported in three of the 15 studies (n=714); 122 revisions were reported. Huisman (2018) also reported studies had methodological limitations including risk of bias and high heterogeneity and that high quality RCTs are needed.

Jufas (2016) published a SR that evaluated balloon dilation, with a transtympanic approach for Eustachian tube dysfunction (ETD).[13] Three limited case series were included. The authors concluded there was a high risk of bias and safety and efficacy outcomes were conflicting.

Randrup (2015) published a SR evaluating balloon eustachian tuboplasty for ETD.[14] The authors evaluated nine case series and health outcomes for 443 patients. All case series were poor quality and had a high risk of bias.

Randomized Controlled Trials

Krogshede (2022) published a randomized controlled trial with six months of follow up evaluating 24 patients.[15] Of the 13 subjects randomized to the treatment group, nine showed normalization from retraction or serous otitis media in addition to showing improved tympanometry. There were no differences in audiometric findings or in Eustachian Tube Dysfunction Questionnaire-7 scores between the two groups. The authors concluded that the treatment is safe and effective for adult patients with mild chronic Eustachian tube dysfunction.

Meyer (2018) published the results of a one-year-follow-up-inclusive, prospective, multi-center RCT of balloon dilation as a treatment for persistent eustachian tube dysfunction (ETD) and compared the intervention to continued medical therapy (control).[16] Inclusion criteria required

patients be diagnosed with medically refractory, persistent ETD. Participants were randomly assigned (1:1) to intervention or control; however, control participants were offered the intervention after six weeks if their symptoms remained. The outcomes measured include primary efficacy endpoint using Eustachian Tube Dysfunction Questionnaire (ETDQ-7) scores and the rate of complications. The trial involved 60 randomized participants (31 intervention, 29 control). Mean (SD) change in overall ETDQ-7 score at six weeks was 2.9 (1.4) for balloon dilation compared with 0.6 (1.0) for control: balloon dilation was superior to control ($p<0.0001$). No complications were reported in either study arm. Among participants with abnormal baseline assessments, improvements in tympanogram type ($p < 0.006$) and tympanic membrane position ($p<0.001$) were significantly better for balloon dilation than control. Improvements in the ETDQ-7 scores were maintained through 12 months after balloon dilation. Limitations of this RCT are its small sample size and the inability to blind the participants to their treatment.

Cutler (2019) reported longer-term follow-up data on a subset of patients from the treatment arm of the RCT reported by Meyer.[17] Of 58 patients from the original study who were eligible for the extension study, 47 were enrolled in the follow up study. The mean follow-up time was 29.4 months post-procedure. Changes from baseline at the end of the longer-term follow-up period were similar to improvements observed at one year on outcome measures including the ETDQ-7, normalized tympanogram, ability to perform the Valsalva maneuver, and patient satisfaction. One patient underwent a revision ET dilation after 362 days, performed concurrently with balloon dilation for recurrent sinus disease. No other surgeries or adverse events were reported.

Poe (2017) published a randomized trial (n=323) comparing balloon dilation of the eustachian tube (BDET) with ET balloon catheter (ETBC) plus medical management versus medical management alone. Participants were 22 years or older, had persistent patient-reported symptoms of ETD (ETDQ-7; mean item score, ≥2.1), abnormal tympanometry (type B or type C), and failed medical management including either a minimum of four weeks of daily use of any intranasal steroid spray or a minimum of one course of an oral steroid.[18] The balloon catheter used in the trial was a custom-designed ET balloon catheter (Acclarent). The RCT results are also described in the AERA (Acclarent) de novo summary from the Food and Drug Administration.[7]

The investigators in this study were required to perform three successful ETBC procedures in nonrandomized “lead-in” patients who were then followed for durability and safety outcomes. Randomization and analyses were performed at the person-level regardless of whether the patient had unilateral or bilateral ETD. The primary efficacy outcome (normalization of tympanometry) was assessed by both site investigators and a blinded, independent evaluator; discrepancies were resolved by a second independent evaluator. For bilaterally treated patients, both ears had to be rated as normalized for that patient to be considered normalized for the primary outcome. Patients completed follow-up visits at 2, 6, 12, 24, and 52 weeks but data from the 52-week visit have not been reported. Patients in the medical management arm were allowed to receive BDET after the six-week visit. Trial enrollment was stopped early after the second preplanned look when the prespecified O’Brien-Fleming stopping boundary for the primary outcome was crossed.

At baseline, the mean ETDQ-7 score was 4.7, 43% of patients had allergic rhinitis, and 61% of patients had at least one prior ear tube surgery. By the second interim analysis, 162 patients had been assigned to ETBC and 141 were included in analysis; 80 had been assigned to

medical management and 72 were included in analysis. Patients were included in analysis if they received the study treatment for which they were randomized and had 6-week follow-up data. Approximately 52% of ETBC patients experienced tympanogram normalization at 6 weeks compared with 14% of medical management patients (p<.001). The publication reported that sensitivity analysis was performed to test the robustness of results for the impact of missing data in the analysis cohort versus an intention-to-treat cohort, but the method of sensitivity analyses was not described. It was noted that there was a significant treatment by site interaction. Two sites had a higher percentage of tympanogram normalization for MM subjects than for ETBC subjects while the remaining sites had higher normalization for ETBC. The pre-specified secondary efficacy outcome (percentage with minimal clinically important difference change of 0.5 points on ETDQ-7) was not reported in the publication but was reported in the FDA summary. The minimal clinically important difference change in ETDQ-7 scores was observed for 91% of ETBC patients at 6 weeks compared with 45% of medical management patients (p not reported). Fifty-six percent of ETBC patients had an ETDQ-7 mean item score of less than 2.1 at six weeks compared with about 9% of medical management patients (p<0.001). See the summary of results in table 1 below.

Comparative analyses were not possible after six weeks because 82% of medical management patients elected to ETBC after 6 weeks. Durability of the effect is supported by analysis of tympanogram normalization in 170 patients with week 24 data (98 randomized to ETBC and 74 from the lead-in); 62% of those randomized to ETBC and 58% of lead-in patients demonstrated tympanogram normalization at 24 weeks. Data from 52 weeks have not been reported.

This trial had methodological limitations, including the inability to blind patients, the exclusion of patients who did not received the assigned treatment, and the premature ending of the study. In addition, there were relevance gaps that prevented the RCT from providing enough evidence to guide treatment for ETDD. These included but are not limited to:

- Patients continued nasal steroids and other medications prescribed prior to the study
- Hearing outcomes were not reported
- Short-term follow-up prevented evaluation of long-term outcomes.

Table 1. Summary of Key RCT Results

Study (Year)	Normalization of Tympanometry (% of patients)	ETDQ-7 Symptom Scores <2.1 (% of patients)[a]	Change in Mean ETDQ-7 Score (SD)	Change in Mucosal Inflammation	Positive modified Valsalva Maneuver (% ears)	SAEs (no. of events)
Poe (2017)[18]						
N	211	208		NR	NR	NR
BDET plus MM	52%	56%		+22%	33%	4
MM	14%	9%		-5%	3%	1
Tx effect	RR=NR	RR=NR		NR	NR	NR
p	<0.001	<0.001				
Meyer (2018)[16]						
N			28			
BDET plus MM			-2.9 (1.4)			
N			27			
MM			-0.6 (1.0)			

Study (Year)	Normalization of Tympanometry (% of patients)	ETDQ-7 Symptom Scores <2.1 (% of patients)[a]	Change in Mean ETDQ-7 Score (SD)	Change in Mucosal Inflammation	Positive modified Valsalva Maneuver (% ears)	SAEs (no. of events)
p			<0.0001			

BDET: balloon dilation of the Eustachian tube; BL: baseline; ETDQ-7: 7-item Eustachian Tube Dysfunction Questionnaire; MM: medical management; NR: not reported; RR: relative risk; SAE: serious adverse event; Tx: treatment.
[a] The prespecified secondary outcome was the proportion of subjects achieving an improvement of at least a minimal clinically important difference of 0.5 points; it was not reported.

Adverse events were only briefly described in the publication but are more fully described in the Food and Drug Administration summary.[7] Two-hundred ninety-nine patients who were treated with ETBC were included in the safety analysis (80 lead-in patients, 149 patients randomized ETBC, 70 patients randomized to medical management who received ETBC). There were 16 nonserious device or procedure-related adverse events in 13 patients—most commonly, epistaxis and ETD. Two patients had three potentially device-related adverse events: mucosal tear, worsened ETD, and conductive hearing loss. The potentially device- or procedure-related adverse events were mild or moderate in severity and resolved without sequelae. Five serious adverse events were reported (four events in the BDET group, one event in the MM group); all were thought to be unrelated to device, procedure, or medication.

A 12-month follow-up on the treatment group was published by Anand (2019), which reported that the overall number of patient with normalized tympanograms and ETDQ-7 scores at one year were comparable to those reported after six weeks (71/128 vs. 73/143 and 71/124 vs. 79/142, respectively).[19] Results in the control group were not assessed.

Nonrandomized Studies

Satmis (2018) published a retrospective cohort study of 42 consecutive adult patients with chronic dilatory eustachian tube dysfunction. Patients in a tertiary referral hospital setting who received transnasal balloon dilation of the Eustachian tube were evaluated. Objective outcome measures included the ETDQ-7 score, bone conduction threshold, and tympanic membrane and middle ear conditions, which were pre and postoperatively collected. Mean ETDQ-7 scores improved from 4.28 to 3.09 and from 4.10 to 2.96 postoperatively at one and three months, respectively. There was a 62.0% improvement in tympanic membrane and middle ear condition. No serious procedure related complications were reported.

PRACTICE GUIDELINE SUMMARY

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

In 2019, The National Institute for Health and Care Excellence (NICE) published updated guidance on balloon dilation of the eustachian tube.[20] The guidance was based on a rapid review of the evidence and stated: "Evidence on the safety and efficacy of balloon dilation for eustachian tube dysfunction is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit." NICE standard arrangements recommendations mean that there is enough evidence for doctors to consider the procedure as an option. The guidance also noted:

- The procedure was not effective in all patients, and there was little evidence on the benefit of repeat procedures.

- The procedure is only indicated for chronic eustachian tube dysfunction refractory to medical treatment.

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY FOUNDATION

In 2019, The American Academy of Otolaryngology published a clinical consensus statement on balloon dilation of the eustachian tube.[21] The target population was defined as adults ages 18 years or older who are candidates for BDET because of obstructive eustachian tube dysfunction (ETD) in 1 or both ears for 3 months or longer that significantly affects quality of life or functional health status. The expert panel concluded:

- BDET is an option for treatment of patients with obstructive ETD.
- The diagnosis of obstructive ETD should not be made without a comprehensive and multifaceted assessment, including otoscopy, audiometry, and nasal endoscopy.
- BDET is contraindicated for patients diagnosed as having a patulous ETD
- Further study will be needed to refine patient selection and outcome assessment.

The authors emphasized the importance of identifying other potentially treatable causes of ETD, including allergic rhinitis, rhinosinusitis, and laryngopharyngeal reflux, and noted that medical management of these disorders is indicated prior to offering BDET. They also noted that potential risks of BDET that are relevant to patient counseling include bleeding, scarring, infection, development of patulous ETD, and/or the need for additional procedures.

SUMMARY

There is enough research to show that balloon dilation of the Eustachian tube improves health outcomes in patients with chronic signs and symptoms under certain circumstances. Additionally, clinical practice guidelines recommend the use of balloon dilation of the Eustachian tube for select patients. Therefore, the use of balloon dilation of the Eustachian tube may be considered medically necessary for the treatment of Eustachian tube dysfunction when policy criteria are met.

Due to not showing positive health outcomes for patients who do meet patient selection criteria, the use of balloon dilation for the treatment of Eustachian tube dysfunction is considered not medically necessary when policy criteria are not met.

There is not enough research to show that balloon dilation of the Eustachian tube improves health outcomes for people with any other indication or for repeat balloon dilation procedures. Therefore, balloon dilation of the Eustachian tube is considered investigational for the treatment for any other indication or repeat balloon dilation procedures.

REFERENCES

1. Schilder AG, Bhutta MF, Butler CC, et al. Eustachian tube dysfunction: consensus statement on definition, types, clinical presentation and diagnosis. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2015;40(5):407-11. PMID: 26347263
2. Seibert JW, Danner CJ. Eustachian tube function and the middle ear. *Otolaryngol Clin North Am.* 2006;39:1221-35. PMID: 17097443

3. Katz J. *Handbook of Clinical Audiology. 5th ed.* Baltimore: Lippincott Williams & Wilkins, 2002, pp.
4. McCoul ED, Anand VK, Christos PJ. Validating the clinical assessment of eustachian tube dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7). *The Laryngoscope.* 2012;122(5):1137-41. PMID: 22374681
5. Gluth MB, McDonald DR, Weaver AL, et al. Management of eustachian tube dysfunction with nasal steroid spray: a prospective, randomized, placebo-controlled trial. *Arch Otolaryngol Head Neck Surg.* 2011;137:449-55. PMID: 21576556
6. Norman G, Llewellyn A, Harden M, et al. Systematic review of the limited evidence base for treatments of Eustachian tube dysfunction: a health technology assessment. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2014;39(1):6-21. PMID: 24438176
7. FDA. Food and Drug Administration. De Novo Classification Request For Acclarent Aera™ Eustachian Tube Balloon Dilation System. 2015. [cited 4/23/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/reviews/den150056.pdf.
8. (FDA) FaDA. The XprESS ENT Dilation System [cited 4/23/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf16/k163509.pdf.
9. Aboueisha MA, Attia AS, McCoul ED, et al. Efficacy and safety of balloon dilation of eustachian tube in children: Systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol.* 2022;154:111048. PMID: 35085875
10. Froehlich MH, Le PT, Nguyen SA, et al. Eustachian Tube Balloon Dilation: A Systematic Review and Meta-analysis of Treatment Outcomes. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2020;163(5):870-82. PMID: 32482125
11. Huisman JML, Verdam FJ, Stegeman I, et al. Treatment of Eustachian tube dysfunction with balloon dilation: A systematic review. *The Laryngoscope.* 2018;128(1):237-47. PMID: 28799657
12. Hwang SY, Kok S, Walton J. Balloon dilation for eustachian tube dysfunction: systematic review. *J Laryngol Otol.* 2016;130 Suppl 4:S2-6. PMID: 27488333
13. Jufas N, Patel N. Transtympanic balloon dilatation of the eustachian tube: systematic review. *J Laryngol Otol.* 2016;130:425-30. PMID: 26965576
14. Randrup TS, Ovesen T. Balloon eustachian tuboplasty: a systematic review. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2015;152:383-92. PMID: 25605694
15. Kjær Krogshede S, Kirchmann M, Peter Schjellerup Jørkov A, et al. Balloon Dilation of the Eustachian Tube: A Randomized Controlled Trial with 6 Months Follow-Up. *J Int Adv Otol.* 2022;18(6):501-06. PMID: 36349672
16. Meyer TA, O'Malley EM, Schlosser RJ, et al. A Randomized Controlled Trial of Balloon Dilation as a Treatment for Persistent Eustachian Tube Dysfunction With 1-Year Follow-Up. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2018;39(7):894-902. PMID: 29912819
17. Cutler JL, Meyer TA, Nguyen SA, et al. Long-term Outcomes of Balloon Dilation for Persistent Eustachian Tube Dysfunction. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* 2019;40(10):1322-25. PMID: 31385858
18. Poe D, Anand V, Dean M, et al. Balloon dilation of the eustachian tube for dilatory dysfunction: A randomized controlled trial. *The Laryngoscope.* 2017. PMID: 28940574

19. Anand V, Poe D, Dean M, et al. Balloon Dilation of the Eustachian Tube: 12-Month Follow-up of the Randomized Controlled Trial Treatment Group. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2019;160(4):687-94. PMID: 30620688
20. Excellence NIfHaC. Balloon Dilation for Chronic Eustachian Tube Dysfunction. [cited 4/19/2022]. 'Available from:' https://www.nice.org.uk/guidance/ipg665.
21. Tucci DL, McCoul ED, Rosenfeld RM, et al. Clinical Consensus Statement: Balloon Dilation of the Eustachian Tube. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2019;161(1):6-17. PMID: 31161864

CODES

Codes	Number	Description
CPT	69705	Nasopharyngoscopy, surgical, with dilation of eustachian tube (ie, balloon dilation); unilateral
	69706	Nasopharyngoscopy, surgical, with dilation of eustachian tube (ie, balloon dilation); bilateral
	69799	Unlisted procedure, middle ear
HCPCS	None	

Date of Origin: *June 2017*

Regence

Medical Policy Manual Surgery, Policy No. 210

Transurethral Water Vapor Thermal Therapy and Transurethral Water Jet Ablation (Aquablation) of the Prostate

Effective: April 1, 2024

Next Review: December 2024
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transurethral water vapor thermal therapy and transurethral waterjet ablation are surgical alternatives to transurethral resection of the prostate (TURP) for the treatment of benign prostatic hyperplasia.

MEDICAL POLICY CRITERIA

I. Transurethral water vapor thermal therapy may be considered **medically necessary** for the treatment of benign prostatic hyperplasia (BPH) when all of the following criteria are met (A. – D.):

   A. Moderate to severe symptomatic BPH (See Policy Guidelines); and

   B. Patient is at least 50 years of age; and

   C. Prostate volume is 30 cc to 80 cc by ultrasound or other radiologic assessment; and

   D. A trial of conservative medical therapy (defined as one month of an alpha blocker, 3 months of a 5-alphareductase inhibitor, or 3 months of an

anticholinergic) for BPH has been unsuccessful, is contraindicated, or is not tolerated (See Policy Guidelines).

II. Transurethral waterjet ablation (e.g., Aquablation) may be considered **medically necessary** for the treatment of benign prostatic hyperplasia (BPH) when all of the following criteria are met (A. – C.):

A. Moderate to severe BPH (See Policy Guidelines); and

B. Prostate volume is 30cc to 150cc by ultrasound or other radiologic assessment; and

C. A trial of conservative medical therapy (defined as one month of an alpha blocker, 3 months of a 5-alphareductase inhibitor, or 3 months of an anticholinergic) for BPH has been unsuccessful, is contraindicated, or is not tolerated (See Policy Guidelines).

III. Transurethral water vapor thermal therapy of the prostate and transurethral waterjet ablation are considered **investigational** when the above criteria are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

BENIGN PROSTATIC HYPERPLASIA SEVERITY

The American Urological Association Symptom Index (AUA-SI) is a validated clinical tool for measuring severity of benign prostatic hyperplasia (BPH).[1] BPH severity is reported as mild (AUA-SI score of 0 to 7), moderate (8 to 19), and severe (20 to 35). The IPSS is the same as the AUA-SI but includes an additional question regarding impact of symptoms on quality of life.

CONSERVATIVE MEDICAL THERAPY

The medications listed in Table 1 may be used for conservative treatment of BPH.

Table 1. Medications for conservative treatment of BPH

Class	Common Examples
Alpha-1-receptor antagonists	Alfuzosin (Uroxatral, Xatral), doxazosin (Cardura), tamsulosin (Flomax), and terazosin (Hytrin)
5-alphareductase inhibitors	Finasteride, dutasteride
Anticholinergics	Fesoterodine (Toviaz), tolterodine (Detrol, Detrol LA), oxybutynin (Ditropan, Ditropan XL), darifenacin (Enablex), solifenacin (Vesicare), trospium (Sanctura, Sanctura XR)

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below must be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Conservative treatment provided, if any

    - If options for more conservative management are relatively or absolutely contraindicated, those contraindications should be specified.
    - If options for more conservative management previously have been tried and have been ineffective or not tolerated, clinical information regarding those previous treatments should be provided.
- Relevant imaging (ultrasound, etc) reports documenting prostate volume.

CROSS REFERENCES

1. Devices for Treatment of Benign Prostatic Hyperplasia, Urethral Stricture, and Urethral Stenosis, Surgery Policy No. 230

BACKGROUND

Benign prostatic hyperplasia (BPH) is a diagnosis that describes the enlargement of the prostate often associated with a group of obstructive symptoms, termed lower urinary tract symptoms (LUTS). These symptoms include decreased force of stream, hesitancy, straining, incomplete bladder emptying, and nocturia. The enlargement is caused by the proliferation of epithelial and smooth muscle cells in the transition zone of the prostate. Proliferation generally increases with age, and the initiation of BPH likely begins by the age of 30.[2] According to a multinational survey, 90% of men ages 50-80 experience BPH, although only 11% of men in the study received medical treatment.[3]

Standard management of BPH includes watchful waiting (active surveillance) in patients not bothered by their symptoms, medical management, surgery, and a number of new minimally invasive therapies. Surgical treatments include transurethral resection of the prostate (TURP), transurethral waterjet ablation (also referred to as robotic waterjet treatment [RWT] or Aquablation), transurethral vaporization, holmium laser enucleation or resection of the prostate, prostatic artery embolization, and prostatectomy. Minimally invasive therapies include transurethral needle ablation of the prostate (TUNA) and transurethral microwave thermotherapy (TUMT), as well as transurethral water vapor thermal therapy.

Transurethral water vapor thermal therapy is a process by which water vapor is created outside of the body and delivered to the prostate with a needle. The treatment is repeated in multiple locations within the prostate. During the procedure, saline irrigation cools and protects the surface of the urethra. The heat from the vapor disrupts cell membranes in the prostate, which leads to cell death and necrosis.

Aquablation cuts tissue by using a pressurized jet of fluid delivered to the prostatic urethra. The American Urological Association does not consider Aquablation to be a minimally invasive treatment because general anesthesia is required.[4]

REGULATORY STATUS

In 2015, the U.S. Food and Drug Administration (FDA) approved the Rezūm™ System (NxThera, Inc., acquired by Boston Scientific in 2018) under the 510(k) process for use in relieving symptoms and obstructions, and reducing prostate tissue associated with BPH. It is indicated for men > 50 years of age with a prostate volume >30cm3 and <80cm3. The Rezum System is also indicated for the treatment of prostate with hyperplasia of the central zone and/or a median lobe.

In April 2017, the Aquabeam® System (Procept Robotics Corporation) was cleared for marketing by the FDA through the 513(f)(2) (de novo) classification process (DEN170024). The device is intended for the resection and removal of prostate tissue in males suffering from LUTS due to benign prostatic hyperplasia.

EVIDENCE SUMMARY

The primary beneficial outcomes of interest are symptom reduction, measured in various ways, including the International Prostate Symptom Score (IPSS), the benign prostatic impact index (BPHII), and the maximum urinary flow rate (Qmax). Evaluating the safety and effectiveness of transurethral water vapor thermal therapy and Aquablation requires randomized comparisons with standard care. These comparisons are necessary to determine whether the benefits of implantable cardiac monitors outweigh any risks and whether they offer advantages over conventional methods with respect to increasing quality of life and decreasing symptoms.

TRANSURETHRAL WATER VAPOR THERMAL THERAPY

Systematic Reviews

Chughtai (2022) published a systematic review and meta-analysis of treatment options for men with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).[5] This study examined the long-term cost-effectiveness of generic combination therapy (CT), prostatic urethral lift (PUL), water vapor thermal therapy (WVTT), photoselective vaporization of the prostate (PVP), and transurethral resection of the prostate (TURP) for the treatment of BPH. The study found that IPSS improvement was highest in TURP and PVP, followed by WVTT. Compared to the other minimally invasive therapies WVTT had the highest quality-adjusted life years (QALY). However, QALYs from WVTT were lower than QALYs from the surgical therapies TURP and PVP.

Another systematic review by Tzeng (2022) reviewed all clinical trials investigating prostatic urethral lift (PUL), water vapor thermal therapy (WVTT), and temporary implantable nitinol device (TIND), with emphasis on clinical efficacy and complications.[6] Eighteen articles were included in this study, Evidence consisted of few randomized controlled trials, and multiple single-arm prospective and retrospective studies. Among the emerging technologies introduced to treat BPE, the in-office PUL, WVTT, and TIND systems are valuable additions to the current surgical options. WVTT demonstrate acceptable outcomes in terms of functional improvement, retreatment, and complications.

A similar Cochrane network meta-analysis by Franco (2022) included randomized controlled trials assessing the following treatments: convective radiofrequency water vapor thermal therapy (WVTT; or Rezūm); prostatic arterial embolization (PAE); prostatic urethral lift (PUL; or Urolift); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT) compared to transurethral resection of the prostate (TURP) or sham surgery.[7] This study reported that PUL and PAE had the highest likelihood of being the most efficacious for urinary symptoms and quality of life, TUMT for major adverse events, WVTT and TIND for erectile function and PUL for ejaculatory function.

Babar (2022) published a systematic review to evaluate the latest efficacy and safety profile of Rezum in patients with LUTS secondary to BPH. [8] Randomized and nonrandomized studies that evaluated urinary outcomes and/or adverse events were deemed eligible. Nineteen studies (N = 1942), published in 25 articles, were included. The study reported an

improvement in the International Prostate Symptom Score (IPSS), quality of life (QoL), and maximum urinary flow rate (Qmax) as early as 1 month postoperatively and remained durable for up to 5 years.

A Cochrane systematic review (SR) was reported by Kang in 2020.[9] The search was limited to parallel-group randomized controlled trials (RCTs), cluster-RCTs, and non-randomized observational prospective studies with concurrent comparison groups, in which men with BPH underwent convective radiofrequency water vapor thermal therapy, another active therapy, or a sham procedure. Only the RCT described below met inclusion criteria. The authors concluded that both urologic symptom scores and quality of life appear to be improved by water vapor thermal therapy, but they were very uncertain about major adverse events and that study limitations and imprecision led to a downgrade of evidence, which ranged from moderate to very low.

Randomized Controlled Trials

A single RCT was identified, with results published in multiple publications through five years of follow-up on a subset of participants.[10-15] The trial began with a three month randomized phase followed by an uncontrolled, open-label crossover phase. One-hundred and ninety-seven men experiencing lower urinary tract symptoms associated with benign prostatic hyperplasia were randomized 2:1. The active treatment group received water vapor ablation therapy with the Rezūm® System and the control group underwent a control procedure including rigid cystoscopy with simulated active treatment sounds. After three months, 53 of 61 control subjects who met criteria elected to participate in a crossover active treatment study. The International Prostate Symptom Score (IPSS) was 10.8 (standard deviation [SD] = 6.5) and 17.5 (SD = 7.6) in the active therapy and sham groups, respectively ($p<0.0001$) at three months post-treatment. The peak flow-rate (Qmax) increased significantly more in the treatment group at three months, to 16.1 (SD ±7.3), compared with 10.8 (SD = 4) in the sham group ($p<0.0001$). Quality of life, as measured by the IPSS-QOL question, was statistically significantly better in the treatment group (2.3; SD = 1.4) than in the sham group (3.5; SD = 1.5; $p<0.0001$).

In the patients that crossed over to the treatment group after unblinding at three months, improvements in IPSS, IPSS-QOL, and Qmax were all reported to be statistically significant compared to baseline values at 3, 6, 12, 24, 36, and 48 months ($p<0.0001$). Sexual function scores (IIEF-EF and MSHQ function) remained unchanged at two years, but declined at four years (-7.6% change, $p=0.0333$ and -14.2% change, $p=0.0038$, respectively).

Adverse events reported include one treated patient each who experienced nausea, vomiting, and de-novo urinary retention. In addition, among active treatment patients, 17% reported dysuria, 15% reported hematuria, 7% reported urinary frequency, and 7% reported hematospermia. Over five years, the surgical retreatment rate was 4.4% and the medication retreatment rate was 11.1%.

At four years, 45 subjects were excluded from the analysis. Of these, seven were excluded due to use of BPH medication. Additionally, further surgical intervention was performed in six patients. Fifty percent of patients had data included for five-year outcomes. This study is limited by duration of follow-up, with no control group present after three months of follow-up, and a lack of comparison to alternative treatments. Additionally, there was a high loss to follow-up, with data available for the primary outcome at four years from 90 of 197 patients.

Nonrandomized Studies

Garden (2021) published a retrospective analysis of Rezūm outcomes in men with prostates ≥ 80 cc (large prostate group; n=36) versus < 80 cc (small prostate group; n=168).[16] For individuals with large prostates, there were significant improvements in Qmax and post-void residual volume (PVR) postoperatively (p=0.039 and p=0.009, respectively), but no changes in AUA-Symptom Score (AUA-SS) or Sexual Health Inventory for Men (SHIM) were reported (p=0.29 and p=0.825, respectively). For men with prostates < 80 cc, the study reported improved PVR (89.51 to 62.72, p=0.027) and AUA-SS (16.59 to 11.21, p=0.003), but not in Qmax (9.47 to 10.90, p=0.187). Passing trial void (large prostate 94.44%, small prostate 93.45%), postoperative UTI (large prostate 19.44%, small prostate 10.12%), ED visits (large prostate 22.22%, small prostate 17.86%), readmissions (large prostate 8.33%, small prostate 4.76%), and retreatment (large prostate 8.33%, small prostate 4.76%) were not significantly different between groups. Mean days to foley removal (large prostate 9, small prostate 5.71, p=0.003) and urosepsis rates (large prostate 5.56%, small prostate 0.00%, p=0.002) were significantly different between groups. No Clavien grade ≥III complications were reported.

Bole (2020) reported a retrospective analysis of Rezūm for large prostates.[17] A total of 182 patients were identified as having undergone Rezūm, 25.8% of whom had prostate volume over 80cc. In this group, mean prostate volume was 119 cc and 55.3% were catheter dependent. AUA-SS improved from 22 pre-treatment to 13.4 following Rezūm (p=0.04). The improvement in peak flow rate was also statistically significant (7.7 to 12.7 mL/second; p=0.002).

Alegorides (2020) reported outcomes of 62 men with BPH treated with convective radiofrequency water vapor thermal therapy.[18] The IPSS decreased significantly from baseline at six months post-treatment, and the decrease persisted at one year (12-point decrease, p<0.001). Also at one year, the QoL score decreased by 3.2 points (p<0.001), the Qmax improved by 6mL/s (p<0.001), and there was a 2.1% rate of surgical retreatment. No serious side effects (>Clavien II) and no cases of de novo erectile dysfunction were reported.

McVary (2020) reported on a retrospective case series of water vapor thermal therapy for nonneurogenic complete urinary retention associated with BPH.[19] A total of 38 men with complete urinary retention and catheter-dependence were treated with water vapor thermal therapy using the Rezūm™ System. Of the 37 men available for follow-up, 26 voided spontaneously and were catheter free at a median of 26 days (range 4 to 65) following the procedure. Median follow-up for the catheter-free patients was 15.8 months. Adverse events included dysuria (n=5), gross hematuria (n=4), and UTIs in patients with indwelling catheters (n=2).

Mollengard (2018) published a retrospective review of 129 patients with BPH who underwent Rezūm. Minimum follow-up was four months. IPSS, and Qmax improved from baseline at the 91-180 day follow-up (18.3 to 6.9 and 10.5 to 16.8 mL/s, respectively; p<0.001). PVR also significantly improved over that time span (108.0 to 73.1, p=0.005). The most commonly reported adverse events were urinary tract infections (17%) and transient urinary retention (14%).

Darson (2017) reported the results of a case series of 131 patients treated with transurethral convective radiofrequency water-vapor thermal therapy with LUTS associated with BPH.[20] Not all values were reported for all patients at all time-points. Statistical significance of changes from baseline was determined using a longitudinal general estimation-equation model using an

exchangeable working correlation structure, which takes into account the correlation within a subject over time. IPSS at baseline, three to six months, and 12 months was 19.9 (SD = 6.7), 9.8 (SD = 6.9), and 10.1 (SD = 7.2). The three to six- and 12-month values were significantly lower than baseline (p<0.001). Qmax values at baseline, three to six, and 12 months were 8.7 (SD = 4.7), 11.6 (SD = 7.7), and 10 (SD = 5). The three- to six-month value was significantly different from baseline, but the 12-month value was not (p=0.04 and p=0.4, respectively). Improvement in IPSS-QOL scores from baseline to three-month follow-up was statistically significant, from 4.3 (SD = 1.2) to 2.3 (SD = 1.5; p<0.0001), and this statistically significant improvement was maintained at the 12-month follow-up. Urinary frequency, urgency, frequency and urgency, hematuria and nocturia were reported in less or equal to 4% of patients.

Dixon (2015 and 2016) reported the results of a case series in two publications.[21, 22] A total of 65 men at or above the age of 45 experiencing LUTS secondary to BPH received convective radiofrequency thermal therapy. Results were gathered as self-administered questionnaires as well as measurements taken at scheduled follow-up visits over the following two years. Not all values were reported for all patients at all time-points. Statistical differences were calculated using a paired Student's *t*-test for each measure. IPSS at one, three, 12, and 24 months was 14.8 (SD = 8.4), 8.3 (SD = 5.8), 9.2 (SD = 6.5), and 9.6 (SD = 6.5), respectively. All values were significantly improved compared to baseline (21.7 SD = 5.5; p<0.001). Qmax at one, three, 12, and 24 months was 9.9 (SD = 3.9), 12.8, 12.7 (SD = 6.3), and 12 (SD = 6.2). These values were also values were significantly improved compared to baseline (7.9 SD ± 3.2; p<0.001 except 24 months, where p=0.001). Improvement in IPSS-QOL scores from baseline to each time point reported were statistically significant (p<0.001). Adverse events reported were hematuria (14%), UTIs (20%), dysuria (22%), and urinary urgency (20%). All were mild to moderate transient events and 75% were reported within the first 30 days.

Section Summary

The evidence regarding transurethral water vapor thermal therapy of the prostate for the treatment of BPH includes systematic reviews, one RCT, two case series, and a non-randomized studies. These studies report clinically significant improvements in several measures of urinary symptoms and quality of life. Limitations of the published evidence include limited comparative follow-up and lack of studies with no industry associations. Despite the limitations, water vapor thermal therapy appears to improve urologic symptom scores and quality of life.

AQUABLATION

SYSTEMATIC REVIEWS

Van Kollenburg (2023) conducted a systematic review and meta-analysis of 10 RCTs in order to compare treatments for LUTS to each other and to TURP.[23] The treatments included Aquablation, prostatic urethral lift, prostatic artery embolization, convective water vapor thermal treatment and temporary implantable nitinol device (TIND). The review found that overall aquablation was most comparable to TURP. Of the treatment alternatives to TURP Aquablation was associated with the greatest improvement in Qmax at both 3- and 12-months follow-up (mean difference 0.80; 95%CI:-4.25, 5.88). However, TURP improved Qmax scores better than the other treatments. Aquablation was also comparable to TURP for post void residual improvement. There were no significant differences between TURP and the other

treatments for IPSS or Quality of Life scores. Overall adverse events were more likely with TURP, but Aquablation was associated with a two times higher incidence of urine retention compared to the other treatments. The authors note the available evidence from RCTs is heterogeneous and of low certainty, but concluded that Aquablation is the most effective of the alternative therapies for LUTS included in the review.

Randomized Controlled Trials

Aquablation for treatment of BPH has been assessed in one RCT, known as WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue; NCT02505919).[24] WATER was a noninferiority trial comparing Aquablation with TURP in 181 participants at 17 sites in four countries. Participants were men ages 45 to 80 years with moderate-to-severe LUTS, defined as IPSS 10 score greater than or equal to 12, and prostate size between 30 and 80 cc. There were 65 participants in the Aquablation group and 116 in the TURP group. The primary efficacy endpoint was the difference between groups in the change in IPSS at six months, and the primary safety end point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications at three months. Primary endpoint results were reported by Gilling in 2018,[24] 12-month results in Gilling (2019),[25] and three-year results in Gilling (2020).[26] Additionally, a synthesis of the trial results up to 12 months was reported in a Cochrane systematic review conducted by Hwang (2019).[27]

WATER trial results at 12 months, as summarized in the Cochrane review, are shown in Table 1. The reviewers assessed the certainty of the evidence for each outcome using the GRADE approach.[27] The reviewers concluded that up to 12 months, Aquablation likely results in a similar improvement in urologic symptom scores to TURP and may result in similar quality of life when compared to TURP. They also concluded that Aquablation may result in little to no difference in major adverse events, but considered the evidence for this finding very low certainty due to study limitations and imprecision of estimates.

Table 1. WATER Trial Results at 12 months (Adapted from Hwang [2019])

Outcome at 12 months	N Analyzed	Mean Difference (95% CI)	Certainty of the Evidence (Reason for downgrading)
IPSS	174	-0.6 (-2.51 to 2.39)	Moderate (study limitations)
IPSS QoL	174	0.27 (-0.024 to 0.78)	Low (imprecision)
Major adverse events	181	15 fewer per 1000 (-64 to 116) RR 0.84 (0.31 to 2.26)	Very low (high risk of performance bias, unclear risk of reporting bias, wide confidence interval crosses assumed threshold of minimal clinically important difference)
Retreatment	181	10 more per 1000 (13 fewer to 228 more) RR 1.68 (0.18 to 15.83)	Very low (imprecision and high risk of performance and attrition bias)
Erectile function	64	2.31 (-0.63 to 5.25)	Very low (imprecision and high risk of performance and attrition bias)
Ejaculatory function	121	2.57 (0.6 to 4.53)	Very low (imprecision: confidence interval crosses assumed threshold of minimal clinically important difference, high risk of performance and attrition bias)

Source: adapted from Hwang (2019). RR: relative risk; WATER: Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue

On the primary efficacy outcome, Aquablation was noninferior to TURP. At six months, mean IPSS decreased from baseline by 16.9 points for Aquablation and 15.1 points for TURP (mean difference 1.8 points; p<0.0001 for noninferiority and p=0.1347 for superiority). The primary safety endpoint rate was lower in the Aquablation group compared to the TURP group (26% vs 42%, p=0.0149). The rate of grade 2 and greater events was similar in the two groups (20% for Aquablation and 23% for TURP; p=0.3038).

Gilling (2020) reported WATER trial results at three years (Table 2).[26] Improvements in symptoms and quality of life were maintained through three years in both treatment groups, and the rate of serious adverse events did not differ between groups any time point.

Table 2. WATER Trial Results at 3 Years

Treatment	Mean IPSS reduction at 3 years	Mean % reduction in IPSS at 3 years	Improvement at least 5 points from baseline at 3 years	IPSS QoL improvement at 3 years	Qmax (mL/s)	Retreatment Rate at 3 years	Serious Adverse Events Subjects (%)
Aquablation	14.4 (6.8)	64%	78%	3.2 (1.8)	11.6	5/116 (4.3%)	0 to 3 months: 7 (6.0%) 3 months to 1 year: 5 (4.3%) 1 to 2 years: 8 (6.9%) 2 to 3 years: 4 (3.4%)
TURP	13.9 (8.6)	61%	82%	3.2 (1.7)	8.2	1/65 (1.5%)	0 to 3 months:04 (6.2%) 3 months to 1 year: 5 (7.7%) 1 to 2 years: 2 (3.1%) 2 to 3 years: 1 (1.5%)
Difference	0.6 (-3.3 to 2.2)	3%	4%	0	3.3 (-0.5 to 7.1)	2.8%	
p-value	0.6848	NS	NS	0.7845	0.0848	0.4219	NS at any time point

AE: adverse events; BPH: benign prostatic hyperplasia Impact Index; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; MSHQ-ED Male Sexual Health Questionnaire-Erectile Dysfunction; NR: not reported; NS: not significant; Qmax: peak urinary flow; QoL: quality of life; RCT: randomized controlled trial; WATER: Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue

Oumedjbeur (2023) published five-year outcomes of the WATER trial in the subgroup of men with prostate volumes 50-80mL.[28] The differences in IPSS scores in which Aquablation showed greater improvement than TURP were maintained at five years (P=0.020); however, the improvement in Qmax and QoL seen at three years did not remain consistent. There was no change in ejaculatory function with Aquablation at five years, but TURP was associated with a decline in MSHQ-EjD scores at all follow-up time points (p= 0.0095). Aquablation was associated with a lower rate of medical and surgical retreatment for LUTS than TURP at 5

years (3.2% vs. 17.6%). The occurrence of serious adverse events was not significantly different between the two treatments (p>0.05). The authors concluded that Aquablation is superior to TURP for prostates 50-80mL. The study was limited by a significant difference in prostate size at baseline, however a sensitivity analysis found no change in IPSS measures when controlling for baseline prostate size.

There were limitations of the WATER trial in outcomes, blinding, and selective reporting. Adverse events occurring after one year were not adjudicated by the clinical events committee. Although patients and outcome assessors were blinded, baseline evaluation and study surgeons were not blinded. Additionally, secondary outcomes were not prespecified.

WATER II was a prospective clinical trial that investigated whether Aquablation is effective for people with larger prostate volumes than were included in the WATER trial. WATER II enrolled 101 men from 16 study sites who had prostate volumes of 80 to 150mL. Bhojani (2023) published 5-year outcomes from the WATER II trial, reporting on 60 subjects who completed their 60-month visit.[29] Study attrition was directly linked to the COVID-19 pandemic for about half of the participants who were not available at five years. Study outcomes included IPSS scores, which showed significant improvement at 5-years compared to baseline (p< 0.001). There was also significant improvement in mean Qmax, which increased from 8.6 to 17.1 mL/s at five years (p<0.001) However, six (6%) of patients were prescribed medication for BPH and an additional 3% had surgical retreatment for LUTS. The majority of these interventions occurred in the initial three years after Aquablation, suggesting stabilization may have occurred. Limitations include the single-arm design of the study.

Nonrandomized studies

Several nonrandomized, single-arm studies have been performed, primarily with small sample sizes and short follow-up. Outcomes from prospective studies with over 100 participants and 12 months or longer follow-up are displayed in Table 3.

Table 3. Nonrandomized Studies of Aquablation.

Study	Study Design	n	Mean prostate volume (range) mL	Follow-up	Urinary/QOL outcomes	Ejaculatory/Sexual function	Adverse Events
Bach (2020) [30]	prospective, multicenter, single-arm, open-label, international clinical trial	178	59.3 (20–148)	12 months	IPSS (21.6 at baseline to 6.5 at 12 months) and Qmax (10 cc/s at baseline to 20.8 cc/s at 12 months) significantly at 12 months (p<0.0001 for both)	No significant change from baseline in any MSHQ measure except Male Sexual Health Questionnaire bother score at 12 months (p=0.0025).	36 Clavien-Dindo grade 2 or higher events. Primarily injection and bleeding
Desai (2020) [31]	prospective case series	101	107 (80-150)	2 years	Mean IPSS (23.2 at baseline to 5.8 at 2 years, p<0.0001) and IPSS quality of life (4.6 at baseline to	Not reported	29% within 1 month

Study	Study Design	n	Mean prostate volume (range) mL	Follow-up	Urinary/QOL outcomes	Ejaculatory/Sexual function	Adverse Events
					1.1 at 2 years, p<0.0001) improved significantly at the two-year follow-up		

PRACTICE GUIDELINE SUMMARY

American Urological Association

The American Urological Association (AUA) published an evidence-based clinical practice guideline "Management of Benign Prostatic Hyperplasia/ Lower Urinary Tract Symptoms: AUA Guideline," which includes the following recommendations:[32]

- WVTT [water vapor thermal therapy] should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc. (Moderate Recommendation; Evidence Level: Grade C)
- WVTT may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)
- Robotic waterjet treatment (RWT) may be offered as a treatment option to patients with LUTS/BPH provided prostate volume 30-80cc. (Conditional Recommendation; Evidence Level: Grade C)

A conditional recommendation is described as:

- Balance between Benefits & Risks/Burdens unclear
- Alternative strategies may be equally reasonable
- Better evidence likely to change confidence

SUMMARY

It appears that transurethral water vapor thermal therapy and transurethral waterjet ablation (Aquablation) of the prostate improve urinary symptoms for some people with benign prostatic hyperplasia. In addition, clinical practice guidelines based on evidence recommend transurethral water vapor thermal therapy and transurethral waterjet ablation of the prostate for certain individuals with benign prostatic hyperplasia. Therefore, transurethral water vapor thermal therapy and transurethral waterjet ablation of the prostate may be considered medically necessary when criteria are met. In all other situations, there is not enough evidence to show that transurethral water vapor thermal therapy or transurethral waterjet ablation of the prostate improves health outcomes. Therefore, transurethral water vapor thermal therapy and transurethral waterjet ablation of the prostate are considered investigational when criteria are not met.

REFERENCES

1. Barry MJ, Fowler FJ, Jr., O'Leary M P, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. *The Journal of urology.* 2017;197(2s):S189-s97. PMID: 28012747
2. Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *The Journal of urology.* 1984;132(3):474-9. PMID: 6206240
3. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol.* 2003;44(6):637-49. PMID: 14644114
4. Foster HE, Dahm P, Kohler TS, et al. Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline Amendment 2019. *The Journal of urology.* 2019;202(3):592-98. PMID: 31059668
5. Chughtai B, Rojanasarot S, Neeser K, et al. A comprehensive analysis of clinical, quality of life, and cost-effectiveness outcomes of key treatment options for benign prostatic hyperplasia. *PLoS One.* 2022;17(4):e0266824. PMID: 35427376
6. Tzeng M, Basourakos SP, Lewicki PJ, et al. New Endoscopic In-office Surgical Therapies for Benign Prostatic Hyperplasia: A Systematic Review. *Eur Urol Focus.* 2022;8(2):522-31. PMID: 33663982
7. Franco JVA, Jung JH, Imamura M, et al. Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis. *BJU Int.* 2022;130(2):142-56. PMID: 34820997
8. Babar M, Loloi J, Tang K, et al. Emerging outcomes of water vapor thermal therapy (Rezum) in a broad range of patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia: A systematic review. *Low Urin Tract Symptoms.* 2022;14(3):140-54. PMID: 35233955
9. Kang TW, Jung JH, Hwang EC, et al. Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia. *Cochrane Database Syst Rev.* 2020;3(3):Cd013251. PMID: 32212174
10. McVary KT, Roehrborn CG. Three-Year Outcomes of the Prospective, Randomized Controlled Rezum System Study: Convective Radiofrequency Thermal Therapy for Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *Urology.* 2018;111:1-9. PMID: 29122620
11. McVary KT, Gange SN, Gittelman MC, et al. Erectile and Ejaculatory Function Preserved With Convective Water Vapor Energy Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Randomized Controlled Study. *The journal of sexual medicine.* 2016;13(6):924-33. PMID: 27129767
12. McVary KT, Gange SN, Gittelman MC, et al. Minimally Invasive Prostate Convective Water Vapor Energy Ablation: A Multicenter, Randomized, Controlled Study for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *The Journal of urology.* 2016;195(5):1529-38. PMID: 26614889
13. Roehrborn CG, Gange SN, Gittelman MC, et al. Convective Thermal Therapy: Durable 2-Year Results of Randomized Controlled and Prospective Crossover Studies for Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *The Journal of urology.* 2017;197(6):1507-16. PMID: 27993667
14. McVary KT, Rogers T, Roehrborn CG. Rezum Water Vapor Thermal Therapy for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia: 4-Year Results From Randomized Controlled Study. *Urology.* 2019;126:171-79. PMID: 30677455

15. McVary KT, Gittelman MC, Goldberg KA, et al. Final 5-Year Outcomes of the Multicenter Randomized Sham-Controlled Trial of a Water Vapor Thermal Therapy for Treatment of Moderate to Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *The Journal of urology.* 2021;206(3):715-24. PMID: 33872051
16. Garden EB, Shukla D, Ravivarapu KT, et al. Rezum therapy for patients with large prostates (≥ 80 g): initial clinical experience and postoperative outcomes. *World J Urol.* 2021:1-8. PMID: 33392646
17. Bole R, Gopalakrishna A, Kuang R, et al. Comparative Postoperative Outcomes of Rezūm Prostate Ablation in Patients with Large Versus Small Glands. *J Endourol.* 2020;34(7):778-81. PMID: 32408768
18. Alegorides C, Fourmarier M, Eghazarian C, et al. Treatment of benign prostate hyperplasia using the Rezum® water vapor therapy system: Results at one year. *Prog Urol.* 2020. PMID: 32826195
19. McVary KT, Holland B, Beahrs JR. Water vapor thermal therapy to alleviate catheter-dependent urinary retention secondary to benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis.* 2019:10.1038/s41391-019-0187-5. PMID: 31740738
20. Darson MF, Alexander EE, Schiffman ZJ, et al. Procedural techniques and multicenter postmarket experience using minimally invasive convective radiofrequency thermal therapy with Rezum system for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *Res Rep Urol.* 2017;9:159-68. PMID: 28861405
21. Dixon CM, Cedano ER, Pacik D, et al. Two-year results after convective radiofrequency water vapor thermal therapy of symptomatic benign prostatic hyperplasia. *Res Rep Urol.* 2016;8:207-16. PMID: 27921028
22. Dixon C, Cedano ER, Pacik D, et al. Efficacy and Safety of Rezum System Water Vapor Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Urology.* 2015;86(5):1042-7. PMID: 26216644
23. van Kollenburg RAA, van Riel L, de Bruin DM, et al. Novel minimally invasive treatments for lower urinary tract symptoms: a systematic review and network meta-analysis. *Int Braz J Urol.* 2023;49(4):411-27. PMID: 37267609
24. Gilling P, Barber N, Bidair M, et al. WATER: A Double-Blind, Randomized, Controlled Trial of Aquablation(®) vs Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia. *The Journal of urology.* 2018;199(5):1252-61. PMID: 29360529
25. Gilling PJ, Barber N, Bidair M, et al. Randomized Controlled Trial of Aquablation versus Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia: One-year Outcomes. *Urology.* 2019;125:169-73. PMID: 30552937
26. Gilling P, Barber N, Bidair M, et al. Three-year outcomes after Aquablation therapy compared to TURP: results from a blinded randomized trial. *Can J Urol.* 2020;27(1):10072-79. PMID: 32065861
27. Hwang EC, Jung JH, Borofsky M, et al. Aquablation of the prostate for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. *Cochrane Database Syst Rev.* 2019;2(2):Cd013143. PMID: 30759311
28. Oumedjbeur K, Corsi NJ, Bouhadana D, et al. Aquablation versus TURP: 5-year outcomes of the WATER randomized clinical trial for prostate volumes 50-80 mL. *Can J Urol.* 2023;30(5):11650-58. PMID: 37838991
29. Bhojani N, Bidair M, Kramolowsky E, et al. Aquablation Therapy in Large Prostates (80-150 mL) for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: Final WATER II 5-Year Clinical Trial Results. *The Journal of urology.* 2023;210(1):143-53. PMID: 37115632

30. Bach T, Gilling P, El Hajj A, et al. First Multi-Center All-Comers Study for the Aquablation Procedure. *J Clin Med.* 2020;9(2). PMID: 32102329
31. Desai M, Bidair M, Bhojani N, et al. Aquablation for benign prostatic hyperplasia in large prostates (80-150 cc): 2-year results. *Can J Urol.* 2020;27(2):10147-53. PMID: 32333733
32. Sandhu JS, Bixler BR, Dahm P, et al. Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia (BPH): AUA Guideline Amendment 2023. *The Journal of urology.* 2024;211(1):11-19. PMID: 37706750

CODES

Codes	Number	Description
CPT	0421T	Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)
	53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy
	53899	Unlisted procedure, urinary system
HCPCS	C2596	Probe, image-guided, robotic, waterjet ablation

Date of Origin: *December 2018*

Regence

Medical Policy Manual Surgery, Policy No. 212

Phrenic Nerve Stimulation for Central Sleep Apnea

Effective: January 1, 2024

Next Review: June 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. The goal of phrenic nerve stimulation treatment is to normalize sleep-related breathing patterns.

MEDICAL POLICY CRITERIA

Note: This policy only addresses phrenic nerve stimulation for *central* sleep apnea (CSA). It does not address hypoglossal nerve stimulation for *obstructive* sleep apnea (OSA). See Cross References section below.

The use of phrenic nerve stimulation for central sleep apnea is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Noninvasive Ventilators in the Home Setting, Durable Medical Equipment, Policy No. 87
2. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166
3. Hypoglossal Nerve Stimulation, Surgery, Policy No.215

BACKGROUND

CENTRAL SLEEP APNEA

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. CSA may be idiopathic or secondary (associated with Cheyne-Stokes breathing, a medical condition, drugs, or high altitude breathing. Cheyne-Stokes breathing is common among patients with heart failure or who have had strokes, and accounts for about half of the population with CSA. CSA is less common than obstructive sleep apnea (OSA). Based on analyses of a large community-based cohort in the Sleep Heart Health Study, the estimated prevalences of CSA and OSA are 0.9% and 47.6%, respectively.[1] Risk factors for CSA include age (>65 years), male gender, history of heart failure, history of stroke, other medical conditions (acromegaly, renal failure, atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases), and opioid use. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, morning headaches, and are at higher risk for accidents and injuries.

TREATMENT

The goal of treatment is to normalize sleep-related breathing patterns. Because most cases of CSA are secondary to an underlying condition, central nervous system pathology, or medication side effects, treatment of the underlying condition or removal of the medication, may improve CSA.

Treatment recommendations differ depending on the classification of CSA as either hyperventilation-related (most common, including primary CSA and those relating to heart failure or high altitude breathing) or hypoventilation-related (less common, relating to central nervous system diseases or use of nervous system suppressing drugs such as opioids).

For patients with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first- line therapy. Due to CPAP discomfort, patient compliance may become an issue. Supplemental oxygen during sleep may be considered for patients experiencing hypoxia during sleep or who cannot tolerate CPAP. Patients with CSA due to heart failure and with an ejection fraction >45% and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure (BPAP) or adaptive servo-ventilation (ASV) as second-line therapy. BPAP devices have two pressure settings, one for inhalation and one for exhalation. ASV uses both inspiratory and expiratory pressure, and titrates the pressure to maintain adequate air movement. However, a clinical trial reported increased cardiovascular mortality with ASV in patients with CSA due to heart failure and with an ejection fraction <45%,[2] and therefore, ASV is not recommended for this group.

For patients with hypoventilation-related CSA, first-line therapy is BPAP.

Pharmacologic therapy with a respiratory stimulant may be recommended to patients with hyper- or hypoventilation CSA who do not benefit from positive airway pressure devices, though close monitoring is necessary due to the potential for adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

PHRENIC NERVE STIMULATION

Currently, there is one phrenic nerve stimulation device approved by the Food and Drug Administration (FDA), the remedē System (Respicardia, Inc.). The remedē System is an

implantable device that stimulates the phrenic nerve in the chest which sends signals to the diaphragm to restore a normal breathing pattern. A cardiologist implants the battery powered device under the skin in the right or left pectoral region. The procedure is conducted using local anesthesia. The device has two leads, one to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and one to sense breathing. The device runs on an algorithm that activates automatically at night when the patient is in a sleeping position, and suspends therapy when the patient sits up. Patient-specific changes in programming can be conducted externally by a programmer.

REGULATORY STATUS

In October 2017, the FDA granted approval for the remedē System (Respicardia, Inc; Minnetonka, MN) through the premarket approval application process. The approved indication is for treatment of moderate to severe central sleep apnea in adults. Product code: PSR.

EVIDENCE SUMMARY

Outcomes of interest include sleep quality metrics and quality of life measures. The Apnea-Hypopnea Index (AHI) is the number of apnea and hypopnea (events per hour of sleep, in which the apnea events last at least 10 seconds and are associated with decreased blood oxygenation. In adults, the AHI scale is: <5 AHI (normal); 5<AHI<15 (mild); 15<AHI<30 (moderate); and>30 AHI (severe). Additional sleep metrics include central apnea index (CAI, number of central apnea events per hour of sleep) and obstructive apnea index (OAI, number of obstructive apnea events per hour of sleep).

Quality of life outcomes can be measured by the Epworth Sleepiness Scale (ESS) or a Patient Global Assessment. The ESS is a short, self-administered questionnaire that asks patients how likely they are to fall asleep (0="no chance" to 3="high chance") in 8 different situations (e.g., watching TV, sitting quietly in a car, or sitting and talking to someone). The scores are added, ranging from 0 to 24, with scores over 10 indicating excessive sleepiness and recommendation to seek medical attention.

SYSTEMATIC REVIEWS

Luni (2020) reported a meta-analysis of five studies (n=204) evaluating the efficacy of transvenous neurostimulation of the phrenic nerve for central sleep apnea.[3] An analysis of the pooled data demonstrated a reduction of mean AHI in the stimulation group compared to the control group by 26.7 events/hour (95% CI -31.99 to -21.46, p 0.00), and a mean AHI difference of -22.47. Compared with the control group, the mean reduction in the oxygen desaturation index of 4% or more was decreased in the stimulation group by -24.16 events/hour (95% CI -26.20 to -22.12, p 0.00).

RANDOMIZED CONTROLLED TRIAL

Costanzo (2015) provided background and methodologic details of the remedē System Pivotal Trial.[4] The trial is a prospective, multicenter, randomized, open-label controlled trial comparing transvenous unilateral phrenic nerve stimulation with no stimulation in patients with CSA of various etiologies (Table 1). All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group (n=73) and activation after six months in the control group (n=78). Activation is delayed one month after implantation to allow for lead healing. The primary efficacy endpoint is percentage of patients

achieving a reduction in Apnea-Hypopnea Index (AHI) of 50%, as interpreted from polysomnography by an assessor blinded to treatment arm. The reduction of 50% was based on assessments showing that a 50% reduction in AHI is associated with reduced mortality risk and is therefore clinically meaningful. Secondary endpoints include mean reductions in CAI, AHI, arousal index, OD14, and Epworth Sleepiness Scale. Quality of life is measured by Patient Global Assessment (PGA), which consists of a 7-point scale (1="markedly improved" to 7="markedly worsened"). Of the 151 patients in the trial, 64% had heart failure, 42% had atrial fibrillation, and a mean left ventricular ejection fraction of 39.6. Six-month per protocol comparative results for the treatment and control groups were published in 2016 by Costanzo .[5] Adverse events were reported in 9% of the intervention group and 8% of the control group (for example, implant site infection, implant site hematoma, and lead dislodgement). Non-serious therapy-related discomfort was reported in 27 (37%) of the intervention group, with all but one case resolved by system reprogramming.

Costanzo (2018) provided 12 months followup results for the intervention arm.[6] At six months followup, 15 of the 73 (21%) in the treatment group were excluded due to no six-month data (n=9: unrelated death, device explant, missed visit, study exit), failed inclusion criteria (n=3), unsuccessful implant (n=2), therapy programmed off (n=1). At 12 months followup, an additional four patients were lost due to unrelated death, device explant, patient refusal, and missed visit. Results from the remaining 54 patients in the intervention group are summarized in Table 3. Subgroup analyses showed consistent improvements in percent experiencing >50% AHI reductions from treatment across all of the following subgroups: age (<65, 65 to <75, and >75), gender, heart failure (yes/no), defibrillator (yes/no), AHI severity (moderate/severe), and atrial fibrillation (yes/no).

Another publication by Costanzo in 2018 provided 12-months follow-up results for the subgroup of patients in the Pivotal Trial who had heart failure.[7] Pooling of results was possible by using 6 and 12 month data from the intervention group and 12 and 18 month data from the control group (the phrenic nerve stimulator was activated in the control group six months after implantation). At baseline, 96 of the patients in the trial had heart failure. By the six-month followup, there had been four deaths, one explant, and five withdrew from the study. By the 12-month followup, there had been an additional five deaths, one implant, and one withdrawal, as well as four missing the final visit. Results at 6 and 12 months followup for the subgroup of patients with heart failure are summarized in Table 2.

Follow-up at 24 months was available for 42 patients in the treatment group, while 22 patients in the treatment group and 28 patients in the control arm had reached 36 month follow-up at the time of study closure.[8] Central apnea events remained low throughout follow-up with a median time to battery depletion of 39.4 months. Median AHI at 24 months and 36 months was 16 and 13, respectively. Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 10% of patients through the 24-month visit. All were reported to be resolved with remedē System revisions or programming.

Five-year outcomes of the Pivotal Trial were published in 2021.[9] Patients in the treatment group and those in the control group, who had therapy activated after the primary endpoint assessment at the six-month visit, were pooled. The 42 patients evaluated for five-year outcomes had a change from baseline of -22 for AHI ($p<0.001$), -23 for CAI ($p<0.001$), 1 for OAI ($p=0.003$), and -5 for ESS ($p=0.008$). Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 15% of patients through the five-year visit, none of which caused long-term harm.

An analysis of the pivotal trial data for safety and efficacy of TPNS in patients with concomitant cardiovascular implantable electronic devices (CIEDs) was reported by Nayak (2020).[10] Of the 151 initially enrolled patients, 64 had a concomitant CIED. There was no difference in safety or efficacy between patients with and without CIEDs.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Intervention	Control
Costanzo (2015)[4]	Germany, Poland, United States	31	2013-2015	Adult patients with moderate to severe CSA of various etiologies confirmed by PSG[a] and medically stable[b]	Implanted phrenic nerve stimulator (remede system) activated at 1 month postprocedure (n=73)	Implanted phrenic nerve stimulator (remede system) activated at 6 months postprocedure (N=78)

[a] AHI>20 events/hr; CAI>50% of all apneas, with>30 central apnea events; OAI<20% of all AHI
[b] For 30 days prior to baseline testing: no hospitalizations for illness, no breathing mask-based therapy, and on stable medications and therapies.
AHI: apnea-hypopnea index; CSA: central sleep apnea; PSG: polysomnography.

Table 2. Summary of Key RCT Results

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo (2018)[5]				
>50% AHI reduction				
Treatment, n=58	NA	51% (39% to 64%)	NA	
Control, n=73	NA	11% (5% to 20%)	NA	41% (25% to 54%)
AHI				
Treatment, n=58	49.7 ± 18.9	25.9 ± 20.5	-23.9 ± 18.6	
Control, n=73	43.9 ± 17.3	45.0 ± 20.3	1.1 ± 17.6	-25.0 ± 18.1
CAI				
Treatment, n=58	31.7 ± 18.6	6.0 ± 9.2	-25.7 ± 18.0	
Control, n=73	26.2 ± 16.2	23.3 ± 17.4	-2.9 ± 17.7	-22.8 ± 17.8
PGA				
Treatment, n=58	NA	60% (47% to 73%)	NA	
Control, n=73	NA	6% (2% to 14%)	NA	55% (40% to 68%)
ESS				
Treatment, n=58	10.7 ± 5.3	7.1 ± 4.1	-3.6 ± 5.6	
Control, n=73	9.3 ± 5.7	9.4 ± 6.1	0.1 ± 4.5	-3.7 ± 5.0
	Baseline	**6-Month**	**12-Month**	**Paired Change, Baseline to 12-Month Mean (95% CI)**
Costanzo (2018)[6]				
Treatment arm alone, N	58	58	54	54
AHI	49.7 ± 18.9	25.9 ± 20.5	23.0 ± 21.9	-25.4 (-44.4 to -11.4)
CAI	31.7 ± 18.6	6.0 ± 9.2	3.4 ± 6.9	-26.0 (-40.2 to -14.6)
OAI	2.1 + 2.2	6.3 + 7.0	4.5 + 5.1	0.9 (-0.5 to 4.4)
PGA[b]	NA	60% (47% to 72%)	60% (47% to 72%)	NA
ESS	10.7 + 5.3	7.1 + 4.1	6.5 + 3.5	-4.0 (-7.0 to -1.0)

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo (2018)[7]				
Pooled HF subgroup, N	96	86	75	79
≥50% AHI reduction	NA	53% (42% to 64%)	57% (45% to 68%)	NA
AHI	47.1 ± 18.5	25.2 ± 14.2	3.5 ± 6.5	-19.9 (-34.6 to -11.8)
CAI	26.2 ± 17.7	4.1 ± 6.0	3.4 ± 6.9	-26.0 (-40.2 to -14.6)
PGA[b]	NA	58% (NR)	55% (NR)	NA
ESS	8.9 ± 5.1	6.2 ± 4.1	6.1 ± 3.7	-2.0 (-5.0 to 0.0)

[a] Data are presented as either % (95% confidence intervals) or mean (standard deviation)
[b] Patients with marked or moderate improvement in 7-point quality of life scale
AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; HF: heart failure; NA: not applicable; NR: not reported; OAI: obstructive apnea index; PGA: Patient Global Assessment; RCT: randomized controlled trial; SD: standard deviation.

An analysis of the Pivotal Trial data to compare PAP-naïve and prior PAP-treated patients was completed by Schwartz (2021).[11] At baseline, CSA was more severe and symptomatic in the PAP-treated vs. PAP-naïve group (median AHI 52/h vs. 38, central apnea index (CAI) 32/h vs. 18, ESS 13 vs. 10, fatigue severity scale 5.2 vs. 4.5). Active therapy resulted in statistically significant improvements in polysomnographic metrics ($p<0.001$ for AHI, 4% ODI, arousal index, and CAI), with little or no change in the inactive control group. Of PAP-treated and PAP-naïve patients, 98% and 94% indicated they would undergo the implant again.

Baumert (2023) published an analysis of effect of transvenous phrenic nerve stimulation (TPNS) on the composition of the nocturnal hypoxemic burden in patients with CSA using data from the Pivotal Trial.[12] TPNS titrated to reduce respiratory events significantly reduced the ODI in the treatment group more than the control group (-15.85 h-1 ± 1.99, +1.32 h-1 ± 1.85; $p < 0001$) and shortened the relative T90 duration by -3.81 percentage points ± 1.23 vs. 0.49 percentage points ± 1.14 increase ($p = 0.012$). This shortening of T90 was primarily accomplished by reducing the brief cyclic desaturations (T90desaturation: -4.32 percentage points ± 0.98 vs. 0.52 percentage points ± 0.91, $p = 0.0004$) while notable non-specific drifts in SpO2 remained unchanged (T90 non-specific: 0.18 percentage points ± 0.62 vs. -0.13 percentage points ± 0.57; $p = 0.72$). The authors conclude that TPNS reduces the nocturnal hypoxemic burden due to sleep-disordered breathing, and that a considerable nocturnal hypoxemic burden from other sources remains.

Baumert (2023) also published a separate analysis of effect of transvenous phrenic nerve stimulation (TPNS) on nocturnal heart rate perturbations in patients with CSA using data from the Pivotal Trial.[13] TPNS titrated to reduce respiratory events is associated with reduced cyclical heart rate variations in the very low-frequency domain across REM (VLFI: 4.12 ±0.79 % vs. 6.87 ± 0.82 %, $p = 0.02$) and NREM sleep (VLFI: 5.05 ± 0.68 % vs. 6.74 ± 0.70 %, $p = 0.08$) compared to the control group. Low-frequency oscillations were reduced in the treatment arm in REM ($p=0.02$) and NREM sleep ($p=0.03$). The authors concluded that long-term follow-up studies are needed to determine if the reduction in heart rate perturbation by TPNS translates to cardiovascular mortality reduction.

NON-COMPARATIVE STUDIES

Fox (2017) presented data on long term durability of the remedē System, measuring battery lifetime, device exchangeability, lead position stability, and surgical accessibility.[14] Three

consecutive patients, mean age 75.7 years, with CSA and HF with preserved ejection fraction were implanted with the remede phrenic nerve stimulation device due to intolerability of conventional mask therapy. Implantation occurred in 2011 and the patients were followed for four years. Mean battery life duration was 4.2+ 0.2 years. Therapy was well tolerated by the patients, with improvements sustained in AHI, oxygen desaturation index, and quality of life (measured by ESS). Mean device replacement procedure time was 23 minutes, under local anesthesia, with a two-day hospital stay.

Abraham (2015)[15] and Jagielski (2016)[16] presented 6-month and 12-month results from a cohort of 47 patients with CSA of various etiologies who received phrenic nerve stimulation with the remedē system. . Sleep disorder parameters were measured by polysomnography, through 12 months, with an optional sleep testing at 18 months. . Quality of life was measured on a seven-point scale, with patients answering the question, "How do you feel today compared with how you felt before having your device implanted?" CSA etiologies included heart failure (79%), other cardiac (13%), and opiate use (4%). Three deaths occurred during the study period, none attributed to the intervention. Five experienced serious adverse events, three at the beginning of the study (two [hematoma, migraine] due to implantation procedure and one chest pain), and two during 12-month followup (pocket perforation and lead failure). A summary of sleep metric and quality of life results are presented in Table 3.

Table 3. Summary of Non-Comparative Study Results[15, 16]

Outcome	Baseline (n=47) mean± SD	3 months (n=47) mean± SD	6 months (n=41) mean± SD	12 months (n=41) mean± SD	18 months (n=17) mean± SD
AHI, events/hour	49.9± 14.6	22.4± 13.6	23.8± 13.1	27.5± 18.3[b]	24.9± 13.5[b]
CAI, events/hour	28.0± 14.2	4.7± 8.6	4.6± 7.4	6.0± 9.2[b]	4.8± 5.8[b]
OAI, events/hour	3.0± 2.9	3.9± 4.7	3.9± 5.4	4.5± 6.0	5.6± 6.2
4% ODI, events/hour	45.2± 18.7	21.6± 13.7	23.1± 13.1	26.9± 18.0[b]	25.2± 13.7[b]
Arousal index, events/hour	36.2± 18.8	23.7± 10.6	25.1± 12.5	32.1± 15.2	26.8± 9.2
QOL, % improvement from baselinea	NA	70.8%	75.6%	83.0%	NR

[a] Patients with marked or moderate improvement in 7-point quality of life scale

[b] p<0.006 compared to baseline

AHI: Apnea-Hypopnea Index; CAI: central apnea index; NA: not applicable; NR: not reported; OAI: obstructive apnea index; ODI: oxygen desaturation index; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation.

SUMMARY OF EVIDENCE

For individuals with central sleep apnea who receive phrenic nerve stimulation, the evidence includes one randomized controlled trial (RCT) and observational studies. Relevant outcomes are change in disease status, functional outcomes, and quality of life. The RCT compared the use of phrenic nerve stimulation to no treatment among patients with central sleep apnea of various etiologies. All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group and activation after six months in the control group. Activation is delayed one month after implantation to allow for lead healing. At six months follow-up, the patients with the activated device experienced significant improvements in several sleep metrics and quality of life measures. At 12 months

followup, patients in the activated device arm showed sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis of patients with heart failure combined 6 and 12 month data from patients in the intervention group and 12 and 18 month data from the control group. Results from this subgroup analyses showed significant improvements in sleep metrics and quality of life at 12 months compared with baseline. Results from observational studies supported the results of the RCT. No RCTs were identified in which phrenic nerve stimulation was compared with the current standard of care, positive airway pressure or respiratory stimulant medication. An invasive procedure would typically be considered appropriate only if non-surgical treatments had failed, but there is very limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure or respiratory stimulant medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified with recommendations regarding the use of phrenic nerve stimulation for central sleep apnea.

SUMMARY

There is not enough research to know if or how well phrenic nerve stimulation works to treat central sleep apnea. This does not mean that it does not work, but more research is needed to know. There are no clinical practice guidelines based on research that recommend phrenic nerve stimulation for this population. Therefore, the use of phrenic nerve stimulation for the treatment of central sleep apnea is considered investigational.

REFERENCES

1. Donovan LM, Kapur VK. Prevalence and Characteristics of Central Compared to Obstructive Sleep Apnea: Analyses from the Sleep Heart Health Study Cohort. *Sleep.* 2016;39:1353-9. PMID: 27166235
2. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *The New England journal of medicine.* 2015;373(12):1095-105. PMID: 26323938
3. Luni FK, Daniels J, Link MS, et al. Meta-analysis of Usefulness of Phrenic Nerve Stimulation in Central Sleep Apnea. *The American journal of cardiology.* 2020;125(11):1738-44. PMID: 32295701
4. Costanzo MR, Augostini R, Goldberg LR, et al. Design of the remede System Pivotal Trial: A Prospective, Randomized Study in the Use of Respiratory Rhythm Management to Treat Central Sleep Apnea. *Journal of cardiac failure.* 2015;21(11):892-902. PMID: 26432647
5. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet.* 2016;388(10048):974-82. PMID: 27598679
6. Costanzo MR, Ponikowski P, Javaheri S, et al. Sustained 12 Month Benefit of Phrenic Nerve Stimulation for Central Sleep Apnea. *The American journal of cardiology.* 2018;121(11):1400-08. PMID: 29735217

7. Costanzo MR, Ponikowski P, Coats A, et al. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *European journal of heart failure.* 2018;20(12):1746-54. PMID: 30303611
8. Fox H, Oldenburg O, Javaheri S, et al. Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea. *Sleep.* 2019;42(11). PMID: 31634407
9. Costanzo MR, Javaheri S, Ponikowski P, et al. Transvenous Phrenic Nerve Stimulation for Treatment of Central Sleep Apnea: Five-Year Safety and Efficacy Outcomes. *Nat Sci Sleep.* 2021;13:515-26. PMID: 33953626
10. Nayak HM, Patel R, McKane S, et al. Transvenous Phrenic Nerve Stimulation for Central Sleep Apnea is Safe and Effective in Patients with Concomitant Cardiac Devices. *Heart rhythm.* 2020. PMID: 32619739
11. Schwartz AR, Goldberg LR, McKane S, et al. Transvenous phrenic nerve stimulation improves central sleep apnea, sleep quality, and quality of life regardless of prior positive airway pressure treatment. *Sleep Breath.* 2021. PMID: 33745107
12. Baumert M, Immanuel S, McKane S, et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnea reduces episodic hypoxemic burden. *Int J Cardiol.* 2023;378:89-95. PMID: 36841294
13. Baumert M, Linz D, McKane S, et al. Transvenous phrenic nerve stimulation is associated with normalization of nocturnal heart rate perturbations in patients with central sleep apnea. *Sleep.* 2023. PMID: 37284759
14. Fox H, Bitter T, Horstkotte D, et al. Long-Term Experience with First-Generation Implantable Neurostimulation Device in Central Sleep Apnea Treatment. *Pacing and clinical electrophysiology : PACE.* 2017;40(5):498-503. PMID: 28211952
15. Abraham WT, Jagielski D, Oldenburg O, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. *JACC Heart failure.* 2015;3(5):360-69. PMID: 25770408
16. Jagielski D, Ponikowski P, Augostini R, et al. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnoea: 12 months' experience with the remede((R)) System. *European journal of heart failure.* 2016;18(11):1386-93. PMID: 27373452

CODES

Codes	Number	Description
		~~Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)~~ (Deleted
	~~0425T~~	~~;sensing lead only~~ (Deleted 01/01/2024)
	~~0426T~~	~~;stimulation lead only~~ (Deleted 01/01/2024)
	~~0427T~~	~~;pulse generator only~~ (Deleted 01/01/2024)
	~~0428T~~	~~Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only~~ (Deleted 01/01/2024)
	~~0429T~~	~~;sensing lead only~~ (Deleted 01/01/2024)
	~~0430T~~	~~;stimulation lead only~~ (Deleted 01/01/2024)
	~~0431T~~	~~Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only~~ (Deleted 01/01/2024)
	~~0432T~~	~~Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only~~ (Deleted 01/01/2024)

Codes	Number	Description
	~~0433T~~	~~;sensing lead only~~ (Deleted 01/01/2024)
	~~0434T~~	~~Interrogation device evaluation implanted neurostimulator pulse generator system for~~ (Deleted 01/01/2024)
	~~0435T~~	~~Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session~~ (Deleted 01/01/2024)
	~~0436T~~	~~;during sleep study~~ (Deleted 01/01/2024)
	33276	Insertion of phrenic nerve stimulator system (pulse generator and stimulating lead[s]), including vessel catheterization, all imaging guidance, and pulse generator initial analysis with diagnostic mode activation, when performed
	33277	Insertion of phrenic nerve stimulator transvenous sensing lead (List separately in addition to code for primary procedure)
	33278	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; system, including pulse generator and lead(s)
	33279	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s) only
	33280	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator only
	33281	Repositioning of phrenic nerve stimulator transvenous lead(s)
	33287	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator
	33288	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s)
	93150	Therapy activation of implanted phrenic nerve stimulator system, including all interrogation and programming
	93151	Interrogation and programming (minimum one parameter) of implanted phrenic nerve stimulator system
	93152	Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography
	93153	Interrogation without programming of implanted phrenic nerve stimulator system
HCPCS	C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

Date of Origin: *June 2019*

Regence

Medical Policy Manual Surgery, Policy No. 213

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites

Effective: January 1, 2024

Next Review: July 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) are radiotherapy techniques that use highly focused radiation beams to treat both neoplastic and non-neoplastic conditions, in contrast to traditional external radiation beam therapy, which involves the use of relatively broad fields of radiation over a number of sessions that may occur over weeks to months.

MEDICAL POLICY CRITERIA

I. Stereotactic radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Body Radiotherapy (SABR), may be considered **medically necessary** for initial treatment or treatment of recurrence for any of the following indications:

   A. Primary neoplasms of the CNS (See Policy Appendix I at the end of the policy), including but not limited to low grade gliomas and high-grade gliomas

   B. Metastatic lesion(s) to the CNS (solitary or multiple) in patients with a current Karnofsky performance score greater than or equal to 60 or a current ECOG score less than or equal to 2 (See Policy Guidelines)

C. Arteriovenous malformations

D. Chordomas and chondrosarcomas of the skull base

E. Craniopharyngiomas

F. Refractory epilepsy when the following criteria are met:

1. Any seizure activity despite treatment with at least two antiepileptic regimens; and
2. Documentation of clinical agreement of medical appropriateness from a neurosurgeon or multidisciplinary body of physician consultants.

G. Essential tremor or Parkinson's disease when the following criteria are met:

1. Symptoms are ongoing despite treatment with at least two drug regimens; and
2. Documentation of clinical agreement of medical appropriateness from a neurosurgeon or multidisciplinary body of physician consultants.

H. Head and neck cancers within intracranial, skull base, and orbital sites, when there is documented prior radiation treatment to the planned target volume

I. Hemangioblastoma within intracranial, skull base, and orbital sites

J. Hemangiopericytoma within intracranial, skull base, and orbital sites

K. Glomus jugulare and Glomus tympanicum tumors

L. Meningiomas, benign, atypical, or malignant

M. Pituitary adenomas

N. Schwannomas (see Policy Guidelines)

O. Trigeminal neuralgia (tic douloureux) refractory to medical management

P. Uveal melanoma

II. Stereotactic radiosurgery and stereotactic body radiation therapy (also known as Stereotactic ablative body radiotherapy) are considered **investigational** when Criterion I. is not met and for all other intracranial, skull base, and orbital indications including but not limited to cavernous malformations, choroidal neovascularization (CNV), chronic pain, and functional disorders other than trigeminal neuralgia and essential tremor.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

For the purposes of this policy, neoplasm is defined as “an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer).”[1]

SCHWANNOMAS

Schwannomas are tumors that occur along nerves. They are typically benign but may be malignant. These may also be referred to as neuromas, neurinomas "of Verocay" or

neurilemmomas. A common type of schwannoma is a vestibular schwannoma, which is also known as an acoustic neuroma.

PERFORMANCE STATUS MEASUREMENT

Performance status is frequently used in oncology practice as a variable in determining prognosis and management strategies. Either the Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) Performance Status scoring systems may be used.

Karnofsky Performance Status

100	Normal, without symptoms
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance; able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated
20	Very sick; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly

ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

FRACTIONATION

Fractionated stereotactic radiotherapy refers to when SRS or SBRT are performed more than once on a specific site. SRS is commonly delivered in 1 fraction and SBRT or SABR is commonly delivered in 2-5 fractions.

DOSE CONSTRAINT REFERENCES

Radiation Therapy Oncology Group (RTOG) Radiation Dose Constraints

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/RTOG

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/QUANTEC

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History/Physical and Chart notes, including requirements as outlined by the policy criteria, as applicable to the indication for treatment.
- As applicable, documentation of sites, size and number of lesions
- As applicable, documented ECOG score or Karnofsky performance score

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
2. Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid, Medicine, Policy No. 164
3. Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, Pelvis, and Extremities, Medicine, Policy No. 165
4. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
5. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214
7. Responsive Neurostimulation, Surgery, Policy No. 216

BACKGROUND

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) rely on three-dimensional imaging to localize the therapy target. SRS and SRBT have been used for a range of malignant and non-malignant conditions. Because they are more targeted than traditional external radiation therapy, SRS and SRBT are often used for treatment at sites that are difficult to reach via surgery, located close to other vital structures, or subject to movement within the body. The term SBRT will be used to describe treatment also referred to as stereotactic ablative body radiotherapy (SABR).

SRS and SBRT (or SABR) employ similar technological "stereotactic" sophistication with elements of advanced pretreatment imaging for localization of target(s), patient immobilization, control of breathing associated tumor movement, focally targeted treatment planning, and daily image guidance to ensure precise delivery of high daily doses of radiation. As commonly used in the medical literature, SRS refers to intracranial treatments and SBRT refers to extracranial treatments. Alternatively, SRS and SBRT may be defined independent of whether treatment is directed to intra or extra cranial tumors volumes. According to this definition, when such treatment is given as a single fraction, it may be referred to as SRS, and when it is delivered in 2-5 fractions it may be referred to as SBRT or SABR.

The fractionation used for SRS and SBRT is referred to as “hypofractionated” because it is fewer treatments than those used for conventional external beam radiotherapy.” Fractionation of stereotactic radiotherapy aims to optimize the therapeutic ratio; that is the ratio between tumor control and late effects on normal tissues. The main advantage of fractionation is that it allows higher total doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues to each individual, fractionated dose. In addition, some lesions

such as large arteriovenous malformations may require more than one procedure to complete the obliteration process.

SRS and SBRT can be administered by several types of devices that are distinguished by their source of radiation, including particle beams (e.g., proton), gamma radiation from cobalt-60 sources, or high-energy photons from linear accelerator (LINAC) systems. The Gamma Knife and linear accelerator systems (including the Cyberknife®) are similar in concept; both use multiple photon radiation beams that intersect at a stereotactically determined target, thus permitting higher doses of radiation delivery with sparing of surrounding normal tissues. The differences between the two relate to how the energy is produced (i.e., through decaying cobalt-60 in the gamma knife devices, or from x-rays in the linear accelerator system) and the number of energy sources used (i.e., multiple energy sources in the gamma knife versus one in the linear accelerator system).

In the United States, certain racial/ethnic groups continue to be at an increased risk of developing or dying from particular cancers. Black men have the highest rate of new cancer diagnoses and Black men and women experience the highest rate of cancer-related death. American Indians and Alaska Natives are disproportionally affected by kidney cancer and also have higher death rates from this cancer when compared to other racial/ethnic groups.

Studies have demonstrated that there are socioeconomic disparities with regard to access to radiation therapy, particularly for patients in ethnic minority groups and those living in rural areas.

IMAGE-GUIDED RADIOSURGERY OR RADIOTHERAPY

Image-guided radiosurgery or radiotherapy is a relatively new development collectively describing units with real-time image guidance systems. Examples include the Cyberknife® device, BrainLAB Novalis®, TomoTherapy®, and LINAC with computerized tomography (CT).

REGULATORY STATUS

Several devices that use cobalt 60 radiation (gamma ray devices) for SRS have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The most commonly used gamma ray device is the GammaKnife (Elekta; approved May 1999). Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by the FDA through the 510(k) premarket notification process including the Novalis Tx®

(Novalis, Westchester, IL); the TrueBeam STx (Varian Medical Systems, Palo Alto, CA, approved December 2012); and the CyberKnife® System (Accuray, Inc.; approved December 1998). LINAC-based devices may be used for intracranial and extracranial lesions.

Note: Particle radiation can also be used without stereotactic guidance. In this setting, the use of particles is referred to as proton, helium, or neutron radiation *therapy*. Proton or helium ion radiation therapies (RT), intraocular RT for age-related macular degeneration, and electromagnetic navigation bronchoscopy for placement of fiducial markers are considered in separate medical policies. See cross-reference section below.

EVIDENCE SUMMARY

The selection of variables used in the delivery of SRS and SBRT is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins All of these variables depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Trials that allow direct comparison of all of the possible variables involved in selecting specific SRS and SBRT methods do not broadly exist making it difficult to draw comparative effectiveness conclusions. Further, for many rare conditions, large comparative studies are unlikely. The evidence below will focus on indications with criteria and investigational indications.

Please note that the evidence review below does not compare specific radiation planning and delivery techniques.

TRIGEMINAL NEURALGIA

Tuleasca published a 2018 systematic review of SRS for trigeminal neuralgia to support the development of a guideline endorsed by the International Society of Stereotactic Radiosurgery (ISRS). A total of 65 studies met inclusion criteria, with a total of 6461 patients. One study was prospective and the remainder were retrospective. Crude rates of hypesthesia ranged from 0% to 68.8% (mean 21.7%, median 19%) for gamma knife surgery (GKS), from 11.4% to 49.7% (mean 27.6%, median 28.5%) for LINAC, and from 11.8% to 51.2% (mean 29.1%, median 18.7%) for CyberKnife radiosurgery. Other toxicities reported were dysesthesias, paresthesias, dry eye, deafferentation pain, and keratitis. Actuarial initial freedom from pain without medication was reported to be 28.6% to 100% (mean 53.1%, median 52.1%), 17.3% to 76% (mean 49.3%, median 43.2%), and 40% to 72% (mean 56.3%, median 58%) for GKS, LINAC, and CyberKnife radiosurgery, respectively. Recurrence rates were reported as ranges of 0 to 52.2% (mean 24.6%, median 23%), 19% to 63% (mean 32.2%, median 29%), and 15.8% to 33% (mean 25.8%, median 27.2%) for GKS, LINAC, and CyberKnife radiosurgery, respectively. The authors concluded that although the evidence is limited, radiosurgery is a safe and effective therapy for drug-resistant trigeminal neuralgia.

In 2017, Gubian and Rosahl published a meta-analysis of the safety and efficacy of SRS and microsurgery for trigeminal neuralgia. PRISMA guidelines were followed. A total of 53 studies met inclusion criteria. Success rates initially and at last follow-up (>five years after intervention) were 71.1% and 63.8% for SRS and 86.9% and 84% for microsurgery, respectively. Mean percentage of recurrence at 36-months post-intervention was 25% for SRS and 11% for microsurgery (p=0.0015). The length of recurrence-free intervals was not significantly different between SRS and microsurgery (30.45 and 30.55 months, respectively; p=0.987). The difference in incidence of hearing loss was also not significant (SRS 1.51% vs microsurgery 0.74%), but facial dysesthesia was more frequent in the SRS group (2.3% versus 28.8% for microsurgery; p=0.02).

A 2011 Cochrane systematic review of 11 trials of neurosurgical interventions for trigeminal neuralgia found that there was very low-quality evidence for the efficacy of most neurosurgical procedures for trigeminal neuralgia because of the poor quality of the trials.[2] All procedures produced variable pain relief, but many resulted in sensory side effects. There were no studies of microvascular decompression which observational data suggests gives the longest pain relief. Only one study was identified that used radiosurgery. The trial was intended to determine if increasing the nerve length within the SRS treatment volume would change

outcomes. The study was stopped before accrual was completed and it was noted that pain measurements using validated scales were not made either before or after surgery.

Other nonrandomized studies and case series have reported on the use of SRS for trigeminal neuralgia.[3-8]

Section Summary

Case series identify improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluate the use of SRS compared with alternative treatments for trigeminal neuralgia are lacking. Only one study specifically addressed the use of radiosurgery and it was stopped before accrual was completed.

REFRACTORY EPILEPSY

Barbaro (2018) published the results of the first randomized controlled trial comparing SRS for the treatment of pharmacoresistant unilateral mesial temporal lobe epilepsy to anterior temporal lobectomy (ATL), the ROSE trial.[9] A total of 37 (64%) patients achieved seizure remission, with 16 (52%) in SRS and 21 (78%) in ATL. Noninferiority of SRS compared to ATL was not demonstrated. SRS did not confer sparing of verbal memory deficits compared to ATL. QOL scores improved significantly in the SRS group at 24 months and remained steady at 36 months, in contrast to the ATL group in whom QOL score improvement was immediately noticeable at 12 months. Adverse events were anticipated cerebral edema and related symptoms for some SRS patients, and cerebritis, subdural hematoma, and others for ATL patients. These all resolved with appropriate protocol specified interventions.

Quigg (2018) published a follow-up report on visual field defects (VFD) observed in patients treated during the ROSE trial.[10] Out of 58 treated patients, 29/31 (93.5%) SRS patients and 25/27 (92.6%) ATL patients completed visual field testing. Ninety-three percent of patients treated with SRS reported VFD compared to 88% of patients treated with ATL (p=0.65). Younger age at diagnosis correlated with worse outcomes; this significance was stronger in the SRS arm compared to the ATL arm (p=0.04 and 0.20), but this difference was not significant upon multivariable regression. Presence or absence of VFD was not correlated with either seizure remission (p=0.22 and p=1.00) or driving status (p=0.53 and p=1.00) for the SRS or ATL treatment arms, respectively.

A 2018 systematic review by Eekers reported on 16 studies including a total of 170 patients.[11] Methodological quality of the included studies was graded using a modified QUADAS checklist. Limitations of the reviewed studies include a lack of control groups and poorly defined exclusion criteria. SRS was reported to have a positive effect on seizure outcome, defined as the total percentage of radiotherapy-adapted Engel class (RAEC) I and II patients, in 12 studies. No favorable effect on seizure outcome was found in two studies, although these contained only two and three patients, respectively. Toxicities reported include radionecrosis, impaired cognitive functioning, and headache, nausea, and vomiting related to increased intracranial pressure and edema. Subsequent resection was reported in nine of the studies. In those studies, 20% of patients underwent subsequent resection. Reasons reported were persisting seizures, cyst formation, edema, intracranial hypertension, and radionecrosis. Authors concluded that there is only level 4 evidence of primary radiotherapy reducing seizure frequency in adult patients and that prospective randomized trials are needed to determine its value.

McGonigal (2017) performed a systematic review of SRS for drug-resistant epilepsy and assessed the level of evidence according to the PRISMA guidelines.[12] A total of 55 articles met inclusion criteria. Level 2 evidence (prospective studies) indicated that SRS may result in superior neuropsychological outcomes and quality of life compared to microsurgery for mesial temporal lobe epilepsy and that SRS has a better risk-benefit ratio for small hypothalamic harmatomas compared to surgical methods. Only Level 4 evidence (case reports, prospective observational studies, and retrospective case series) was available for the other indications and no Level 1 evidence was identified.

In 2016, Feng published a systematic review and meta-analysis of data from 13 studies on the use of SRS to treat mesial temporal lobe epilepsy.[13] They calculated approximately half of the patients were seizure free over a follow-up period that ranged from six months to nine years (pooled estimate, 50.9%; 95% CI, 38.1% to 63.6%), with an average of 14 months to seizure cessation (pooled estimate, 14.08 months; 95% CI, 11.95 to 12.22 months). Nine of 13 included studies reported data for adverse events, which included visual field deficits and headache (the two most common adverse events), verbal memory impairment, psychosis, psychogenic nonepileptic seizures, and dysphasia. Patients in the individual studies experienced adverse events at rates that ranged from 8%, for nonepileptic seizures, to 85%, for headache.

A 1998 TEC Assessment[14] cited two studies of 11 and 9 patients, respectively, in which radiosurgery was used to treat epilepsy. The subsequent literature search revealed three small studies on the use of radiosurgery for medically refractory epilepsy. Regis (2000)[15] selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided minimum two-year follow-up. Seizure-free status was achieved in 13 patients, two patients were improved, and three patients had radiosurgery-related visual field defects.

A study by Schrottner (1998)[16] included 26 patients with tumor-related epilepsy, associated mainly with low-grade astrocytomas. Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in six (three with generalization) and complex partial in 18 (five with generalization, one gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in four patients and none in seven. Whang and Kwon (1996)[17] performed radiosurgery in 31 patients with epilepsy associated with nonprogressive lesions. A minimum of one-year follow-up was available in 23 patients, 12 of whom were seizure-free (and three of whom had antiseizure medications discontinued), two had seizures reduced in frequency, and nine experienced no change. While the Regis series selected a fairly homogeneous clinical sample, the other two studies were heterogeneous.

Section Summary

For individuals with epilepsy refractory to medical management, the evidence on the use of SRS as a treatment for epilepsy includes case reports in primary epileptic disorders and case reports for tumor-related epilepsy. For mesial temporal lobe epilepsy, there is a pilot prospective non-comparative intervention and a single RCT comparing SRS to anterior temporal lobectomy (ATL).

TREMOR AND PARKINSON DISEASE

SRS has been used for the treatment of tremor via stereotactic radiofrequency thalamotomy.

Martínez-Moreno published a systematic review of stereotactic radiosurgery for tremor in association with International Stereotactic Radiosurgery Society practice guidelines.[18] The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. A total of 34 studies met inclusion criteria. Of these, 30 were retrospective noncomparative studies and 14 studies had fewer than 10 patients. Three studies were prospective and one was a retrospective comparative study. Rates of tremor reduction were similar across the included studies, with an average of 88%. The one comparative study reported similar tremor control rates between SRS, deep brain stimulation, and radiofrequency thermocoagulation. There were fewer permanent complications and longer latency to clinical response following SRS than the two other modalities. The authors concluded based on level IV evidence that SRS for tremor is well-tolerated and effective.

Dallapiazza (2018) conducted a systematic review comparing the outcomes of various surgical procedures for the treatment of refractory essential tremor, including deep brain stimulation (DBS), thalamotomy with radiofrequency (RF), stereotactic radiosurgery (SRS), and focused ultrasound (FUS).[19] Studies were pooled and graded for their overall level of evidence according to the Oxford Centre for Evidence-based Medicine standards. Measured outcomes included tremor control according to the Fahn-Tolosa-Marin (FTM) rating scale, quality of life (QOL) improvements, and complication rates. Overall, while complication rates were generally lower for SRS compared to other interventions, alternative approaches presented higher control rates and QOL improvements at more robust tiers of evidence.

Raju (2017) assessed outcomes of SRS for medically refractory tremor associated with Parkinson disease (PD) in a retrospective analysis of 33 patients.[20] All patients underwent gamma knife thalamotomy. Median follow-up was 23 months (range, 9 to 144 months). A total of 31 patients (93.9%) experienced improvements in tremor and 23 patients (70.0%) had complete or nearly complete tremor arrest. Improvements in other PD symptoms were also observed, including one patient (3%) with improvements in bradykinesia, three patients (9%) with improvements in rigidity, and three patients (9%) who reduced their dosage of dopa after SRS.

Section Summary

The evidence related to the use of SRS for tremor consists of uncontrolled cohort studies, many of which report outcomes from the treatment of tremor of varying etiologies. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies that compared SRS with alternative methods of treatment or a control group were identified. Limited long-term follow-up is available, making the long-term risk: benefit ratio of an invasive therapy uncertain.

CHRONIC PAIN

A 2022 systematic review published by Franzini evaluated medial thalamotomy using SRS for the treatment of intractable pain.[21] A total of six studies met inclusion criteria. There was some overlap with the Roberts and Pouratian systematic review below, but three included studied were published after the publication of the previous review. Across the six studies, 125 patients were treated with SRS and 118 were included in the outcome analysis. Meaningful pain reduction was reported in 55% of patients overall (with 38% persisting to last follow-up) and 43.3 to 100% per study. Adverse events were reported in six patients (5%).

Lu (2018) reported a systematic review and meta-analysis of neurosurgical treatments for glossopharyngeal neuralgia.[22] A total of 23 studies were included on nerve section (NS; 6 studies), microvascular decompression (MVD; 11 studies), and SRS (6 studies). The meta-analysis indicated that short-term and long-term pain relief rate was highest after NS (IR, 94%; 95% CI, 88%-98%; IR, 96%; 95% CI, 91%-99%). The short-term and long-term pain relief rate was lowest after SRS (three months postoperatively, IR, 80%; 95% CI, 68%-96%; IR, 82%; 95% CI, 67%-94%). The postoperative complication rate was highest and lowest following MVD (IR, 26%; 95% CI, 16%-38%) and SRS (IR, 0%; 95% CI, 0%-4%), respectively.

In 2017, Roberts and Pouratian performed a systematic review to evaluate the efficacy of SRS for chronic pain.[23] They identified six articles with 113 patients that underwent SRS and had at least a three month follow-up for nonmalignant pain or at least a one month follow-up for malignant pain. At least 35% of patients reported having significant pain relief, but 21% of patients reported adverse events.

Section Summary

The evidence related to the use of SRS for chronic pain is limited and there remains a lack of comparative studies and long-term outcomes. This evidence is not sufficient to understand the safety and effectiveness of SBRT for the treatment of chronic pain or to adequately describe the subpopulation of patients with chronic pain most likely to benefit.

BRAIN METASTASES

Systematic Reviews

Garsa (2021) conducted a systematic review of available evidence comparing WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy for adults with brain metastases due to lung cancer, breast cancer, or melanoma.[24] Despite the identification of 97 studies, statistical analyses were limited due to heterogeneity across the available data. Based on pooled data from 4 RCTs, there was no statistically significant difference in OS when comparing SRS plus WBRT to SRS alone or to WBRT alone (HR, 1.09; 95% CI, 0.69 to 1.73). Based on pooled data from 3 RCTs, OS did not differ when comparing postsurgical WBRT to postsurgical SRS (HR, 1.17; 95% CI, 0.61 to 2.25). Lastly, pooled data from 4 RCTs did not show a significant difference in the risk of serious adverse events with WBRT plus SRS versus WBRT or SRS alone (RR, 1.05; 95% CI, 0.12 to 8.89).

Chen (2021) published a systematic review of the use of SRS for brainstem metastases.[25] A total of 32 studies, all retrospective, including 1,446 patients, met inclusion criteria. Heterogeneity across studies was low to moderate (median I^2=35%; range 30 to 62%). No significant publication bias was identified. According to the meta-analyses, the one-year local control was 86% (95% CI 83 to 88%) based on 31 studies, the objective response rate was 59% (95% CI 47 to 71%) based on 17 studies, and the rate of symptom improvement was 55% (95% CI 47 to 63%) based on 13 studies. Deaths from brainstem metastases progression following SRS occurred in 19 patients across the 19 reporting studies. Grade 3 to 4 toxicities occurred in 2.4% (95% CI 1.5 to 8.7%) of patients.

An Agency for Healthcare Research and Quality Comparative Effectiveness Review of radiation therapy for brain metastases was published in 2020.[26] The review included randomized controlled trials and large observational studies of whole brain radiation (WBRT) and SRS alone or in combination. These were used as initial or postoperative treatment and

with or without systemic therapy. A total of 91 studies met inclusion criteria. These included 60 RCTs that addressed WBRT and 13 RCTs that addressed SRS. For SRS, the authors deemed the evidence insufficient for assessing overall survival, disease-free survival, deaths due to brain metastases, intracranial progression, functional status, and cognitive effects. Differences reported include a statistically significant difference between WBRT using radiosensitizers and WBRT alone, with improved survival associated with the addition of radiosensitizers (hazard ratio [HR] 0.87; 95% CI 0.83 to 0.90; three RCTs; moderate strength of evidence [SoE]). Most outcomes were not different between these groups. These included quality of life, which was not different between patients receiving SRS plus WBRT and patients receiving SRS alone, overall survival, which was not different between surgery plus radiation therapy and surgery alone, and serious adverse events, adverse events, radiation necrosis, fatigue, and seizures, for which there were systemic differences across interventions. The risk of dying from brain metastases was numerically but not statistically different in favor of radiation post-surgery versus surgery alone (relative risk [RR] 0.64; CI 0.22 to 1.84; three RCTs; low SoE).

Liu (2020) conducted a systematic review to compare SRS to surgical resection in the initial treatment of brain metastases.[27] The review included 20 studies (18 retrospective cohorts; 2 RCTs) involving 1,809 patients. Results revealed that SRS and surgical resection were comparable with regard to local control (HR, 1.02; 95% CI 0.64 to 1.64; p=0.92), distant intracranial control (HR, 0.78; 95% CI, 0.38 to 1.60; p=0.49), and OS (HR, 0.91; 95% CI, 0.65 to 1.27; p=0.57) in patients with single or solitary brain metastases. However, the authors noted that a prospective RCT with a larger patient population and a longer follow-up is necessary to confirm their findings.

Loi (2020) published a systematic review of SRS for local failure following SRS of brain metastases.[28] Eleven studies with a total of 335 patients met inclusion criteria. The pooled one-year local failure and median OS were 24% (95% CI 19 to 30%) and 14 months (95% CI 8.8 to 22.0%), respectively. The cumulative crude radionecrosis rate was 13% (95% CI 8 to 19%). According to a subgroup analysis, higher incidence of radionecrosis occurred in studies with median patient age of 59 years and above (13% [95% CI 8 to 19%] vs 7% [95% CI 3 to 12%], p=0.004), while lower radionecrosis incidence occurred following prior While Brain Radiotherapy (WBRT, 19% [95% CI 13 to 25 %] vs 7% [95% CI 30 to 13%], p=0.004). Heterogeneity was reported as acceptable.

Fuentes (2018) published a systematic review of RCTs to compare surgery with SRS for patients with a single brain metastasis.[29] Risk of bias was assessed with the Cochrane tool. Two RCTs met inclusion criteria. These included 85 patients. Both included studies were closed early due to poor participant accrual. Meta-analysis was not possible due to heterogeneity between the studies. Certainty of evidence was rated as low or very low for the various outcomes. Neither RCT reported differences in overall survival between the interventions. There were also no differences in progression-free survival, quality of life, or adverse events.

Khan (2017) published a meta-analysis of comparing WBRT, SRS, and treatment with a combination of the two for brain metastases.[30] Five studies with a total of 763 patients met inclusion criteria and were included in the meta-analysis. Out of those, 26% received WBRT alone, 26% received SRS alone, and 48% received WBRT plus SRS. No significant differences between treatment groups were found for survival benefit or adverse events. However, combination therapy provided significantly better local control than WBRT alone (hazard ratio 2.05; 95% CI 1.36 to 3.09; p=0.0006) or SRS alone (hazard ratio 1.84; 95% CI:

1.26 to 2.70; p=0.002).

In 2017, Ghidini conducted a systematic review on CNS metastases from esophageal and gastric cancer.[31] The authors analyzed data from 37 studies that met the criteria for inclusion. SRS was found to result in better OS, with the caveat that the studies examined included combination therapies that could cause an overestimate of survival.

Randomized Controlled Trials

Since publication of the systematic reviews, no new RCTs that compare SRS to other treatments have been published.

Nonrandomized Comparative Studies

In 2013, Verma retrospectively reviewed patients receiving different radiotherapy modalities for brain metastases with or without tyrosine kinase inhibitor (TKI) therapy.[32] Among 34 patients (89 lesions) those receiving SRS and TKIs had six-month local control rates of 94.7% vs 73.7% in the group who received SRS without TKIs. The difference was not statistically significant (p=0.09).

Tian (2013) reported results from a retrospective, single-institution cohort study comparing neurosurgical resection to SRS for solitary brain metastases from non-small-cell lung cancer (NSCLC). Seventy-six patients were included, 38 of whom underwent neurosurgery.[33] Median survival was 14.2 months for the SRS group and 10.7 months for the neurosurgery group. In multivariable analysis, treatment mode was not significantly associated with differences in OS.

Noncomparative Studies

Noncomparative studies continue to evaluate the use of SRS without WBRT for the management of brain metastases and the role of SRS for the management of larger numbers of brain metastases.[34-40]

Section Summary

For cases of brain metastases, evidence from RCTs, nonrandomized studies, and systematic reviews indicate that the use of SRS improves outcomes in the treatment of brain metastases. SRS appears to be feasible in the treatment of larger numbers (e.g., >10) of brain metastases, and outcomes after SRS treatment do not appear to be worse for patients with larger numbers of metastases, at least for patients with 10 or fewer metastases.

CAVERNOUS MALFORMATIONS

Systematic Reviews

Gao (2021) published a systematic review comparing microsurgery and gamma knife radiosurgery for the treatment of brainstem cavernous malformations.[41] Cohort studies reporting on 20 or more patients of any age with brainstem cavernous malformations with at least 80% completeness of follow-up were included, resulting in an analysis of 43 cohorts with 2,492 patients. Rehemorrhage rates were reduced by both microsurgery (RR=0.04, 95% CI 0.01 to 0.16, p<0.01) and radiosurgery (RR=0.11, 95% CI 0.08 to 0.16, p<0.01). The difference in median number of patients experiencing symptomatic intracranial hemorrhage between groups was statistically significant (microsurgery median 0, range 0 to 33; radiosurgery median 4, range 1 to 14; p<0.05). Persistent focal neurological deficit was also significantly different

between groups (neurosurgery median 5, range 0 to 140; radiosurgery median 1, range 0 to 3; p<0.05)

Poorthuis (2019) performed a systematic review of SRS for cerebral cavernous malformations.[42] A total of 30 studies met inclusion criteria. The median follow-up was 48 months. The annual incidence of death, intracerebral hemorrhage, and nonhemorrhagic persistent focal neurological deficit were 0.18% (95% CI 0.10 to 0.31), 2.40% (95% CI 2.05 to 2.80), and 0.71% (95% CI 0.53 to 0.96), respectively. The composite index including the incidence of all of these outcomes was 3.63% (95% CI 3.17 to 4.16).

Kim (2019) performed a systematic review of outcomes following SRS for brainstem cavernous malformations.[43] A total of 14 studies with 576 patients met inclusion criteria and were included in a meta-analysis. The hemorrhage rate was significantly lower post-SRS versus pre-SRS (pooled incidence rate ratio [IRR] 0.123; p<0.001) and two-years post-SRS versus within two years after SRS (IRR 0.317; p<0.001). At last follow-up, lesion volume was reduced in 47.3% of patients and unchanged in 49.4%. Symptomatic adverse radiation effects were reported in 7.3% of patients, with 2.2% of patients reporting permanent adverse radiation effects.

Wen (2019) performed a systematic review and meta-analysis of gamma knife radiosurgery for cavernous malformations.[44] A total of nine studies met inclusion criteria, representing 747 patients. All studies were retrospective, and one was case-controlled. The authors calculated the overall risk ratio (RR) of hemorrhage rate of pre-GKRS and post-GKRS (6.08 [95% CI 5.04 to 7.35]), the RR comparing hemorrhage rate of pre-GKRS and the first two years post-radiosurgery (3.03 [95% CI 2.65 to 4.11]), and the overall RR (12.13 [95% CI 1.73 to 85.07]) comparing pre-GKRS with two years after GKRS. There was no significant difference of the hemorrhage rate between the first two years following treatment and two years after treatment (RR=2.81; 95% CI 0.20 to 13.42). Adverse events reported in eight of the studies were cyst formation, edema, new lesions, and neurologic deficiency.

Non-randomized studies

Phuong (2017) reported on a case series of 79 patients with symptomatic cerebral cavernomas treated with SRS.[45] Complete response, partial response, and stable disease (best response) were reported in 17%, 82%, and 2%, respectively, of the 60 patients with headache. Complete response, partial response, and stable disease were reported in 31%, 64%, and 5% of the 39 patients with seizures. Complete response, partial response, stable disease, progression, and pseudoprogression were reported in 6%, 75%, 15%, 1%, and 5% of all patients, respectively, with respect to the size of cavernomas at 15 months. Four patients developed recurrent seizures after one year and five patients experienced bleeding within two years after SRS.

A 2014 case series by Lee reported on 31 patients who were treated with SRS for CMs.[46] Treatment followed a single symptomatic bleed in 31 patients (group A) and two or more symptomatic bleeds in 18 patients (group B). The annual hemorrhage rate following SRS within the first two years and after two years (up to a mean follow-up of 64 months) was 7.06% and 2.03% for group A and 9.84% and 1.50% for group B, respectively. Pretreatment hemorrhage rate was 38.36% for group B. Adverse events were reported in four patients, one of which was did not resolve during the trial.

A case series of 30 patients treated with SRS for single or multiple CMs was reported by Huang in 2006.[47] For six patients, radiosurgery was for residual lesions identified following[48] craniotomy. Mean follow-up was 59.9 months. Of the 13 patients presenting with seizures, following SRS eight were seizure-free, three had rare episodes of seizures, and two continued to have seizures. Hemorrhage rate pretreatment for the 22 patients presenting initially as acute hemorrhage was 1.9%. For all 30 patients, posttreatment hemorrhage rate was 1.9%. Posttreatment edema was observed in two patients.

Section Summary

The evidence related to the use of SRS for cavernous malformations consists of case series, which have reported improvements in hemorrhage rates. However, there remains a lack of comparative studies that evaluate long term outcomes.

DURAL ARTERIOVENOUS FISTULAS

Singh (2022) published a systematic review and meta-analysis of 21 studies involving 706 patients with dural arteriovenous fistula (dAVF) treated with SRS.[48] Median clinical follow-up was 2.75 years (range: 3.8 months -15.5 years). Nineteen studies with 688 dAVFs included data on complete obliteration (CO) rates. The pooled CO rate was 68.6% (95% CI 60.7%-76.5%). Thirteen studies with 452 patients included data on symptom improvement. The pooled symptom improvement rate was 97.2% (95% CI 93.2%-100%). Eight studies with 390 patients reported symptom cure rates. The pooled symptom cure rate after SRS was 78.8% (95% CI 69.3%-88.2%). Significant heterogeneity was noted for studies including CO rates, symptom improvement, and symptom cure rate. Twelve studies with 283 patients included data on post-SRS permanent neurological deficit (PND) rates. The pooled PND rate after SRS was 1.3% (95% CI 0.8%-1.8%). There was no significant heterogeneity in the studies reporting PND rates. The authors note that all included studies were retrospective and the analysis has significant risk of bias. Importantly, previous treatment for dAVF, especially embolization, was not controlled for, and the authors were unable to adequately compare SRS alone to multimodality treatment.

OTHER INDICATIONS

SRS has been used for other indications, including rare tumors gamma ventral capsulotomy for obsessive compulsive disorder, and cluster headache. The evidence for these other indications is limited in volume and in quality.[49-51]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Network (NCCN) provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers.[52]

Cancer Site	Tumor Type	Recommendation	Version
Bone	Chondrosarcoma Chordoma	Consider SRS to allow high-dose therapy while maximizing normal tissue sparing (category 2A)	1.2024
CNS	Adult intracranial and spinal ependymoma – spine or brain reoccurrence	• Resection with radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A) • If unresectable, radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A)	1.2023

Cancer Site	Tumor Type	Recommendation	Version
CNS	Glioma: Reirradiation	Highly focal techniques like intensity-modulated RT (IMRT), proton therapy, or SRS may be required in reirradiation settings in order to improve dose distribution to critical structures, and reduce overlap with prior radiation fields. Treatment may be performed with highly focused modern SRS techniques for lower volume disease10; fractionated IMRT, including doses of 35 Gy in 10 fractions for recurrent glioblastoma11, and proton therapy to help spare previously irradiated normal brain.	1.2023
CNS	Meningiomas	Observe (preferred for small asymptomatic tumors) or if accessible, surgery with or without RT (external beam or SRS; Recommendations based on WHO grade: Grade 3 – RT; Grade 2 with incomplete resection: RT; Grade 2 with complete resection – consider RT; Grade 1: observation or consider RT for symptomatic patients) or RT (external beam or SRS)	2.2023
CNS	Limited Brain Metastases, primary treatment	For newly diagnosed or stable systemic disease or reasonable systemic treatment options exist, SRS (preferred) or WBRT. SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances. For disseminated systemic disease with poor systemic treatment options, SRS in select patients.	1.2023
CNS	Limited Brain Metastases, recurrence	• If local recurrence and previous surgery only, options include surgery followed by SRS or RT to the surgical bed and single dose or fractionated stereotactic RT (category 2A) • If local recurrence and previous WBRT or SRS, options include surgery followed by SRS or RT to the surgical bed or single dose (category 2B) or fractionated SRS (category 2A) • If distant brain recurrence and limited brain metastases, options include surgery followed by SRS or RT to the surgical bed and single dose or fractionated stereotactic RT (category 2A)	1.2023
CNS	Extensive Brain Metastases, primary treatment	WBRT or SRS (category 2A). SRS can be considered for patients with good performance status and low overall tumor volume and/or radioresistant tumors such as melanoma.	1.2023
CNS	Leptomeningeal Metastases	SRS or RT (involved-field and/or whole brain) to bulky disease and neurologically symptomatic (such as cranial neuropathies) or painful sites. Consider craniospinal irradiation (CSI) in select patients	1/2023
Uveal Melanoma	Primary treatment	SRS is an option for tumors with: • Largest diameter >19mm (any thickness) OR • Thickness >10mm (any diameter) OR • Thickness >8mm with optic nerve involvement (any diameter). SRS is the least often used form of definitive radiotherapy for the treatment of primary or recurrent intraocular tumors.	1.2023

NCCN Categories

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Central Nervous System

- ASTRO, the American Society of Clinical Oncology (ASCO), and the Society for Neuro-Oncology (SNO) published 2022 guidelines on the treatment of brain metastases that include the following recommendations:[53]
    - Radiation therapy should not be offered to patients with asymptomatic brain metastases who have:
        - Performance status Karnofsky Performance Status (KPS) ≤ 50 or less, or
        - Performance status KPS < 70 and no systemic therapy options (Type: evidence-based; Evidence quality: low; Strength of recommendation: moderate).
    - SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with one to four unresected brain metastases, excluding small-cell carcinoma. (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).
    - SRS alone should be offered to patients with one to two resected brain metastases if the surgical cavity can be safely treated and considering the extent of remaining intracranial disease. (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)
    - SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (eg, KPS ≥ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS is available (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Glioblastoma

- “SRS and hypofractionated stereotactic RT appear to provide promising outcomes compared with chemotherapy, with median survival from reirradiation typically 8 to 12 months”.[54]

AMERICAN HEART ASSOCIATION SCIENTIFIC STATEMENT

In 2017, the American Heart Association and American Stroke Association published a scientific statement on the management of brain arteriovenous malformations (AVMs).[55] The statement concludes that the available literature supports the use of SRS for small- to moderate volume brain AVMs that are generally 12 cm^3 of less in volume or located in deep or eloquent regions of the brain.

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology published evidence-based recommendations in the Treatment of Essential Tremor Practice Parameter in 2005 (updated in 2011 and reaffirmed in

2022).[56, 57] It states “There is insufficient evidence regarding the surgical treatment of head and voice tremor and the use of gamma knife thalamotomy (Level U).”

CONGRESS OF NEUROLOGICAL SURGEONS

The Congress of Neurological Surgeons published 2019 evidence-based guidelines on “Use of Stereotactic Radiosurgery in the Treatment of Adults with Metastatic Brain Tumors.” These guidelines make the following level 3 recommendations regarding SRS:

- SRS is recommended as an alternative to surgical resection in solitary metastases when surgical resection is likely to induce new neurological deficits, and tumor volume and location are not likely to be associated with radiation-induced injury to surrounding structures.
- SRS should be considered as a valid adjunctive therapy to supportive palliative care for some patients with brain metastases when it might be reasonably expected to relieve focal symptoms and improve functional quality of life in the short term if this is consistent with the overall goals of the patient.
- After open surgical resection of a solitary brain metastasis, SRS should be used to decrease local recurrence rates.
- For patients with solitary brain metastasis, SRS should be given to decrease the risk of local progression.
- For patients with 2 to 4 brain metastases, SRS is recommended for local tumor control, instead of whole brain radiotherapy, when their cumulative volume is < 7 mL.
- The use of stereotactic radiosurgery alone is recommended to improve median overall survival for patients with more than 4 metastases having a cumulative volume < 7 mL.

In 2021, the Congress of Neurological Surgeons published updated guidelines on the treatment of recurrent glioblastoma in adults with radiotherapy.[58] These guidelines provide the following Level III recommendation: “When the target tumor is amenable for additional radiation, re-irradiation is recommended as it provides improved local tumor control, as measured by best imaging response. Such re-irradiation can take the form of conventional fractionation radiotherapy, fractionated radiosurgery, or single fraction radiosurgery.”

INTERNATIONAL STEREOTACTIC RADIOSURGERY SOCIETY

The International Stereotactic Radiosurgery Society (ISRS) has published a variety of relevant clinical practice guidelines and practice opinions related to SRS. For select guidelines, recommendations are based on a ranking of evidence quality with a corresponding strength of recommendation rating scheme:

Strength of Evidence

- Class I:
    - High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals
    - Systematic review of Class I RCTs (and study results were homogenous)
- Class II:
    - Lesser quality (eg, <80% follow-up, no blinding, or improper randomization
    - Prospective comparative study
    - Systematic review of Class II studies or Class I studies with inconsistent results
    - Case control study

    - Retrospective comparative study
- Class III:
    - Case series
    - Expert Opinion

Strength of Recommendation

- Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence)
- Level II: Clinical certainty (Class II evidence or a strong consensus of Class III evidence)
- Level III: Clinical uncertainty (Inconclusive or conflicting evidence or opinion)

Recommendations and conclusions from various ISRS guidelines and practice opinions include:

Intracranial noncavernous sinus benign meningioma: Current literature supporting SRS for this condition "lacks level I and II evidence. However, when summarizing the large number of level III studies, it is clear that SRS can be recommended as an effective evidence-based treatment option (recommendation level II) for grade 1 meningioma.[59]

Non-functioning pituitary adenomas: SRS is an effective and safe treatment for patients with non-functioning pituitary adenomas via consensus opinion.[60] The position paper states that "encouraging short-term data support hypofractionated stereotactic radiotherapy for select patients, and mature outcomes are needed before definitive recommendations can be made."

Benign (World Health Organization Grade I) cavernous sinus meningiomas: Current literature is "limited to level III evidence with respect to outcomes of SRS in patients with cavernous sinus meningiomas. Based on the observed results, SRS offers a favorable benefit to risk profile for patients with cavernous sinus meningioma."[61]

Arteriovenous malformations: Current literature cautiously suggests that "SRS appears to be a safe, effective treatment for grade I-II arteriovenous malformation and may be considered a front-line treatment, particularly for lesions in deep or eloquent locations." However, the literature is "low quality, limiting interpretation."[62]

Epilepsy: Current literature states that "radiosurgery is an efficacious treatment to control seizures in mesial temporal lobe epilepsy, possibly resulting in superior neuropsychological outcomes and quality of life metrics in selected subjects compared to microsurgery."[12]

Tremor: For medically refractory tremor, "SRS to the unilateral thalamic ventral intermediate nucleus, with a dose of 130 to 150 Gy, is a well-tolerated and effective treatment....and one that i recommended by the International Stereotactic Radiosurgery Society."[18]

Trigeminal neuralgia: Current literature is "limited in its level of evidence, with only 1 comparative randomized trial reported to date. At present, one can conclude that stereotactic radiosurgery is a safe and effective therapy for drug-resistant trigeminal neuralgia."[63]

Dural arteriovenous fistulas: SRS is recommended for patients with "complex dural arteriovenous fistula who are planned for embolization and are at high risk for not achieving complete obliteration with embolization alone; dural arteriovenous fistula who have received previous embolization without complete obliteration and have refractory symptoms; high-risk

noncavernous sinus dural arteriovenous fistula or symptomatic cavernous sinus dural arteriovenous fistula who are not candidates for or have refused both embolization or microsurgery."[48]

SUMMARY

There is enough research to show that use of stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) of intracranial, skull base, and orbital sites for initial treatment or treatment of recurrence improves health outcomes for the following conditions: primary neoplasms of the central nervous system; metastasis to CNS with adequate performance score; arteriovenous malformations; chordomas and chondrosarcomas of the skull base; craniopharyngiomas; drug-resistant epilepsy when criteria are met; head and neck cancers when reirradiation is delivered; hemangioblastoma; hemangiopericytoma; glomus jugulare and glomus tympanicum tumors; meningiomas; pituitary adenomas; schwannomas; trigeminal neuralgia that is refractory to medical management; and uveal melanoma. In addition, clinical practice guidelines recommend the use of SRS or SBRT for many of these indications. Therefore, the use of SRS and SBRT may be considered medically necessary when policy criteria are met for these indications.

For all other tumors or indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) of intracranial, skull base, and orbital sites leads to improved health outcomes. Therefore, SRS and SBRT of intracranial, skull base, and orbital sites is considered investigational when policy criteria are not met.

REFERENCES

1. NCI Dictionary of Cancer Terms [cited 08/31/2023]. 'Available from:' https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neoplasm.
2. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *The Cochrane database of systematic reviews.* 2011(9):CD007312. PMID: 21901707
3. Dhople AA, Adams JR, Maggio WW, et al. Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: implications of treatment and critical review of the literature. Clinical article. *Journal of neurosurgery.* 2009;111(2):351-8. PMID: 19326987
4. Mendelson ZS, Velagala JR, Kohli G, et al. Pain-Free Outcomes and Durability of Surgical Intervention for Trigeminal Neuralgia: A Comparison of Gamma Knife and Microvascular Decompression. *World neurosurgery.* 2018;112:e732-e46. PMID: 29382615
5. Holland MT, Teferi N, Noeller J, et al. Stereotactic radio surgery and radio frequency rhizotomy for trigeminal neuralgia in multiple sclerosis: A single institution experience. *Clinical neurology and neurosurgery.* 2017;162:80-84. PMID: 28972890
6. Chen CJ, Paisan G, Buell TJ, et al. Stereotactic Radiosurgery for Type 1 versus Type 2 Trigeminal Neuralgias. *World neurosurgery.* 2017;108:581-88. PMID: 28927915

7. Inoue T, Hirai H, Shima A, et al. Long-term outcomes of microvascular decompression and Gamma Knife surgery for trigeminal neuralgia: a retrospective comparison study. *Acta Neurochir (Wien).* 2017;159(11):2127-35. PMID: 28905114
8. Li L, Seaman SC, Bathla G, et al. Microvascular Decompression versus Stereotactic Radiosurgery for Trigeminal Neuralgia: A Single-Institution Experience. *World neurosurgery.* 2020;143:e400-e08. PMID: 32745644
9. Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia.* 2018;59(6):1198-207. PMID: 29600809
10. Quigg M, Barbaro NM, Ward MM, et al. Visual field defects after radiosurgery versus temporal lobectomy for mesial temporal lobe epilepsy: Findings of the ROSE trial. *Seizure.* 2018;63:62-67. PMID: 30408713
11. Eekers DBP, Pijnappel EN, Schijns O, et al. Evidence on the efficacy of primary radiosurgery or stereotactic radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults: A systematic review. *Seizure.* 2018;55:83-92. PMID: 29414140
12. McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. *Epilepsy research.* 2017;137:123-31. PMID: 28939289
13. Feng ES, Sui CB, Wang TX, et al. Stereotactic radiosurgery for the treatment of mesial temporal lobe epilepsy. *Acta neurologica Scandinavica.* 2016;134(6):442-51. PMID: 26846702
14. Special report: stereotactic radiosurgery for intracranial lesions by gamma beam, linear accelerator, and proton beam methods. *Tecnologica MAP supplement Blue Cross and Blue Shield Association Medical Advisory Panel.* 1999:26-7. PMID: 10346748
15. Regis J, Bartolomei F, Rey M, et al. Gamma knife surgery for mesial temporal lobe epilepsy. *Journal of neurosurgery.* 2000;93 Suppl 3:141-6. PMID: 11143232
16. Schrottner O, Eder HG, Unger F, et al. Radiosurgery in lesional epilepsy: brain tumors. *Stereotact Funct Neurosurg.* 1998;70 Suppl 1:50-6. PMID: 9782235
17. Whang CJ, Kwon Y. Long-term follow-up of stereotactic Gamma Knife radiosurgery in epilepsy. *Stereotact Funct Neurosurg.* 1996;66 Suppl 1:349-56. PMID: 9032879
18. Martinez-Moreno NE, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for tremor: systematic review. *Journal of neurosurgery.* 2018:1-12. PMID: 29473775
19. Dallapiazza RF, Lee DJ, De Vloo P, et al. Outcomes from stereotactic surgery for essential tremor. *J Neurol Neurosurg Psychiatry.* 2019;90(4):474-82. PMID: 30337440
20. Raju SS, Niranjan A, Monaco EA, III, et al. Stereotactic Radiosurgery for Intractable Tremor-Dominant Parkinson Disease: A Retrospective Analysis. *Stereotact Funct Neurosurg.* 2017;95(5):291-97. PMID: 28869946
21. Franzini A, Rossini Z, Moosa S, et al. Medial thalamotomy using stereotactic radiosurgery for intractable pain: a systematic review. *Neurosurg Rev.* 2022;45(1):71-80. PMID: 33978923
22. Lu VM, Goyal A, Graffeo CS, et al. Glossopharyngeal Neuralgia Treatment Outcomes After Nerve Section, Microvascular Decompression, or Stereotactic Radiosurgery: A Systematic Review and Meta-Analysis. *World neurosurgery.* 2018;120:572-82 e7. PMID: 30240868
23. Roberts DG, Pouratian N. Stereotactic Radiosurgery for the Treatment of Chronic Intractable Pain: A Systematic Review. *Operative neurosurgery (Hagerstown, Md).* 2017. PMID: 28521018
24. Garsa A, Jang JK, Baxi S, et al. Radiation Therapy for Brain Metastases: A Systematic Review. *Practical radiation oncology.* 2021;11(5):354-65. PMID: 34119447

25. Chen WC, Baal UH, Baal JD, et al. Efficacy and Safety of Stereotactic Radiosurgery for Brainstem Metastases: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2021;7(7):1033-40. PMID: 33983393
26. Radiation Therapy for Brain Metastases Draft Comparative Effectiveness Review. Agency for Healthcare Research and Quality; 2020 [cited 08/31/2023]. 'Available from:' https://effectivehealthcare.ahrq.gov/products/radiation-therapy-brain-metastases/research.
27. Liu Z, He S, Li L. Comparison of Surgical Resection and Stereotactic Radiosurgery in the Initial Treatment of Brain Metastasis. *Stereotact Funct Neurosurg.* 2020;98(6):404-15. PMID: 32898850
28. Loi M, Caini S, Scoccianti S, et al. Stereotactic reirradiation for local failure of brain metastases following previous radiosurgery: Systematic review and meta-analysis. *Critical reviews in oncology/hematology.* 2020;153:103043. PMID: 32650217
29. Fuentes R, Osorio D, Exposito Hernandez J, et al. Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis. *The Cochrane database of systematic reviews.* 2018;8:CD012086. PMID: 30125049
30. Khan M, Lin J, Liao G, et al. Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: Review and meta-analysis. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine.* 2017;39(7):1010428317702903. PMID: 28675121
31. Ghidini M, Petrelli F, Hahne JC, et al. Clinical outcome and molecular characterization of brain metastases from esophageal and gastric cancer: a systematic review. *Medical oncology (Northwood, London, England).* 2017;34(4):62. PMID: 28315230
32. Verma J, Jonasch E, Allen PK, et al. The impact of tyrosine kinase inhibitors on the multimodality treatment of brain metastases from renal cell carcinoma. *American journal of clinical oncology.* 2013;36(6):620-4. PMID: 22892430
33. Tian LJ, Zhuang HQ, Yuan ZY. A comparison between cyberknife and neurosurgery in solitary brain metastases from non-small cell lung cancer. *Clinical neurology and neurosurgery.* 2013;115(10):2009-14. PMID: 23850045
34. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *The Lancet Oncology.* 2014;15(4):387-95. PMID: 24621620
35. Raldow AC, Chiang VL, Knisely JP, et al. Survival and intracranial control of patients with 5 or more brain metastases treated with gamma knife stereotactic radiosurgery. *American journal of clinical oncology.* 2013;36(5):486-90. PMID: 22706180
36. Rava P, Leonard K, Sioshansi S, et al. Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery. *Journal of neurosurgery.* 2013;119(2):457-62. PMID: 23662828
37. Yomo S, Hayashi M. Upfront stereotactic radiosurgery in patients with brain metastases from small cell lung cancer: retrospective analysis of 41 patients. *Radiation oncology (London, England).* 2014;9(1):152. PMID: 25005424
38. Yamamoto M, Serizawa T, Higuchi Y, et al. A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores. *International journal of radiation oncology, biology, physics.* 2017;99(1):31-40. PMID: 28816158

39. Keller A, Dore M, Cebula H, et al. Hypofractionated Stereotactic Radiation Therapy to the Resection Bed for Intracranial Metastases. *International journal of radiation oncology, biology, physics.* 2017;99(5):1179-89. PMID: 28974415
40. Westover KD, Mendel JT, Dan T, et al. Phase II trial of hippocampal-sparing whole brain irradiation with simultaneous integrated boost for metastatic cancer. *Neuro Oncol.* 2020;22(12):1831-39. PMID: 32347302
41. Gao X, Yue K, Sun J, et al. Microsurgery vs. Gamma Knife Radiosurgery for the Treatment of Brainstem Cavernous Malformations: A Systematic Review and Meta-Analysis. *Front Neurol.* 2021;12:600461. PMID: 33574793
42. Poorthuis MHF, Rinkel LA, Lammy S, et al. Stereotactic radiosurgery for cerebral cavernous malformations: A systematic review. *Neurology.* 2019;93(21):e1971-e79. PMID: 31659093
43. Kim BS, Kim KH, Lee MH, et al. Stereotactic Radiosurgery for Brainstem Cavernous Malformations: An Updated Systematic Review and Meta-Analysis. *World neurosurgery.* 2019;130:e648-e59. PMID: 31276856
44. Wen R, Shi Y, Gao Y, et al. The Efficacy of Gamma Knife Radiosurgery for Cavernous Malformations: A Meta-Analysis and Review. *World neurosurgery.* 2019;123:371-77. PMID: 30583131
45. Phuong PC, Luan ND, Trang VTH, et al. Radiosurgery with a Rotating Gamma System: A Very Effective Treatment for Symptomatic Cerebral Cavernomas. *Anticancer Res.* 2017;37(7):3729-33. PMID: 28668867
46. Lee SH, Choi HJ, Shin HS, et al. Gamma Knife radiosurgery for brainstem cavernous malformations: should a patient wait for the rebleed? *Acta Neurochir (Wien).* 2014;156(10):1937-46. PMID: 24965071
47. Huang YC, Tseng CK, Chang CN, et al. LINAC radiosurgery for intracranial cavernous malformation: 10-year experience. *Clinical neurology and neurosurgery.* 2006;108(8):750-6. PMID: 16701940
48. Singh R, Chen CJ, Didwania P, et al. Stereotactic Radiosurgery for Dural Arteriovenous Fistulas: A Systematic Review and Meta-Analysis and International Stereotactic Radiosurgery Society Practice Guidelines. *Neurosurgery.* 2022;91(1):43-58. PMID: 35383682
49. Gupta A, Shepard MJ, Xu Z, et al. An International Radiosurgery Research Foundation Multicenter Retrospective Study of Gamma Ventral Capsulotomy for Obsessive Compulsive Disorder. *Neurosurgery.* 2019;85(6):808-16. PMID: 30476294
50. Oushy S, Graffeo CS, Perry A, et al. Single-fraction stereotactic radiosurgery for spindle cell oncocytoma: preliminary experience and systematic review of the literature. *J Neurooncol.* 2019;144(2):325-32. PMID: 31254265
51. Franzini A, Clerici E, Navarria P, et al. Gamma Knife radiosurgery for the treatment of cluster headache: a systematic review. *Neurosurg Rev.* 2022;45(3):1923-31. PMID: 35112222
52. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Treatment of Cancer by Site. [cited 08/31/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/default.aspx.
53. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *Journal of Clinical Oncology.* 2022;40(5):492-516. PMID: 34932393
54. Cabrera AR, Kirkpatrick JP, Fiveash JB, et al. Radiation therapy for glioblastoma: Executive summary of an American Society for Radiation Oncology Evidence-Based

Clinical Practice Guideline. *Practical radiation oncology.* 2016;6(4):217-25. PMID: 27211230
55. Derdeyn CP, Zipfel GJ, Albuquerque FC, et al. Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2017;48(8):e200-e24. PMID: 28642352
56. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology.* 2011;77(19):1752-5. PMID: 22013182
57. Neurology AAo. Update: Treatment of Essential Tremor. [cited 08/29/2023]. 'Available from:' https://www.aan.com/Guidelines/Home/GuidelineDetail/492.
58. Ziu M, Goyal S, Olson JJ. Congress of Neurological Surgeons systematic review and evidence-based guidelines update on the role of radiation therapy in the management of progressive and recurrent glioblastoma in adults. *J Neurooncol.* 2021. PMID: 34748120
59. Marchetti M, Sahgal A, De Salles AAF, et al. Stereotactic Radiosurgery for Intracranial Noncavernous Sinus Benign Meningioma: International Stereotactic Radiosurgery Society Systematic Review, Meta-Analysis and Practice Guideline. *Neurosurgery.* 2020;87(5):879-90. PMID: 32463867
60. Kotecha R, Sahgal A, Rubens M, et al. Stereotactic radiosurgery for non-functioning pituitary adenomas: meta-analysis and International Stereotactic Radiosurgery Society practice opinion. *Neuro Oncol.* 2020;22(3):318-32. PMID: 31790121
61. Lee CC, Trifiletti DM, Sahgal A, et al. Stereotactic Radiosurgery for Benign (World Health Organization Grade I) Cavernous Sinus Meningiomas-International Stereotactic Radiosurgery Society (ISRS) Practice Guideline: A Systematic Review. *Neurosurgery.* 2018;83(6):1128-42. PMID: 29554317
62. Graffeo CS, Sahgal A, De Salles A, et al. Stereotactic Radiosurgery for Spetzler-Martin Grade I and II Arteriovenous Malformations: International Society of Stereotactic Radiosurgery (ISRS) Practice Guideline. *Neurosurgery.* 2020;87(3):442-52. PMID: 32065836
63. Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *Journal of neurosurgery.* 2018;130(3):733-57. PMID: 29701555
64. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021;23(8):1231-51. PMID: 34185076

CODES

NOTE: Coding for stereotactic radiosurgery typically consists of a series of CPT codes describing the individual steps required; medical radiation physics, clinical treatment planning, attachment of stereotactic head frame, treatment delivery and clinical treatment management.

The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the treatment planning.

Treatment Planning Services:

Treatment delivered with LINAC based MLC may involve planning with the following codes.

Codes	Number	Description
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

NOTE: Treatment delivery:

The codes used for treatment delivery will depend on the energy source used, typically either photons or protons.

Codes	Number	Description
CPT	32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
	77371	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
	77372	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
	77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fraction
	77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

NOTE: Codes for treatment delivery primarily reflects the cost related to the energy source used, and not physician work.

Clinical treatment management:

Codes	Number	Description
CPT	77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.)
	61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
	61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
	61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
	61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
	61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
	63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
	63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
HCPCS	C9795	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance and real-time positron emissions-based delivery adjustments to 1 or more lesions, entire course not to exceed 5 fractions

Codes	Number	Description
	G0339	Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment.
	G0340	Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

APPENDIX I: WHO Classification of Tumors of the Central Nervous System	
Gliomas, glioneuronal tumors, and neuronal tumors	**Cranial and paraspinal nerve tumors**
Adult-type diffuse gliomas	Schwannoma
Astrocytoma, IDH-mutant	Neurofibroma
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	Perineurioma
Glioblastoma, IDH-wildtype	Hybrid nerve sheath tumor
Pediatric-type diffuse low-grade gliomas	Malignant melanotic nerve sheath tumor
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	Malignant peripheral nerve sheath tumor
Angiocentric glioma	Paraganglioma
Polymorphous low-grade neuroepithelial tumor of the young	**Meningioma**
Diffuse low-grade glioma, MAPK pathway-altered	**Mesenchymal, non-meningothelial tumors**
Pediatric-type diffuse high-grade gliomas	Soft tissue tumors
Diffuse midline glioma, H3 K27-altered	Fibroblastic and myofibroblastic tumors
Diffuse hemispheric glioma, H3 G34-mutant	Solitary fibrous tumor
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	Vascular tumors
Infant-type hemispheric glioma	Hemangiomas and vascular malformations
Circumscribed astrocytic gliomas	Hemangioblastoma
Pilocytic astrocytoma	Skeletal muscle tumors
High-grade astrocytoma with piloid features	Rhabdomyosarcoma
Pleomorphic xanthoastrocytoma	Uncertain differentiation
Subependymal giant cell astrocytoma	*Intracranial mesenchymal tumor, FET-CREB fusion-positive*
Chordoid glioma	*CIC*-rearranged sarcoma
Astroblastoma, *MN1*-altered	Primary intracranial sarcoma, *DICER1*-mutant
Glioneuronal and neuronal tumors	Ewing sarcoma
Ganglioglioma	Chondro-osseous tumors
Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma	Chondrogenic tumors
Dysembryoplastic neuroepithelial tumor	Mesenchymal chondrosarcoma
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chondrosarcoma
Papillary glioneuronal tumor	Notochordal tumors
Rosette-forming glioneuronal tumor	Chordoma (including poorly differentiated chordoma)
Myxoid glioneuronal tumor	**Melanocytic tumors**
Diffuse leptomeningeal glioneuronal tumor	Diffuse meningeal melanocytic neoplasms
Gangliocytoma	Meningeal melanocytosis and meningeal melanomatosis

APPENDIX I: WHO Classification of Tumors of the Central Nervous System	
Multinodular and vacuolating neuronal tumor	Circumscribed meningeal melanocytic neoplasms
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	Meningeal melanocytoma and meningeal melanoma
Central neurocytoma	**Hematolymphoid tumors**
Extraventricular neurocytoma	Lymphomas
Cerebellar liponeurocytoma	CNS lymphomas
Ependymal tumors	Primary diffuse large B-cell lymphoma of the CNS
Supratentorial ependymoma	Immunodeficiency-associated CNS lymphoma
Supratentorial ependymoma, *ZFTA* fusion-positive	Lymphomatoid granulomatosis
Supratentorial ependymoma, *YAP1* fusion-positive	Intravascular large B-cell lymphoma
Posterior fossa ependymoma (multiple subtypes)	Miscellaneous rare lymphomas in the CNS
Spinal ependymoma (multiple subtypes)	MALT lymphoma of the dura
Myxopapillary ependymoma	Other low-grade B-cell lymphomas of the CNS
Subependymoma	Anaplastic large cell lymphoma (*ALK*+/*ALK*−)
Choroid plexus tumors	T-cell and NK/T-cell lymphomas
Choroid plexus papilloma	Histiocytic tumors
Atypical choroid plexus papilloma	Erdheim-Chester disease
Choroid plexus carcinoma	Rosai-Dorfman disease
Embryonal tumors	Juvenile xanthogranuloma
Medulloblastoma	Langerhans cell histiocytosis
Medulloblastomas, molecularly defined (multiple types)	Histiocytic sarcoma
Medulloblastomas, histologically defined	**Germ cell tumors**
Other CNS embryonal tumors	Teratoma (multiple types)
Atypical teratoid/rhabdoid tumor	Germinoma
Cribriform neuroepithelial tumor	Embryonal carcinoma
Embryonal tumor with multilayered rosettes	Yolk sac tumor
CNS neuroblastoma, *FOXR2*-activated	Choriocarcinoma
CNS tumor with *BCOR* internal tandem duplication	Mixed germ cell tumor
CNS embryonal tumor	**Tumors of the sellar region**
Pineal tumors	Adamantinomatous craniopharyngioma
Pineocytoma	Papillary craniopharyngioma
Pineal parenchymal tumor of intermediate differentiation	Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma
Pineoblastoma	Pituitary adenoma/PitNET

APPENDIX I: WHO Classification of Tumors of the Central Nervous System	
Papillary tumor of the pineal region	Pituitary blastoma
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	**Metastases to the CNS**
	Metastases to the brain and spinal cord parenchyma
	Metastases to the meninges

Adapted from Louis (2021).[64]

Date of Origin: *July 2019*

Regence

Medical Policy Manual Surgery, Policy No. 214

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites

Effective: January 1, 2024

Next Review: July 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) are radiotherapy techniques that use highly focused radiation beams to treat both neoplastic and non-neoplastic conditions, in contrast to traditional external radiation beam therapy, which involves the use of relatively broad fields of radiation over a number of sessions that may occur over weeks to months.

MEDICAL POLICY CRITERIA

I. Stereotactic radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Body Radiotherapy (SABR), may be considered **medically necessary** for initial treatment or treatment of recurrence for any of the following indications:

   A. Head and neck cancers outside of intracranial, skull base, and orbital sites, when there is documented prior radiation treatment to the planned target volume

   B. Hemangiopericytoma outside of intracranial, skull base, or orbital sites

C. Hepatobiliary tumor, including biliary tract cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma; excluding hepatocellular carcinoma (see Criterion D) and metastatic hepatic tumors from different primary cancers (see Criterion F).

D. Hepatocellular carcinoma (hepatoma) when all of the following criteria are met:

1. Five or fewer hepatic lesions; and
2. Size of largest lesion is 6 cm diameter or less; and
3. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

E. Primary lung cancer: Non-small cell lung cancer (NSCLC) and Small-cell lung cancer (SCLC); tumor stage T1 or T2 and node negative.

F. Oligometastases when the following criteria are met:

1. Five or fewer synchronous metastatic lesions in any one metastatic site; and
2. Primary is controlled, stable, or expectation of the same; and
3. Metastases are limited to one to three organs; and
4. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

G. Pancreatic adenocarcinoma, locally advanced, borderline resectable, inoperable (See Policy Guidelines) or local recurrence after resection

H. Paraganglioma

I. Prostate cancer; very low, low, and intermediate-risk (See Policy Guidelines)

J. Renal cell cancer, inoperable primary, when a urological surgeon has documented inoperability

K. Schwannomas (see Policy Guidelines)

L. Spinal or paraspinal tumors (primary or metastatic) including but not limited to hemangioblastoma

II. Stereotactic radiosurgery and stereotactic body radiation therapy (also known as Stereotactic ablative body radiotherapy) are considered **investigational** when Criterion I. is not met and for all other indications outside of intracranial, skull base, or orbital sites, including but not limited to: Primary tumors of the following sites: cervix, endometrium, esophagus, hemangiomas, large bowel, ovaries, rectum, and small bowel.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

For the purposes of this policy, neoplasm is defined as “an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer).”[1]

SCHWANNOMAS

Schwannomas are tumors that occur along nerves. They are typically benign but may be malignant. These may also be referred to as neuromas, neurinomas "of Verocay" or neurilemmomas. A common type of schwannoma is a vestibular schwannoma, which is also known as an acoustic neuroma.

PERFORMANCE STATUS MEASUREMENT

Performance status is frequently used in oncology practice as a variable in determining prognosis and management strategies. Either the Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) Performance Status scoring systems may be used.

Karnofsky Performance Status

100	Normal, without symptoms
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance; able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated
20	Very sick; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly

ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Pancreatic Adenocarcinoma Resectability

See National Comprehensive Cancer Network criteria defining resectability at diagnosis of pancreatic adenocarcinoma.[2]

Prostate Cancer Risk Groups

The National Comprehensive Network (NCCN) Clinical Practice Guideline for Prostate Cancer defines very low risk prostate cancer as clinical T1c stage, Gleason score less than or equal to 6 /Grade Group 1, and PSA <10ng/ml and low risk prostate cancer as cT1-T2a, Gleason score less than or equal to six/Grade Group 1, and PSA less than 10ng/mL. Intermediate risk is defined as cT2b-cT2c or Gleason score of seven/Grade Group 2 or 3, or PSA 10-20ng/ml.[3]

FRACTIONATION

Fractionated stereotactic radiotherapy refers to when SRS or SBRT are performed more than once on a specific site. SRS is commonly delivered in 1 fractions and SBRT or SABR is commonly delivered in 2-5 fractions.

DOSE CONSTRAINT REFERENCES

Radiation Therapy Oncology Group (RTOG) Radiation Dose Constraints

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/RTOG

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/QUANTEC

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History/Physical and Chart notes, including requirements as outlined by the policy criteria, as applicable to the indication for treatment.
- As applicable, documentation of sites, size and count of lesions
- As applicable, documented ECOG score or Karnofsky performance score
- As applicable, absent or minimal extra hepatic disease for extracranial site treatment
- For prostate cancer, PSA and Gleason score.

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
2. Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid, Medicine, Policy No. 164
3. Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, Pelvis, and Extremities, Medicine, Policy No. 165
4. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
5. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
6. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204
7. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213

BACKGROUND

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) rely on three-dimensional imaging to localize the therapy target. SRS and SRBT have been used for a range of malignant and non-malignant conditions. Because they are more targeted than traditional external radiation therapy, SRS and SRBT are often used for treatment at sites that are difficult to reach via surgery, located close to other vital structures, or subject to movement within the body. The term SBRT will be used to describe treatment also referred to as stereotactic ablative body radiotherapy (SABR).

SRS and SBRT (or SABR) employ similar technological "stereotactic" sophistication with elements of advanced pretreatment imaging for localization of target(s), patient immobilization, control of breathing associated tumor movement, focally targeted treatment planning, and daily image guidance to ensure precise delivery of high daily doses of radiation. As commonly used in the medical literature, SRS refers to intracranial treatments and SBRT refers to extracranial treatments. Alternatively, SRS and SBRT may be defined independent of whether treatment is directed to intra or extra cranial tumors volumes. According to this definition, when such treatment is given as a single fraction, it may be referred to as SRS, and when it is delivered in 2-5 fractions it may be referred to as SBRT or SABR.

The fractionation used for SRS and SBRT is referred to as “hypofractionated” because it is fewer treatments than those used for conventional external beam radiotherapy.” Fractionation of stereotactic radiotherapy aims to optimize the therapeutic ratio; that is the ratio between tumor control and late effects on normal tissues. The main advantage of fractionation is that it allows higher total doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues to each individual, fractionated dose. In addition, some lesions such as large arteriovenous malformations may require more than one procedure to complete the obliteration process.

SRS and SBRT can be administered by several types of devices that are distinguished by their source of radiation, including particle beams (e.g., proton), gamma radiation from cobalt-60 sources, or high-energy photons from linear accelerator (LINAC) systems. The Gamma Knife and linear accelerator systems (including the Cyberknife®) are similar in concept; both use multiple photon radiation beams that intersect at a stereotactically determined target, thus permitting higher doses of radiation delivery with sparing of surrounding normal tissues. The differences between the two relate to how the energy is produced (i.e., through decaying cobalt-60 in the gamma knife devices, or from x-rays in the linear accelerator system) and the number of energy sources used (i.e., multiple energy sources in the gamma knife versus one in the linear accelerator system).

IMAGE-GUIDED RADIOSURGERY OR RADIOTHERAPY

Image-guided radiosurgery or radiotherapy is a relatively new development collectively describing units with real-time image guidance systems. Examples include the Cyberknife® device, BrainLAB Novalis®, TomoTherapy®, and LINAC with computerized tomography (CT).

REGULATORY STATUS

Several devices that use cobalt 60 radiation (gamma ray devices) for SRS have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The most commonly used gamma ray device is the GammaKnife (Elekta; approved May 1999). Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by the FDA through the 510(k) premarket notification process including the Novalis Tx®

(Novalis, Westchester, IL); the TrueBeam STx (Varian Medical Systems, Palo Alto, CA, approved December 2012); and the CyberKnife® System (Accuray, Inc.; approved December 1998). LINAC-based devices may be used for intracranial and extracranial lesions.

Note: Particle radiation can also be used without stereotactic guidance. In this setting, the use of particles is referred to as proton, helium, or neutron radiation *therapy*. Proton or helium ion radiation therapies (RT), intraocular RT for age-related macular degeneration, and electromagnetic navigation bronchoscopy for placement of fiducial markers are considered in separate medical policies. See cross-reference section below.

EVIDENCE SUMMARY

The selection of variables used in the delivery of SRS and SBRT is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins. All of these variables depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Trials that allow direct comparison of all of the possible variables involved in selecting specific SRS and SBRT methods do not broadly exist making it difficult to draw comparative effectiveness conclusions. Further, for many rare conditions, large comparative studies are unlikely. The evidence below will focus on indications with criteria and investigational indications.

Please note that the evidence review below does not compare specific radiation planning and delivery techniques.

Lung Cancer

Systematic Reviews

Viani (2022) published a meta-analysis evaluating the efficacy of SBRT versus surgery for early-stage NSCLC.[4] Thirty studies met inclusion criteria, with 29,511 patients (17,146 patients in the surgery group and 12,365 patients in the SBRT group). Of these, 26 were retrospective studies with propensity score matching, one was a randomized clinical trial, one was a retrospective study with adjustment for prognostic covariates, and two were retrospective studies without adjustment for covariates. Statistically significant publication bias for OS was identified at three years in favor of surgery (p=0.027). A statistically significant difference between groups in favor of surgery was identified in three-year OS (HR=1.35; 95% CI 1.22 to 1.44; I^2=66%) and three-year cancer-specific survival (HR=1.23; 95% CI 1.09 to 1.37; I^2=17%). Three-year LC was not significantly different between groups (HR = 0.97; 95% CI 0.93 to 1.08; I^2=19%). Subgroup analyses identified no significant differences between groups in OS in the T1N0M0 subgroup or cancer-specific survival between the sublobar resection subgroup and the SBRT group.

Zhang (2022) published a systematic review of 87 studies involving SBRT (n=12,811) and 18 studies involving RFA (n=1,535) for patients with inoperable stage I NSCLC.[5] The local control rates with SBRT were 98%, 95%, 92%, and 92%, respectively, at one, two, three, and five years; the local control rates for RFA were significantly lower (75%, 31%, 67%, and 41%, respectively, at one, two, three, and five years; p<0.01 for all comparisons). The OS rates were similar between SBRT and RFA at one year (87% vs 89%, respectively; p=0.07) and two years (71% vs 69%, respectively; p=0.42), whereas the OS was significantly improved with SBRT over RFA at three years (58% vs 48%; p<0.01) and five years (39% vs 21%; p<0.01). The most common complication of SBRT was radiation pneumonitis (9.1%), whereas pneumothorax was the most common complication of RFA (27.2%).

A systematic review by Alcibar (2021) evaluated the use of SBRT for treating inoperable stage III non-small cell lung cancer.[6] A total of six studies with 134 patients met inclusion criteria.

Half of the studies were prospective and the half were retrospective. Overall median follow-up was 18.75 months. Median local control was 76% and grade 3 or higher toxicity occurred in 12% of patients.

Ijsseldijk (2020) conducted a systematic review and meta-analysis comparing oncologic outcomes of surgery versus SBRT for patients with stage I NSCLC.[7] The analysis included a total of 100 studies. Results revealed that long-term OS and disease-free survival after lobar resection was better than SBRT in all comparisons, and for the majority of comparisons, sublobar resection was better than SBRT. Included studies were heterogeneous and of low quality; however, results remained essentially unchanged after many stratifications and sensitivity analyses.

In 2019 Li published a systematic review comparing SBRT to surgery for early-stage NSCLC. A total of 14 cohort studies (n=1,438 participants) met inclusion criteria.[8] Matching was performed for the main bias sources between the groups, including age, gender, tumor diameter, forced expiratory volume in one second, and Charlson comorbidity index. There was a statistically significant benefit for surgery over SBRT for early-stage NSCLC, with pooled OR for one-, three-, and five-year OS of 1.56 (95% CI 1.12 to 2.15), 1.86 (95% CI 1.50 to 2.31), and 2.43 (95% CI 1.8 to 3.28), respectively. The five-year distant control was 2.74 (95% CI 1.12 to 6.67). No significant differences were identified between groups for one-year or three-year disease-free survival, locoregional control, or distant control or five-year locoregional control.

In 2014, Zheng reported results from a systematic review and meta-analysis comparing survival after SBRT with survival after surgical resection for the treatment of stage I NSCLC.[9] The authors included 40 studies reporting outcomes from SBRT, including 4850 patients, and 23 studies reporting outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at one, three, and five years were 83.4%, 56.6%, and 41.2%, respectively. The mean unadjusted OS rates at one, three, and five years were 92.5%, 77.9%, and 66.1%, respectively, with lobectomy, and 93.2%, 80.7%, and 71.7% with limited lung resections. After adjustment for surgical eligibility (for the 27 SBRT studies that reported surgical eligibility) and age, in a multivariable regression model, the treatment modality (SBRT vs surgical therapy) was not significantly associated with OS (p=0.36).

A review by Nguyen (2008)[10] cites a number of studies of SBRT for early-stage lung cancer receiving a biologic equivalent dose of 100 Gy or more. Three of the studies cited reported 5-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the five-year survival was 42%. Koto reported on a phase two study of 31 patients with stage one NSCLC.[11] Patients received 45 Gy in 3 fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the three-year OS was 72%, while disease-free survival was 84%. Five patients developed grade two or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported three-year disease-specific survival rates of 49% for those with stage one disease.[12]

Randomized Controlled Trials

Peng (2023) performed an RCT to assess the efficacy and safety of SBRT plus targeted therapy with epidermal growth factor tyrosine kinase inhibitors (EGFR-TKIs) in patients with Stage IV NSCLC who had EGFR sensitive mutations and fewer than five metastatic lesions.[13] After three months of first line treatment with demonstrated response, 62 patients were

randomized to either receive SBRT with continued EGFR-TKI therapy (31 patients) or continued EGFR-TKI therapy alone (31 patients). After a median follow-up of 29.4 months eight (26.67%) patients in the SBRT group were living, compared to five (16.3%) in the EGFR-TKI group. Median PFS was 17.3 months in the SBRT group and 9.0 months in the control group (HR=0.52, 95% CI 0.31 to 0.89, p=0.016). Overall survival was also statistically significant (p=0.033) with median survival of 35.2 months in the SBRT+EGFR-TKI group and 23.2 months in the EGFR-TKI group. The study suggests that adding SBRT to EGFR targeted therapy prolongs survival by delaying acquired resistance to therapy, but larger randomized trials are needed.

Altorki (2021) published an RCT assessing neoadjuvant durvalumab with compared to without SBRT.[14] A total of 60 patients with potentially resectable early-stage NSCLC were randomized to receive durvalumab monotherapy (n=30) or the durvalumab plus radiotherapy (n=30). There was a statistically significant difference in major pathological response rate between the monotherapy and SBRT-treated groups (6.7% [95% CI 0.8 to 22.1] vs. 53.3% [34.3 to 71.7%]; p<0.0001). Grade 3 to 4 adverse events were reported in 17% of monotherapy- and 20% of SBRT-treated patients. The second cycle of durvalumab was withheld in three (10%) of 30 patients in the SBRT-treated group due to immune-related adverse events (grade 3 hepatitis, grade 2 pancreatitis, and grade 3 fatigue and thrombocytopenia). Two patients in each group experienced serious adverse events. There were no treatment-related deaths or any deaths within 30 days of surgery.

Nonrandomized Comparative Studies

Numerous nonrandomized, comparative studies have compared SBRT with surgery for NSCLC. A few of them used matching and are therefore the strongest methodologically of this group. Chi (2019) reported results of a cohort study comparing surgery and SBRT for the treatment of early-stage NSCLC using data from the National Cancer Database.[15] Survival comparisons used the multivariable Cox proportional hazards model and propensity score matching incorporating preoperative risk factors significantly associated with OS. A total of 104,709 patients were included in the analysis. Of these, 91,330 were in the surgery group and 13,379 were in the SBRT group. For the propensity score–matched cohorts, 12,632 patients undergoing sublobar resection were compared with 12,632 patients undergoing SBRT and 12,632 patients undergoing lobar resection were compared with 12,632 patients undergoing SBRT. Resection, both sublobar (HR, 0.56; 95% CI 0.54 to 0.58, p<0.001) and lobar (HR, 0.47; 95% CI 0.45 to 0.49, p<0.001) were associated with reduced mortality risk compared with SBRT. Survival comparisons calculated using a stratified multivariable Cox model to adjust for confounding variables also showed an association between surgery and a reduction in mortality risk. This association was not found for less extensive surgery when 0 nodes were examined in patients aged 80 years or older with stage T2 to T3 tumors (HR for lobectomy, 0.90; 95% CI 0.65 to 1.25; p=0.53) and in selected operable patients older than 75 years with stage T1 tumors (HR for lobectomy, 1.07; 95% CI 0.57 to 2.00; p=0.84). Wu (2020) performed a similar analysis comparing sublobar resection versus SBRT or ablation for stage I NSCLC using data from the National Cancer Database. This analysis also identified shorter OS for SBRT and ablation versus sublobar resection.[16]

Lam (2018) performed a matched analysis of cases in the National Cancer Database of stage 1a and 1b NSCLC treated with primary RF ablation or SBRT.[17] A total of 4,454 SBRT- and 335 RF-treated patients were included. There were significantly more comorbidities (p<0.001) and unplanned readmission within 30 days (p<0.001) in the RF ablation group. A multivariate

Cox regression analysis of OS for the unmatched groups showed no significant difference (p=0.285). In the matched groups, no difference was found with one-, three- and five-year OS of 85.5%, 54.3%, and 31.9% in the SBRT group vs 89.3%, 52.7%, and 27.1% in the RF ablation group (p=0.835).

von Reibnitz (2018) analyzed 497 patients with early-stage NSCLC (T1-T2N0M0) treated with conventional radiation (n=127) or SBRT (n=398).[18] Median follow-up was 24.4 months. The Kaplan-Meier method was used to estimate OS and the Cox regression model was used to compare between groups. Propensity score matched analysis was performed using seven patient and clinical variables: age, gender, Karnofsky performance status (KPS), histology, T stage, biologically equivalent dose (BED), and history of smoking. Three-year local failure and OS rates were 38.9% for conventional radiation and 13.6% for SBRT (p<0.001) and 38.9% for conventional radiation and 53.1% for SBRT, respectively. Propensity score matching indicated a statistically significant improvement of OS for SBRT (p=0.0497).

Two matched analyses used the SEER (Surveillance, Epidemiology, and End Results) database to identify patients. Yu (2015) identified elderly patients with stage I NSCLC who received either SBRT or surgery from 2007 to 2009.[19] Propensity matching was used to select two surgery patients for each SRS patient. A total of 367 SBRT patients were matched with 711 surgery patients. Early mortality at three months was significantly better for the SBRT group compared to the surgery group (2.2% vs 6.1%, p=0.005). However, late mortality at 24 months was significantly worse for the SBRT group (40.1%) compared with the surgery group (22.3%; p<0.001). Across the 24-month follow-up, patients in the SBRT group had fewer complications (incidence rate ratio, 0.74; 95% CI, 0.64 to 0.87). A similar study was performed by Ezer (2015),[20] and the two studies likely had overlapping populations. A total of 362 patients with stage I or II NSCLC and negative lymph nodes were matched with patients who received limited resection. There was no difference in OS for the SBRT patients compared with the surgery patients (HR=1.19; 95% CI, 0.97 to 1.47). Complications were less common in patients undergoing SBRT (14% of total) compared with patients undergoing resection (28%; p<0.001).

Tubin (2019) compared the novel SBRT-based PArtial Tumor irradiation of HYpoxic clonogenic cells (SBRT-PATHY) to standard of care in unresectable stage IIB/IV bulky NSCLC.[21] A total of 60 patients who were considered inoperable or unsuitable for radical radio-chemotherapy were treated using SBRT-PATHY (group I, n = 20 patients), recommended standard of care chemotherapy (group II, n = 20 patients), and institutional conventional palliative radiotherapy (group III, n = 20 patients). The median follow-up was 13 months. No statistically significant differences between groups were identified for one-year overall survival (75, 60, and 20% in groups 1, 2 and 3, respectively; p = 0.099) or one-year cancer specific survival (90, 60, and 20% in groups 1, 2, and 3, respectively (p = 0.049). However, multi-variate analysis for cancer specific survival was significant for treatment effect with SBRT-PATHY (p<0.001) independent of age, sex, performance status, histology, stage, treated bulky site and tumor diameter. Bulky tumor control rate was 95, 20, and 20% in groups 1, 2, and 3, respectively. Compared to chemotherapy and conventional palliative radiotherapy, toxicity was lower and symptom control was improved in the SBRT-PATHY group.

Jeppeson (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).[22] The study included 100 subjects treated with SBRT and 32 treated with conventional radiotherapy. At baseline, the SBRT-treated patients had smaller tumor volume, lower FEV_1, and a greater proportion of T1 stage disease. Median OS was 36.1

months versus 24.4 months for SBRT and conventional radiotherapy, respectively (p=0.015). Local failure-free survival rates at one year were 93% in the SBRT group versus 89% in the conventional radiotherapy group and at five years 69% versus 66%, SBRT and conventional radiotherapy, respectively (p=0.99).

Noncomparative Studies

Raman (2018) reported an institutional prospective database review of 180 central and 26 ultracentral lung tumors.[23] Most patients received 60 Gy in eight fractions or 48 Gy in four fractions. Rates of toxicity were 8.4% for grade 2 or higher in the central group an d7.9 in the ultracentral group. No grade 4 or 5 toxicities were reported. The two-year cumulative rates of local, regional, and distant failure were 3.3% vs 0 (p=0.36), 9.1% vs 5.0% (P = .5), and 17.7% vs 18.7% (P = .63) in the central and ultracentral groups, respectively.

A report of a seven-year follow-up of 65 patients treated with SBRT for medically inoperable, clinical stage I NSCLC was published in 2017 by Sun.[24] A dose of 50 Gy was delivered in four fractions. Recurrence occurred in 27.7% of patients at a median of 14.5 months following SBRT. Five- and seven-year estimated local, regional, and distant recurrence were 8.1, 10.9, and 11.0%, and 8.1, 13.6, and 13.8%, respectively. Five- and seven-year estimated OS were 55.7 and 47.5% and PFS were 49.5 and 38.2%, respectively. Three patients experienced grade 3 treatment-related adverse events, but there were no reported grade 4 or 5 adverse events.

In a 2017 study of 71 patients undergoing SBRT for stage I NSCLC by Miyakawa, dose escalation was used with the goal of attaining improved local control of large tumors.[25] Doses used were 48, 50, and 52 Gy for tumors with a longest diameter of < 1.5 cm, 1.5-3 cm, and > 3 cm, respectively. OS and PFS at the median follow-up of 61 months for living patients (44 months for all patients) were 65% and 55%, respectively. The cumulative incidence of local recurrence was 15% at five years.

A retrospective database study (n=3,147) by Nanda (2015) evaluated patients aged 70 years or older with early stage (T1-T3N0M0) NSCLC for three years.[26] Overall survival was compared between stereotactic body radiotherapy alone and no treatment. SBRT was associated with improved survival in elderly patients who have concurrent comorbid conditions compared with no treatment.

Timmerman (2007) evaluated the toxicity and efficacy of SBRT in a high-risk population of patients with early stage but medically inoperable lung cancer.[27] in a phase two North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small-cell tumors (<5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 to two weeks. The primary end point was two-year actuarial primary tumor control; secondary end points were DFS (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and OS. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors, 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only one patient had primary tumor failure; the estimated three-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had recurrence within the involved lobe; the three-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the three-

year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates for DFS and OS at three years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade three adverse events were reported in seven patients (12.7%; 95% CI, 9.6% to 15.8%); grade four adverse events were reported in two patients (3.6%; 95% CI, 2.7% to 4.5%). No grade five adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at three years, high rates of local tumor control, and moderate treatment-related morbidity.

In 2014, Stanic reported additional analysis of pulmonary toxicity in participants from the Timmerman study.[28] During two-year follow-up pulmonary function test results were collected. Mean percentage of predicted FEV1 and DLCO declines were 5.8% and 6.3%, respectively. There was no significant decline of oxygen saturation. Baseline pulmonary function testing was not predictive of any pulmonary toxicity following SBRT. Whole lung V5, V10, V20 and mean dose to the whole lung were almost identical between patients who developed pneumonitis and patients who were pneumonitis-free. Poor baseline pulmonary function testing did not predict decreased overall survival. Patients with poor baseline pulmonary function testing as a reason for medical inoperability had higher median and overall survivals than patients with normal baseline pulmonary function testing but with cardiac morbidity.

Hof (2007) reported on outcomes (median follow-up, 15 months) for 42 patients with stages I and II lung cancer who were not suitable for surgery and who were treated with stereotactic radiotherapy.[29] In this series, at 12 months, OS was 75% and DFS was 70%. Better local control was noted with higher doses of radiation.

In a prospective evaluation of 185 medically inoperable patients with early (T1-T2N0M0) NSCLC treated with SBRT, Allibhai (2014) evaluated the influence of tumor size on outcomes.[30] Over a median follow-up of 15.2 months, tumor size (maximum gross tumor diameter) was not associated with local failure but was associated with regional failure (p=0.011) and distant failure (p=0.021). Poorer OS (p=0.001), DFS (p=9.001), and cause-specific survival (p=0.005) were also significantly associated with tumor volume more significant than diameter.

Harkenrider (2014) reported outcomes after SBRT for 34 patients with unbiopsied lung cancer, with estimated rates of two-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.[31]

Section Summary

Although limited randomized data are available, studies have shown that SBRT for patients with stage one NSCLC who are not candidates for surgical resection because of comorbid conditions or for those with early stage disease who refuse surgery, survival rates may be comparable with surgical resection.

Hepatic and Hepatobiliary Tumors

In order to understand the impact of SBRT in the management of hepatocellular carcinoma and other hepatic malignancies, well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved.

Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs.

Systematic Reviews

Yang (2023) performed a systematic review and meta-analysis to compare the efficacy and safety of radiofrequency ablation (RFA) to SBRT in patients with inoperable HCC.[32] Seventeen studies involving 22,180 patients were included. One and two-year OS rates were better in the RFA group (OR 0.69, 95% CI 0.50-0.96, p=0.141; OR 0.69, 95% CI 0.53-0.89, p=0.082); however, 3-5 year OS rates were similar in both groups (OR 0.94, 95% CI 0.65-1.38, p=0.001; OR 0.98, 95% CI 0.68-1.34, p=0.016) moderate to high (I2=29.6-69.7%) heterogeneity. SBRT groups had higher rates of local control (freedom from local progression; FFLP) compared to RFA at one, two, and three years (OR 2.19, 95% CI 1.44-3.34, P=0.303; OR 1.57, 95% CI 1.12-2.19, P=0.268; OR 2.22, 95% CI 1.7-2.9, p=0.474). Heterogeneity was low to moderate (I2=0-20.4%). No significant differences were found in the reported treatment-related complications, but the SBRT group had worse outcomes related to liver function and failure (p<0.01). The authors state baseline characteristics (e.g., liver function) likely contributed to the differences in the groups and future studies need to take into account baseline differences such as tumor size and location, prior treatment, and liver function.

Wu (2022) reported a systematic review compare external beam radiation therapy modalities for HCC with macrovascular invasion (MVI).[33] A total of 44 studies including 3,730 patients were included. Particle therapy had a pooled one-year OS (60.9%) that was significantly greater than conventional radiotherapy (45.3%; p=0.005) and SBRT (44.9%; p=0.002). Particle therapy and SBRT had significantly objective response rate compared to conventional radiotherapy, whereas only particle therapy was significantly greater than conventional radiotherapy with respect to local control rate. The most frequent types of grade ≥ 3 complications were hematological toxicity, hepatotoxicity, dermatological toxicity.

Bisello (2021) performed a systematic review of SBRT for the treatment of intrahepatic cholangiocarcinoma.[34] Six publications with a total of 145 patients met inclusion criteria. SBRT followed previous systemic or local treatments for 28.6 to 66.7% of patients. No meta-analysis was conducted. Median follow-up was reported in five studies and was 16 months (range 8.8 to 18.0). Median OS was reported in all studies and was 14 months (range 10 to 48 months). Reports of tumor response, local control, and toxicities were not consistently.

Shanker (2021) published a systematic review analyzing local control, survival and toxicity outcomes following SABR for HCC.[35] A total of 49 cohorts including 2,846 patients met inclusion criteria. Pooled LC rates were 91.1% (95% CI 88.3 to 93.2) at one year, 86.7% (95% CI 82.7 to 89.8) and two years, and 84.2% (95% CI 77.9 to 88.9) at three years. Pooled OS rates were 78.4% (95% CI 73.4 to 82.6) at one year, 61.3% (95% CI 55.2 to 66.9) at two years, and 48.3% (95% CI 39.0 to 57) at three years. Grade 3 and grade 4/5 toxicity rates, calculated as population-weighted medians, were 6.5% (IQR 3.2 to 16) and 1.4% (IQR 0 to 2.1), respectively.

Long (2021) reported a systematic review of therapeutic outcome of SBRT for small liver-confined HCC (≤ 3 lesions with longest diameter ≤ 6 cm).[36] A total of 14 observational studies including 1,238 patients met inclusion criteria. Pooled one-year OS and LC rates were 93.0% (95% CI 88.0 to 96.0%) and 96.0% (95% CI 91.0 to 98.0%), respectively. Pooled three-year OS and LC rates were 72.0% (95% CI 62.0 to 79.0%) and 91.0% (95% CI 85.0 to 95.0%), respectively. Subgroup differences were identified for Child-Pugh class one- and three-year

OS rate, but not for number of lesions, pretreatment situation, age (median/mean age of 65), macrovascular invasion, tumor size, or radiation dose (median BED10 of 100 Gy). Pooled rates of grade 3 or greater hepatic complications and radiation-induced liver disease were 4.0% (95% CI 2.0 to 8.0%) and 14.7% (95% CI 7.4 to 24.7%), respectively.

Lee (2020) evaluated the efficacy of SBRT versus RFA for the treatment of liver malignancies via a meta-analysis of 11 studies involving 2,238 patients.[37] Of the 11 studies, eight involved treating patients for early HCC and three for liver metastases. Results revealed that the pooled two-year local control rate was significantly improved in the SBRT versus RFA arm (83.8% versus 71.8%; p=0.024). The pooled two-year control rate was also significantly higher in the SBRT versus RFA arm among patients in the liver metastases studies only (83.6% versus 60%; p<0.001) while no such significant difference was seen in HCC studies (84.5% versus 79.5%; p=0.431). Pooled analysis of OS in HCC studies showed an odds ratio of 1.43 (95% CI 1.05 to 1.95; p=0.023), favoring RFA. Only two liver metastases studies had comparative survival data; no significant difference was seen.

Dobrzycka (2019) published a systematic review on outcomes following SBRT for early-stage hepatocellular carcinoma.[38] A total of 16 studies met inclusion criteria, 14 of which were retrospective. The average diameter of the treated tumor was 23 mm. Weighted one-year local control was 94.1% based on 11 studies. Seven and four studies reported two- and three-year local control, respectively, and the weighted means from those studies were 92.2% and 93.7%. Weighted one-year mean OS was 90.9% based on 14 studies. Nine and four studies reported two- and three-year OS, respectively, and the weighted means from those studies were 67.4% and 73.3%. Based on all 16 included studies, 171 grade 1 to 2 toxicities (17.5%) and 53 ≥ grade 3 toxicities (5.3%) were reported.

Frakulli (2019) performed a systematic review SBRT for the treatment of advanced cholangiocarcinoma.[39] Studies were included if they analyzed at least 10 patients with advanced cholangiocarcinoma. A total of 10 studies with 231 patients met inclusion criteria. Nine of the 10 showed moderate to serious risk of bias, as calculated by the ROBINS-I risk of bias tool. Median follow up was 15 months (range: 7.8-64.0 months). Pooled one- and two-year OS was 58.3% (95% CI: 50.2-66.1%) and 35.5% (95% CI: 22.1-50.1%), respectively. Pooled local control at one-year was 83.4%, (95% CI: 76.5-89.4%). There was one treatment-related death.

A 2012 systematic review conducted by Tao and Yang, assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms.[40] The review included prospective clinical trials published in English. Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included. Treatment was performed in 1 to 10 fractions to total doses of 18 to 60 Gy. Most studies that were included reported outcomes for patients with both primary and metastatic disease, without separating out outcome data for primary tumors only. In addition, some studies reported on outcomes for primary liver tumors including cholangiocarciomas. At Indiana University, in a phase I study, Cardenes (2010) treated 17 HCC patients with Child-Turcotte-Pugh (CTP) CTP-A or CTP-B, one to three lesions and cumulative tumor diameter of 6 cm or less.[41] Patients with CTP-A were treated in three fractions with the dose escalated from 12 to 16 Gy. For patients with CTP-B, the dose was modified to 5 fractions starting at 8 Gy per fraction and was not escalated because two patients treated at 3 × 14 Gy developed grade three hepatic toxicity. The one-year OS was 75%, and there were no local failures during the median 24 months of follow-up.

Meng (2009) conducted a systematic review and meta-analysis of transcatheter arterial chemoembolization (TACE) in combination with radiotherapy compared with TACE alone for unresectable hepatocellular carcinoma (HCC) using meta-analysis of data from the literature involving available trials.[42] Seventeen trials involving 1476 patients were identified. Five were RCTs, and 12 were non-RCTs. In terms of quality, five RCTs were graded B, and the 12 nonrandomized studies were graded C. Results showed that TACE plus radiotherapy significantly improved survival and tumor response over TACE alone. The authors concluded that considering the strength of the evidence, additional RCTs are needed before combination TACE and radiotherapy can be routinely recommended.

Randomized Controlled Trials

Shi (2022) compared SBRT after surgical resection with hepatectomy to hepatectomy alone in 76 patients with microvascular invasion (MVI)-positive early stage HCC.[43] Seventy-six patients were randomized to either surgery or surgery with adjuvant SBRT at the surgical margin, and there were 38 subjects in each arm. In the SBRT group DFS was 92.1% in one year, 65.8% in two years, and 56.1% at three years, and DFS in the surgery control group was 76.3%, 36.8%, and 26.3% (p=0.005). OS at one, three, and 5 years was 100%, 89.5%, and 75.0% in the SBRT group and 100%, 68.4%, and 53.7% in the surgery control group (p=0.053). Nearly one third of the people in the SBRT group (12/38) experienced radiotherapy-related adverse events but none were grade 3 or higher.

Nonrandomized Comparative Studies

Larger studies and those addressing the policy criteria (e.g. number of lesions) are addressed below.

Yang (2019) compared the outcomes of SBRT and conventionally fractionated radiotherapy in HCC patients with portal vein invasion.[44] A total of 104 patients were evaluated, 45 in the SBRT group and 59 in the conventionally fractionated radiotherapy group. The differences in rates of overall response (62.2% vs. 33.8%; p=0.003), one-year OS (34.9% vs. 15.3%; p=0.012), and in-field progression-free survival (69.6% vs. 32.2%; p=0.007) were statistically significant, with higher values in the SBRT group for all measures. After propensity score matching, the rates all remained higher in the SBRT group. No significant differences were identified in incidence of radiation-induced liver disease or increase of Child-Pugh score greater than or equal to 2 within three months of radiotherapy.

Bettinger (2019) reported on a multi-center retrospective comparative study of SBRT (n=122) or sorafenib (n=901), a tyrosine kinase inhibitor, for the treatment of advanced HCC.[45] Unadjusted median OS was 18.1 months (95% CI, 10.3 to 25.9) for SBRT and 8.8 (95% CI, 8.2 to 9.5) for sorafenib. Adjusted median OS was 17.0 months (95% CI, 10.8 to 23.2) and 9.6 (95% CI, 8.6 to 10.7), respectively. No survival benefit was observed for patients with SBRT in patients with portal vein thrombosis. Over 80% of patients were male in each study arm. Patients in the sorafenib group had significantly worse ECOG PS scores (p<0.001), were more frequently pre-treated with radiofrequency ablation (RFA) (p<0.001) or transarterial chemoembolization (TACE) (p=0.016), had a higher incidence of multifocal disease and extrahepatic metastases (p<0.001), and had more advanced illness on the basis of the Barcelona Clinic Liver Cancer (BCLC) staging system (Grade B, intermediate and Grade C, advanced; p<0.001). Although propensity score matching was utilized to adjust for differences in baseline characteristics, the data are limited by extensive heterogeneity in the respective treatment populations. Presently, the FDA indication for the use of sorafenib is for patients with

unresectable HCC. Due to the inclusion of patients who had previously been treated by surgery and with early or intermediate stage disease on the basis of BCLC criteria, it is unclear whether some patients were candidates for re-resection, potentially limiting the relevance of this study.

Roman (2019) performed a retrospective analysis of short- and long-term outcomes of SBRT (n=118) and surgical treatment (n=142) for patients with liver malignancies.[46] Median OS was 27.63 months for all patients, 22.93 months in the SBRT group, and 30.65 months in the surgical group. According to a Kaplan-Meier analysis, there was no statistically significant difference in disease specific survival between groups (p=0.082).

Nakano (2018) reported results of a retrospective analysis of 281 patients with one to three small (≤3 cm in diameter) hepatocellular carcinoma tumors who were treated with curative intent via surgical resection or SBRT.[47] The surgical resection group on average was younger, had more tumors, and had better hepatic function than those in the stereotactic body radiotherapy group (p<0.05). The five-year OS rate was 75.2% vs 47.8% (p=0.0149) in the surgical resection and SBRT groups, respectively. The five-year disease-free survival rate was 33.8% vs 16.4% (p=0.0512) in the surgical resection and SBRT groups, respectively. According to the multivariate analysis, surgical resection was a significant favorable factor for OS and disease-free survival.

Parikh (2018) secondary analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to compare SBRT with RFA as primary treatment for early-stage HCC.[48] A total of 408 patients treated with RFA and 32 with SBRT were included. Ninety-day hospitalization and one-year mortality were not significantly different between groups. Overall survival was significantly better in the RFA group (p<0.001). In a multivariate analysis, advanced age, higher stage, decompensated cirrhosis, and treatment with SBRT (HR 1.80; 95%CI: 1.15-2.82) were associated with worse survival, but in the propensity score adjusted analysis, survival and costs were similar between the two groups.

Su (2017) retrospectively compared the efficacy of SBRT and liver resection for small HCC (less than or equal to 5 cm).[49] A total of 117 patients with small HCCs with one or two nodules were included, with 82 receiving SBRT and 35 undergoing liver resection. No significant differences between groups were found in OS or PFS. Prior to propensity score matching, the one-, three-, and five-year OS was 96.3%, 81.8%, and 70.0% in the SBRT treated patients and 93.9%, 83.1%, and 64.4% in the resection patients, respectively (p=0.558). One-, three-, and five-year PFS in the SBRT and resection groups were 100%, 91.8%, and 74.3% and 96.7%, 89.3%, and 69.2%, respectively. Hepatotoxicity was also similar between groups.

In 2016, Wahl reported on single U.S. site experience with 224 patients with nonmetastatic HCC accumulated between 2004 and 2012.[50] Radiofrequency ablation (RFA) was used to treat 161 patients and 249 lesions with a freedom from local progression (FFLP) rate at one year of 83.6% and two years of 80.2%. SBRT was used to treat 63 patients with 83 lesions with a FFLP rate of 97.4% at one year and 83.8% at two years.

In an attempt to extend the use of SBRT to larger lesions, Shin (2010) treated six patients with large tumors (median tumor volume, 1288 mL; range, 1008-1815 mL) with no worse than CTP-A liver disease and without extrahepatic metastases.[51] The 4 × 8–10 Gy regimen was relatively safe with only one case of grade three changes in transaminases. However, one-year OS was only 33%, in part due to advanced disease. One-year LC and OS rates were

50% to 100% and 33% to 100%, respectively. There were 13 cases of radiation-induced liver disease and four, grade five; six, grade four; and 69, grade three adverse events reported.

Comparison with TACE

Comito (2022) performed a single center RCT parallel-group superiority trial comparing SBRT to a second course of TACE for the curative treatment of unresectable early or intermediate stage HCC in patients with residual disease after initial TACE treatment.[52] Forty patients were randomized to SBRT (n=21) or continued TACE (n=19). There were no significant differences in baseline patient and treatment characteristics between the study groups. Local control was better with SBRT with 84% of SBRT cases having local control at one year, vs. 23% of TACE cases. PFS was also superior with SBRT. PFS with SBRT was 37% at one year and 21% at two years, compared to PFS with TACE of 13% at one year and 6% at two years. Distant recurrence-free survival (DRFS) was longer in the TACE arm but the difference was not statistically significant (p=0.494). Median OS in both study arms was 30 months and OS was not significantly different between the two treatment groups (p=0.472).

In 2019, Shen reported results of a comparison between SBRT and TACE.[53] A total of 188 patients with medium-sized HCC (3 to 8 cm) were treated with TACE (n=142) or SBRT (n=46). For surviving patients, the median follow-up was 26.6 months and for all patients it was 17.1 months. The three-year infield control was 63.0% and 73.3% for TACE- and SBRT-treated patients, respectively. The three-year OS was 22.9% and 47.7% for the TACE- and SBRT-treated patients, respectively. Treatment modality, sex, and recurrence status were independent predictors of infield control, which number of tumors, treatment modality, albumin-bilirubin grade, tumor volume, Eastern Cooperative Oncology Group status, and recurrence status were independent predictors of OS. According to the propensity score matching analysis, the SBRT group had superior three-year infield control (p=0.007) and three-year OS (p<0.001) compared with the TACE group.

Sapir (2018) assessed 209 patients that underwent TACE (n=84) or SBRT (n=125) for HCC at a single institution.[54] Baseline differences between the groups included age (SBRT 65 versus TACE 61; p=0.01), tumor size (SBRT 2.3 cm versus TACE 2.9 cm; p<0.01), and frequency of liver transplantation (SBRT 8% versus TACE 18%; p=0.01). However, there were no significant differences in number of tumors treated per patient, underlying liver disease, or baseline liver function. One- and two-year local control were significantly different between treatment groups (SBRT 97 and 91% versus TACE 47 and 23%, respectively). Toxicities grades 3 and higher were reported in 8% of the SBRT group and 13% of the TACE group.

Cai (2018) included 121 patients with primary hepatocellular carcinoma in a retrospective comparison of transarterial chemoembolization (TACE), gamma knife, and a combination of the two.[55] The TACE alone group included 46 patients, the gamma knife alone group 36 patients, and the combination group 39 patients. Statistically significant differences were reported for overall survival rates between the three groups at 6, 12, and 18 months (TACE alone 50%, 34.8%, and 28.3%; gamma-knife alone 36.1%, 30.6%, and 16.7%; TACE and gamma-knife combined 84.6%, 71.8%, 61.5%). However, there was no significant difference between groups in overall survival at 24 months. (p=0.117). Median survival time for the TACE, gamma knife, and combination groups was seven months, three months, and 20 months, respectively, with the differences reported as significant. There were also statistically significant differences reported in leukopenia, but not in thrombocytopenia, anemia, nausea, vomiting, or liver function lesions.

In 2015, Jacob evaluated HCC lesions 3 cm or more and compared TACE alone (n=124) with TACE plus SBRT (n=37) from 2008 to 2013.[56] Sorafenib, the tyrosine kinase inhibitor (TKI), was used by 36.1% of the TACE alone group and 41.9% in the combination therapy group. Both groups had received pre- and posttreatment chemotherapy. Local recurrence was significantly decreased in the TACE plus SBRT group (10.8%) in comparison with the TACE-only group (25.8%) (CI, not reported, p=0.04). After censoring for liver transplantation, OS was found to be significantly increased in the TACE plus SBRT group (33 months) compared with the TACE-only group (20 months) (CI, not reported, p=0.02). Chronic HCV infection was the cause of HCC in most patients in both groups.

In 2016, Su, reported on a single-site experience with 77 HCC lesions greater than 5 cm treated with SBRT followed by TACE and 50 patients who had SBRT alone.[57] The patients who had SBRT alone either refused TACE or had hepatic arteriovenous fistulas precluding TACE. The median follow-up was 20.5 months and median tumor size was 8.5 cm (range, 5.1-21.0 cm). The PFS and local relapse-free survival did not differ significantly between groups.

In 2014, Zhong reported on a single-site experience with 72 of 1086 HCC patients consecutively treated with SBRT between 2006 and 2012.[58] These patients had lesions 10 cm or larger and incomplete ablation with prior TACE. The median total dose of 35.6 Gy was delivered over 12 to 14 days with a fractional dose of 2.6 to 3.0 Gy at 6 fractions per week. A complete response (CR) achieved in 6 (8.3%), partial response (PR) in 51 (70.8%), stable disease (SD) in 9 (12.5%) and progressive disease (PD) in 6 patients (8.3%) within a median follow-up of 18 months.

Bridge to Transplantation

The increasing prevalence of chronic liver conditions progressing to HCC such as HCV infection and alcoholic cirrhosis has led to interest in the use of SBRT and other liver-directed therapies as bridge therapy to transplantation for persons who are on organ waitlists.

Wong (2021) reported outcomes in patients bridged to liver transplantation for HCC. A prospective cohort of SBRT-treated patients was compared with a retrospective cohort of TACE- or HIFU-treated patients.[33] A total of 40 SBRT patients, 59 TACE patients, and 51 HIFU patients were evaluated. The primary endpoint of tumor control rate at one year post-bridging therapy was 92.3%, 43.5%, and 33.3% after SBRT, TACE, and HIFU, respectively (p=0.02). Time-to-progression at one and three years was significantly different between groups (10.8%, 18.5% in SBRT, 45%, 54.9% in TACE, and 47.6%, 62.8% in HIFU; p<0.001). There were no statistically significant differences between groups in perioperative complications and patient and recurrence-free survival rates after transplant.

Sapisochin (2017) performed an intention-to-treat analysis to examine the safety and efficacy of SBRT as a bridge to liver transplantation for HCC.[59] A total of 379 patients were treated with SBRT (n=36), TACE (n=99), or RFA (n=244). The dropout rate was not significantly different between groups (p=0.7). The numbers of patients transplanted per group were 30, 79, and 203 in the SBRT, TACE, and RFA groups, respectively. The one-, three-, and five-year actuarial survival from time of listing was not significantly different between groups and the values reported ranged from 83-86%, 72-75%, and 56-61%, respectively. The one-, three-, and five-year survival from the time of transplant was also not significantly different between groups (83%, 75% and 75% in the SBRT group, 96%, 75% and 69% in the TACE group, and 95%, 81% and 73% in the RFA group, p=0.7).

Section Summary

The current evidence base is largely heterogenous and includes mostly prospective cohort studies that report outcomes for patients with HCC. Many of the studies were conducted on patients eligible for transplant or who were not eligible for other treatment modalities. Local control and overall survival among the study participants were generally over 70% at one-three-years follow-up. Studies reported a reduction in these outcomes after two-three years follow-up. Multiple studies reported better outcomes when tumors were 6 cm or less. It is important to note that multiple studies reported severe adverse events (≥ grade three) after SBRT for a small number of study participants. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant.

Prostate Cancer

Systematic Reviews

Foerster (2021) published a systematic review of SBRT for high-risk prostate cancer. A total of 21 studies met inclusion criteria.[60] The majority evaluated SBRT of the prostate alone, while three reported on prostate and pelvic node SBRT. Acute and chronic GU toxicity grade ≥2 was 12 to 46.7% and 7 to 60%, respectively, in studies that included pelvic nodal irradiation and 0 to 89% and 2 to 56.7%, respectively in the prostate-only studies. Acute and chronic grade ≥2 GI toxicity was 0% to 4% and 4 to 50.1%, respectively, in studies that included pelvic nodal irradiation, and 0 to 18% and 0 to 40%, respectively, for studies without pelvic nodes irradiation. The range of biochemical control rates was 82 to 100% after two years and 56 to 100% after three years.

A systematic review and meta-analysis by Valle (2021) evaluated local salvage therapies after radiotherapy for prostate cancer.[61] A total of 150 studies met inclusion criteria. The within modality between study heterogeneity was significant and therefore adjustment was required. Adjusted five-year recurrence-free survival was not significantly different between any modality and radical prostatectomy, but severe GU toxicity was significantly higher with radical prostatectomy than with any form of radiotherapeutic salvage. Severe GI toxicity was significantly lower in patients with high-dose-rate brachytherapy salvage than with radical prostatectomy (adjusted rates 1.8 vs. 0.0%, $p<0.01$). No other significant differences were identified between groups for severe GI toxicity.

Achard (2020) performed a systematic review of SBRT vs. elective nodal radiotherapy for nodal oligorecurrent prostate cancer.[62] A total of 22 articles were included, four of which were prospective phase II trials. PFS rates were better in the elective nodal radiotherapy-treated patients (52 to 80%) than in those treated with SBRT (16 to 58%). The toxicity rate was slightly lower in the SBRT group.

Jackson (2019) performed a systematic review and meta-analysis on SBRT for localized prostate cancer. [63] Thirty-eight prospective studies between 1990 and 2018 were retrieved featuring low- (45%), intermediate- (47%), and high-risk (8%) patients (n=6116). Most common dose received was 7.25 Gy/fraction (range 5 to 10) in a median of 5 fractions (range 4 to 9). Five-and seven-year biochemical relapse-free survival (bRFS) rates were 95.3% (95% CI 91.3 to 97.5; I^2 87.96; Q value 74.9, $p<0.001$)) and 93.7% (95% CI 91.4 to 95.5), respectively. Late grade 3 or higher genitourinary (GU) or gastrointestinal (GI) toxicity rates were 2.0% (95% CI, 1.4 to 2.8) and 1.1 (95% CI, 0.6 to 2.0), respectively. In 33 studies that reported on the use of androgen-deprivation therapy (ADT), 15% of patients received ADT alongside SBRT. The

impact of ADT on pooled outcomes is unknown. Furthermore, studies did not stratify bRFS rates by patient risk level, contributing to high heterogeneity in the results.

Kishan (2019) pooled long-term outcomes from 10 single-center and two multi-center prospective trials evaluating SBRT for the treatment of low-to-intermediate risk prostate cancer (n=2142).[64] Doses of SBRT ranged from 33.5 to 40.0 Gy in 4 to 5 fractions. Overall, 115 patients (5.4%) received concurrent ADT. Mean overall follow-up duration was 6.9 years (interquartile range [IQR], 4.9 to 8.1). For patients with low, intermediate-favorable, and intermediate-unfavorable, and any intermediate risk level, biochemical recurrence rates were 4.5% (95% CI 3.2 to 5.8), 8.6% (95% CI 6.2 to 11.0), 14.9% (95% CI 9.5 to 20.2), and 10.2% (95% CI 8.0 to 12.5), respectively. Corresponding overall survival rates were 91.4% (95% CI, 89.4 to 93.0), 93.7% (95% CI, 91.0 to 95.6), 86.5% (95% CI, 80.6 to 90.7), and 91.7% (95% CI, 89.2 to 93.6), respectively. There were 13 (0.6%) and 2 (0.09%) reported cases of acute grade 3 or higher genitourinary (GU) or gastrointestinal (GI) toxicities. The incidence of late grade 3 or higher GU and GI toxicities was 2.4% (95% CI, 1.8 to 3.2) and 0.4% (95% CI, 0.2 to 0.8), respectively. The analysis was limited by heterogeneity in toxicity reporting and scoring criteria and lack of comparative studies.

Loi (2019) published a systematic review assessing sexual function in prostate cancer patients who had been treated with SBRT.[65] A total of 12 studies representing 1221 patients who had not received androgen-deprivation therapy (ADT) and were available at final follow-up were analyzed. Studies used varying definitions for erectile dysfunction (ED); some were based on the Sexual Health Inventory for Men (SHIM) scale whereas others were based on the Expanded Prostate Cancer Index Composite (EPIC)-26. At 60 months, ED was reported by 26 to 55% of previously sexually functioning patients in 5 of 12 studies.

Linney and Barrett (2018) performed a systematic review of the literature on the use of SBRT for early-stage prostate cancer. Sixteen articles met inclusion criteria. The range of reported biochemical progression-free survival rates was 77.1 to 100% for SBRT and 55 to 98% for conventionally fractionated EBRT. Rates of grades 1, 2, and 3 acute genitourinary toxicity were reported as 13.3 to 71%, 12 to 25% and 0 to 3% for SBRT and 28.7 to 51.9%, 15.6 to 41.4%. and 1.1 to 8.1% for EBRT, respectively. Authors noted a lack of randomized trials and long-term follow-up.

Randomized Controlled Trials

Poon (2021) reported results of a randomized trial comparing SBRT (36.25 Gy delivered in five fractions over two weeks) and conventionally fractionated radiotherapy (76 Gy delivered in 38 fractions over 7.5 weeks) for the treatment of low- and intermediate-risk localized prostate cancer.[66] A total of 64 men were randomized to receive SBRT (n=31) or conventional fractionation (n=33). Median follow-up was 2.3 years. There were no significant differences between groups in the primary endpoint, variation in patient-reported quality of life (PRQOL) at one year assessed by changes in the Expanded Prostate Cancer Index Composite (EPIC) questionnaire scores, at 3, 6, 9 and 12 months. There were statistically significant differences between groups in grade ≥ 1 acute and one-year late gastrointestinal toxicities, with 35% vs. 87% acute toxicities for conventional fractionation versus SBRT, respectively ($p<0.0001$), and 64% vs. 84% toxicities at one year for conventional fractionation versus SBRT, respectively ($p=0.03$).

Brand (2019) reported acute toxicity findings from a randomized trial comparing SBRT with conventionally fractionated and moderately hypofractionated radiotherapy (PACE-B study).[67]

A total of 874 men with WHO performance status 0-2, low-risk or intermediate-risk prostate adenocarcinoma (Gleason 4 + 3 excluded) were enrolled in this international, phase 3, open-label, randomized, non-inferiority trial. Patients were randomly assigned to receive conventionally fractionated or moderately hypofractionated radiotherapy (n=4,41; 78 Gy in 39 fractions over seven to eight weeks or 62 Gy in 20 fractions over four weeks, respectively), or stereotactic body radiotherapy (n-433; 36.25 Gy in five fractions over one to two weeks). The primary endpoint of the trial was freedom from biochemical or clinical failure, and the coprimary outcomes for this acute toxicity substudy were worst grade 2 or more severe Radiation Therapy Oncology Group (RTOG) gastrointestinal or genitourinary toxic effects score up to 12 weeks after radiotherapy. No statistically significant differences in toxicity were reported. Grade 2 or more severe toxic gastrointestinal events were reported in 12 and 10% of patients in the conventionally fractionated or moderately hypofractionated group and stereotactic body radiotherapy groups, respectively (p=0.38). Grade 2 or worse genitourinary toxicity were reported in 27 and 23% of the conventionally fractionated or moderately hypofractionated group and stereotactic body radiotherapy groups, respectively (p=0.16).

Tree (2022) published a follow-up toxicity analysis of the PACE-B study after two years.[68] Outcomes of interest were the cumulative incidence of grade 2 or worse genitourinary or gastrointestinal toxicity, grade 2 or worse erectile dysfunction, and other symptoms, including hot flashes, other pain, fatigue, anorexia, weight loss, and radiation dermatitis. Data was available for 796 of 844 patients (91%) at 24 months. Nine patients died between radiotherapy treatment and the 24-month follow-up; and no deaths were treatment-related. Cumulative grade 2 or worse genitourinary (GU) toxicity rates were higher in the SBRT group, using both radiation therapy oncology group (RTOG) grades (p=0.0015) and Common Terminology Criteria for Adverse Events (CTCAE) grades (p=0.0001). The most frequent GU toxicity was urinary frequency, but grade 3 urinary frequency was rare; less than 1% in both groups. Cumulative gastrointestinal toxicity at grade 2 or worse nearly the same in both treatment groups using both RTOG and CTCAE measures (p=0.92; p=0.91), and incidence of gastrointestinal toxicity was low overall. Erectile dysfunction and other symptoms were not significantly different.

Nonrandomized Comparative Studies

Gogineni (2021) compared low-dose-rate (LDR) brachytherapy and SBRT for the treatment of low- and intermediate-risk prostate cancer.[69] Sequential low- and intermediate-risk prostate cancer patients treated definitively with SBRT (n=118) and low-dose-rate brachytherapy (n=219). Five-year biochemical control was 91.6% and 97.6% for low-dose-brachytherapy and SBRT, respectively (p=0.108). The difference between groups in pre- to post-treatment increase in American Urologic Association (AUA) scores was statistically significant, with the LDR and SBRT groups reporting 17.2 and 10.3, respectively at one month (p<0.001) and 14.0 and 9.7, respectively, at three months (p<0.001). The LDR and SBRT groups reported 0.8% and 2.5% late grade 3 GU toxicity (p=0.238) and 0.0% and 2.5% late grade 3 GI toxicity (p=0.018).

Patel (2020) reported a comparison of SBRT and EBRT using data from the National Cancer database on men > 40 years old with localized prostate cancer treated with radiation therapy and concomitant ADT with curative intent.[70] Median follow-up was 74 months. Regardless of risk group, there was no difference in estimated six-year OS between radiation therapy modality. The multivariate analysis did not identify any difference in risk of death following

SBRT versus EBRT (unfavorable intermediate: adjusted HR 1.09, 95% CI 0.68 to 1.74, p=0.72; high risk: adjusted HR 0.93, 95% CI 0.76 to 1.14, p=0.51).

In 2014, Yu compared toxicities after treatment with either SBRT (n=1335) or IMRT (n=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries.[71] The authors identified early stage prostate cancer patients aged 66 to 94 years treated from January 2008 to June 2011 who received either IMRT (n=53,841) or SBRT (n=1335) as primary treatment. SBRT patients were matched in a 2:1 manner based on potential confounders. SBRT was associated with higher rates of genitourinary (GU) toxicity. By six months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity versus 12.6% of IMRT patients (odd ratio [OR]=1.29; 95% CI 1.05 to 1.53; p=0.009). By 12 months posttreatment, 27.1% of SBRT versus 23.2% of IMRT patients had a claim indicative of GU toxicity (OR=1.23; 95% CI 1.03 to 1.43; p=0.01), and by 24 months after treatment initiation, 43.9% of SBRT versus 36.3% of IMRT patients had a claim indicative of GU toxicity (OR=1.38;95% CI 1.12 to 1.63; p=0.001). At six months posttreatment, there was increased gastrointestinal (GI) toxicity for patients treated with SBRT, with 5.8% of SBRT patients having had a claim indicative of GI toxicity versus 4.1% of IMRT patients (OR=1.42; 95% CI, 1.00 to 1.85; p=0.02), but at 12 and 24 months posttreatment, there were no significant differences in GI toxicity between groups.

Katz (2012) compared quality of life (QOL) after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early-stage prostate cancer.[72] QOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC), addressing urinary, sexual and bowel function. The EPIC data from the SBRT group was compared with the surgery group at baseline, three weeks, 5, 11, 24 and 36 months (SBRT group) and baseline, 1, 6, 12, 24, and 36 months (surgery group). The largest differences in QOL occurred one to six months after treatment, with larger declines in urinary and sexual QOL occurring in the surgery group, but a larger decline in bowel QOL after SBRT. The long-term urinary and sexual QOL declines remained clinically significantly lower for the patients who underwent prostatectomy but not for the SBRT patients.

Noncomparative Studies

Multiple cohort studies have report outcomes for patients treated with a standard dose of SRS or SBRT, or for groups of patients treated with SRS or SBRT at escalating doses. [73-96] Other noncomparative studies have reported on reirradiation using SBRT for recurrence[97] and on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence,[98] rectal tolerance,[99] and health-related QOL outcomes.[100]

Section Summary

Data on the use of SBRT in prostate cancer consists primarily of single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared with historical controls and a few looking at recurrence-free survival with a follow-up of three years or longer. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates and relatively high rates of biochemical recurrence-free survival.

Pancreatic Cancer

This section will focus on systematic reviews, comparative studies and larger case series.

Systematic Reviews

Liu (2021) reported a meta-analysis of survival outcomes following SBRT for locally advanced and borderline resectable pancreatic cancer.[101] A total of 19 studies met inclusion criteria. Overall study quality was rated as good using the Newcastle-Ottawa scale. For patients with locally advanced pancreatic cancer, the pooled median OS rates were 57% at one year, 19% at two years, and 10% at three years. The median PFS was 10 months. Pooled PFS rates at one, two, and three years were 36%, 12%, and 4%, respectively. Pooled incidence rates of acute gastrointestinal (GI), acute hematologic and late GI toxicity (grade≥3) were 2%, 4% and 8%, respectively. For patients with borderline resectable pancreatic cancer, pooled one- and two-year OS rates were 75% and 29%, respectively, while pooled one- and two-year PFS rates were 48% and 18%, respectively. The median PFS was 12.2 months and incidence rates of toxicity (grade ≥ 3) were 0%.

Zaorsky (2019) reported a systematic review of SBRT with varying doses for nonmetastatic pancreatic cancer.[102] A total of 15 studies met inclusion criteria and included 508 patients. Median follow-up was nine months. Local control rates were 60% to 83%. Acute and late grade 3+ toxicity were 3.5% and 5%, respectively. There were no significant differences in local control at one year or acute toxicity between biologically equivalent doses (calculated with an α/β of 10) <70 Gy versus ≥70 Gy.

Buwenge (2018) published a systematic review that evaluated the impact of SBRT on pain reduction.[103] Fourteen studies were identified, seven prospective and seven retrospective. Of these, 12 reported the percentage of pain relief in 190 patients. In these studies, global overall response rate to pain in patients with pain at presentation (complete and partial) was 84.9%, and heterogeneity was high. Acute and late toxicity (grade ≥3) rates were 3.3% to 18.0% and 6.0% to 8.2%, respectively. A 2022 update included 19 studies and continued to report high heterogeneity.[104] The pooled rate of complete response, reported in three studies, was 51.9% (95% CI 39.3 to 64.3%), and the rate of partial plus complete pain response, reported in nine studies, ranged between 44.4 and 100% (median: 78.6%).

A 2017 systematic review from Petrelli evaluated the safety and efficacy of SBRT for the treatment of pancreatic cancer. Nineteen studies, with a total of 1009 patients, including nonrandomized and single-center series with mixed populations, were analyzed.[105] No publication bias was identified, but the heterogeneity among studies was substantial. A meta-analysis calculated the OS rate at one year and the median OS to be 51.6% and 17 months, respectively. The rate of acute severe toxicity ranged from 0% to 36%. The authors concluded that no evidence supports the claim that SBRT results in better outcomes than conventional RT, but there are benefits of SBRT, including shorter treatment time.

Groot (2016) published a systematic review comparing outcomes from re-resection, chemoradiotherapy, and SBRT in patients with isolated local recurrence (ILR) after initial curative-intent resection of primary pancreatic cancer.[106] A total of 18 studies reporting on 313 patients was included for analysis, which included four retrospective case series (n=60) on SBRT. Morbidity and mortality were reported for re-resection (29% and 1%), chemoradiotherapy (54% and 0%), and SBRT (3% and 1%). Morbidity for re-resection was defined as the sum of surgical complications and non-surgical 30-daycomplications. For chemoradiotherapy and SBRT, it was defined as toxicities of grade 3 or higher as defined by the Common Terminology Criteria for Adverse Events v4.0 guidelines. Mortality was defined as death within 30 days post-intervention. Median survival post-treatment was 32 months (range, 16 to 32), 19 months (range, 16 to 19), and 16 months (range, 9 to 16) for re-resection, chemoradiotherapy, and SBRT, respectively. The disease-free interval for the re-resection

group tended to be longer than for chemoradiotherapy or SBRT, a finding that is known to correlate with improved outcomes for patients with ILR. Acute and late toxicity rates were reported for chemoradiotherapy (52% and 2%) and SBRT (3% and 2%), respectively. The analysis was limited by heterogeneity in treatments, including inconsistent use of combination systemic therapies.

Comparative Studies

Ma (2022) conducted a RCT focused on adjuvant therapy for stage II pancreatic adenocarcinoma.[107] After surgical resection 38 patients were randomized to receive SBRT followed by gemcitabine chemotherapy, or gemcitabine therapy alone. Most patients in both groups (34/38) experienced tumor recurrence prior to the last follow-up. Median OS was 28 months in the gemcitabine-only arm and 15 months in the SBRT arm. The HR for death was 0.56 (95% CI 0.23-1.36, p=0.20). There were no significant differences in adverse events between the two groups.

Arcelli (2020) reported a multicenter case-control study comparing SBRT plus chemotherapy and conventionally fractionated chemoradiation for locally advanced pancreatic cancer.[108] A total of 80 patients were matched according to age (over versus equal to or younger than 65 years), tumor diameter (two cut-offs: </≥3.0 and </≥3.9 cm), clinical tumor stage and clinical nodal stage, neoadjuvant CHT, and adjuvant CHT. There were no statistically significant differences in acute or late toxicity, DMFS, PFS, or OS between the two cohorts. Median one-year and two-year LC was 53.1% and 40.5% in the chemoradiation cohort and 80.4% and 49.8% in the SBRT cohort, respectively. There was no significant difference in OS between groups (p=0.031).

Wu (2019) reported the effects of SBRT and conventionally fractionated radiation therapy, both with concurrent chemotherapy, on total lymphocyte counts in patients with pancreatic adenocarcinoma.[109] Included patients were treated with conventionally fractionated radiation therapy with concurrent Nelfinavir (n=28), SBRT with concurrent Nelfinavir (n=27), or SBRT with concurrent chemotherapy (n=45). The conventionally fractionated group had significantly lower median lowest total lymphocyte counts (p<0.0001) and median total lymphocyte count over time (p<0.0001). There was no significant difference in median OS between SBRT and conventional fractionation.

Park (2017) published a retrospective review of patients treated with SBRT (n=44) or IMRT (n-226) for unresectable stage I-III pancreatic adenocarcinoma.[110] Baseline characteristics were analyzed and only age was found to be significantly different between groups. There were no significant differences in OS, local or distant failure, or subsequent resection. Acute grade 2+ gastrointestinal toxicity, grade 2+ fatigue, and grade 3+ hematologic toxicity were significantly different between groups, with IMRT associated with higher levels (p=0.008, p<0.0001, p=0.001, respectively).

In 2017, Zhong published a retrospective database analysis comparing conventional fractionated radiotherapy (CFRT) with SBRT for locally advanced primary pancreatic carcinoma.[111] Using a large hospital-based registry, the National Cancer Data Base (NCDB), clinical outcomes were described in 10,534 cases (CFRT in 7819, SBRT in 631) diagnosed and treated between 2004 and 2012. To minimize the treatment selection bias, a propensity score matching method was used. A logistic regression model predicting CFRT treatment vs SBRT treatment was used to calculate propensity scores for covariates of interest. The covariates chosen were ones found to be significant in the multivariate analysis or ones

thought to be clinically significant and included the following: patient age, AJCC clinical T and N staging, chemotherapy use, Charlson-Deyo comorbidity score, year of diagnosis, and receipt of definitive surgery. In the multivariate analysis, treatment with SBRT was associated with significantly improved OS with a hazard ratio of 0.84 (95% CI, 0.75 to 0.93; p<.001). With matched propensity score analysis, a total of 988 patients were analyzed, with 494 patients in each cohort. The median follow-up time was 26 months. After propensity matching as described above, SBRT usage continued to be associated with significantly improved OS with a median survival of 13.9 months vs 11.6 months (p<0.001). Kaplan-Meier curves for the propensity-matched groups demonstrate a significantly better OS curve for the SBRT cohort (p=0.001) with two-year OS rates of 21.7% and 16.5% for the SBRT and CFRT groups, respectively (p=0.001).

Section Summary

Combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. The role of SBRT as a radiation technique for pancreatic tumors has not been established, and it is not clear which patients would most likely benefit. However, studies have shown promising LC rates, and outcomes are comparable to other forms of EBRT but with shorter treatment time.

Renal Cell Carcinoma

Stereotactic radiotherapy (SRT) is being considered in the setting of oligoprogression to delay the need to change systemic therapy. Cheung (2021) conducted a prospective multicenter study to evaluate the use of SRT in oligoprogressive mRCC patients to determine the local control (LC), progression-free survival (PFS), cumulative incidence of changing systemic therapy, and overall survival (OS) after SRT to oligoprogressive metastatic renal cell carcinoma (mRCC) lesions in patients who are on tyrosine kinase inhibitor (TKI) therapy.[112] Patients with mRCC who had previous stability or response after ≥3 months of TKI therapy were eligible if they developed progression of five of fewer metastases. Thirty-seven patients with 57 oligoprogressive tumors were enrolled. Oligoprogressive tumors were treated with SRT, and the same TKI therapy was continued afterward. Competing risk analyses and the Kaplan-Meir methodology were used to report the outcomes of interest. The median duration of TKI therapy prior to study entry was 18.6 months; one year of LC of the irradiated tumors was 93% (95% confidence interval [CI] 71-98%). The median PFS after SRT was 9.3 mo (95% CI 7.5-15.7 months). The cumulative incidence of changing systemic therapy was 47% (95% CI 32-68%) at 1 yr, with a median time to change in systemic therapy of 12.6 months (95% CI 9.6-17.4 months). One-year OS was 92% (95% CI 82-100%). There were no grade 3-5 SRT-related toxicities. LC of irradiated oligoprogressive mRCC tumors was high, and the need to change systemic therapy was delayed for a median of >1 year. The use of stereotactic radiotherapy in metastatic kidney cancer patients, who develop growth of a few tumors while on oral targeted therapy, can significantly delay the need to change to the next line of drug therapy.

Correa (2019) published a PRISMA-based systematic review and meta-analysis of SBRT for primary RCC.[113] The primary outcome was LC (defined as tumor-size reduction and/or absence of local progression). The secondary outcomes were toxicity and renal function. A total of 26 studies met inclusion criteria. Of the 372 patients included, 78.5% had confirmed RCC histology upon pre-treatment biopsy and 80% had localized disease (stage I-II) while 20% had stage III to IV disease. The random-effect estimate of local control, based on 25

studies, was 97.2% (95% CI 93.9 to 99.5%). For toxicity (grade 3 to 4) and renal function (post-SBRT change in estimated glomerular filtration rate), random effect estimates, based on 23 and 8 studies, respectively, were, 1.5% (95% CI 0.0 to 4.3%), and -7.7 ml/min (95% CI -12.5 to -2.8). Heterogeneity was minimal (I^2 0 to 20%).

Siva (2018) retrospectively evaluated 223 patients who received single- or multi-fraction SBRT for primary RCC.[114] Average maximum tumor dimension was 43.6 mm (SD 27.7 mm) Grade 1 and 2 toxicity were reported in 35.6% of patients and grade 3 and 4 toxicities were reported in 1.3%. The rates of LC at two and four years were 97.8% and 97.8%, respectively. Cancer-specific survival, and progression-free survival were 95.7%, and 77.4%, respectively, at two years and 91.9%, and 65.4%, respectively, at four years.

A 2017 systematic review by Prins assessed options for the treatment of T1 renal cell carcinoma (RCC) for patients where surgery is not the treatment of choice.[115] Treatment options assessed included active surveillance, radiofrequency ablation, cryoablation, microwave ablation, and SBRT. PRISMA criteria were used to assess the literature and a total of 73 articles with methodological quality between 2b and 4 met inclusion criteria. No RCTs were identified. The authors concluded that all of the assessed treatment modalities were options for patients unfit to undergo invasive treatment, but that due to the quality of available studies was low.

In 2016, Yamamoto reported on 14 patients (11 males, 3 females) who received SBRT for RCC at a single site between April 2010 and February 2014.[116] The dose constraints for planning organ at risk volume of 10-fraction SBRT were 30 Gy for patients who retained both kidneys and 26 Gy in patients with single kidneys. Significant renal atrophic change was observed at a median observation interval of 16.9 months (range, 12.0 to 21.8 months). No patient experienced worsening of hypertension or required hemodialysis.

Ranck (2013) reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT.[117] For patients with five or fewer metastatic lesions, all lesions were treated; in patients with greater than five lesions, rapidly-growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of two lesions per patient. The two-year lesion-control rate was reported as 91.4% in the 12 patients who underwent treatment for all metastases, over a median follow-up of 21.3 months. However, in these patients, two-year freedom from new metastases was 35.7%. OS was 85% at two years. No patients who underwent treatment at all lesion sites died.

Section Summary

The literature on the use of SBRT for RCC consists of very small case series, which generally report high rates of LC. However, little evidence about the impact on patient outcomes can be derived from these data, nor any comparison made between this treatment modality and more established treatment modalities for RCC.

Paraganglioma

Glomus jugulare tumors (GJTs) are benign paragangliomas of the jugular foramen. Traditional management of these tumors involves surgical resection; however, considering the proximity of these tumors to important neurovasculature, stereotactic radiosurgery (SRS) may be an appropriate noninvasive treatment to consider. Campbell (2023) published a systematic review and meta-analysis focused on tumor control and treatment complications from surgery vs.

stereotactic radiosurgery (SRS) for jugular paraganglioma.[118] Data from 107 studies involving 3498 patients (2215 surgical patients and 1283 patients who were treated with SBRT). All studies were retrospective. The quality of the evidence was deemed “good” for 85 studies using the Newcastle-Ottawa Scale. The SRS group was older than the surgery group. The SRS group had larger tumor volume and were more likely to have had prior surgery. The SRS group was also more likely to present with dysphagia, tongue weakness, and headache, while the surgery group was more likely to have tinnitus and deafness. Recurrence rates were low for both groups but were lower for SRS (7% long-term recurrence vs. 15% with surgery). Surgery was associated with more complications, specifically cranial nerve (CN) VII, IX, X, XI, and XII palsies, cerebral spinal fluid leaks and postoperative dysphagia. A major limitation of the study was the authors were unable to analyze the available data for statistical significance. However, the study shows that both treatments are effective in the treatment of jugular paraganglioma.

Ong (2022) published a systematic review and meta-analysis to evaluate SRS as a treatment option for GJTs.[119] An online search using PubMed, Web of Science, Scopus, and Cochrane databases was performed in March 2019 for articles on radiosurgery treatment of GJTs. The screening process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The final analysis comprised 23 studies including 460 patients. Average rates of tinnitus, hearing loss, and lower cranial nerve deficit as presenting symptoms were 56% (95% confidence interval [CI], 46%-66%), 56% (95% CI, 44%-68%), and 42% (95% CI, 31%-54%), respectively. Overall clinical status improvement rate after treatment was 47% (95% CI, 37%-57%). Rates of tinnitus, hearing loss, and lower cranial nerve improvement after treatment were 54% (95% CI, 44%-63%), 28% (95% CI, 19%-40%), and 22% (95% CI, 11%-39%), respectively. The mean follow-up time across studies was 47 months (range, 4-268 months). The aggregate tumor control rate at the time of follow-up was 95% (95% CI, 93%-97%). The tumor control rate of 95% and 47% symptomatic improvement suggest that SRS may be a suitable treatment modality for these hypervascular skull base tumors.

Primary Spinal Tumors

Conti (2022) published a systematic review and meta-analysis of radiosurgery for benign spinal hemangiomas.[120] Three series of cases involving 24 patients were assessed. The review found that the complete response rate from radiosurgery was 45.7% and the overall response rate was 94.1%. The review found that radiosurgery was effective for spinal hemangioma but did not include studies that compare radiosurgery to other treatments for spinal hemangioma.

Oligometastases

In order to understand the impact of SBRT on metastatic cancer outcomes well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved. Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs.

Systematic Reviews

Bone metastasis is a frequent cause of cancer-related pain and external beam radiation therapy can be an effective palliative treatment. The role of SBRT is being investigated as a way to improve pain and local control for people with metastasis to the bones. Ito (2022) published a systematic review and meta-analysis of RCTs comparing SBRT to conventional

radiotherapy (cEBRT) for painful bone metastases.[121] Seven studies involving 964 patents were assessed. Two studies were phase III and five were phase II trials. Four studies were of spinal metastasis, one was of bone metastases, and three studies involved both spine and bone metastases. In the studies 522 patients were treated with SBRT and 442 were treated with conventional radiotherapy. Overall pain response rates at three months were 45% in the SBRT arm and 36% in the cEBRT group, which was not significant (RR=1.19; 95% CI 0.93-1.53; p=0.14). A focused analysis of studies involving spine metastases also was not statistically significant with response rates of 40% in the SBRT arm and 35% in the cEBRT arm (RR=0.14; 95% CI 0.71-1.84; p=0.44). No significant differences were seen in adverse events, quality of life, or survival. The authors state that the results of the meta-analysis may be inconsistent with retrospective research in particular that favors SBRT because SBRT tends to be offered to patients in better condition than those who are treated with cEBRT.

Viani (2021) reported a systematic review evaluating the efficacy of SBRT for the treatment of breast cancer metastases.[122] The ten studies that met inclusion criteria included 467 patients. Local control rates were 97% (95% CI 95 to 99%) and 90% (95% CI 84 to 94%) and OS was 93% (95% CI 89 to 96%) and 81% (95% CI 72 to 88%) at one and two years, respectively. The rate of any grade 2 was 4.1 % (95% CI 0.1 to 5%) and any grade 3 toxicity was 0.7% (0 to 1%), respectively.

Deodato (2021) reported a systematic review of outcomes following SBRT for nodal metastases.[123] A total of 29 studies including 969 patients met inclusion criteria. There was statistically significant heterogeneity in patient and treatment characteristics. Pooled two-year LC was 79.3% (95% CI 72.8% to 85.7%) based on 11 reporting studies and pooled two-year PFS was 35.9% (95% CI 22.1% to 49.7%) based on eight reporting studies. Grade ≥ 3 and grade 5 toxicity rates were 2.0% and 0.2%, respectively.

Yan (2020) performed a systematic review of SBRT for oligometastatic prostate cancer involving 10 studies (six observational cohorts; one phase I single arm prospective trial; one phase II single arm prospective trial; two phase II RCTs) with 653 patients and 1,111 lesions.[124] Results revealed an overall local control rate of 97% (95% CI 94 to 100), median ADT-free survival of 24.7 months (95% CI 20.1 to 29.2 months), two-year biochemical free survival of 33% (95% CI 11 to 55), two-year PFS of 39% (95% CI 24 to 54), and two-year ADT-free survival of 52% (95% CI 41 to 62). Patients treated with SBRT were half as likely to experience PSA progression than those on observation when evaluating RCT data alone.

Yegya-Raman (2020) assessed the efficacy and safety of SBRT for oligometastatic gynecologic malignancies. A total of 16 unique studies with 667 patients met inclusion criteria.[125] Metastases were located in the abdomen (44.2%), pelvis (18.8%), thorax (15.5%), neck (4.6%), central nervous system (4.3%), bone (1.6%), and other/unspecified (11%). Response rate ranged from 49 to 97%, with seven of the eight studies reporting over 75% response rate. Local control ranged from 71% to 100% and median PFS ranged from 3.3 to 21.7 months. No grade ≥ 3 toxicities were observed in 9/16 (56%) studies.

Tsao (2019) completed a systematic review of SBRT for extracranial oligometastatic NSCLC involving four prospective phase II randomized trials (n=188), four prospective nonrandomized studies (n=140), and 11 retrospective studies (n=1,288). Results revealed a median OS ranging from 13.5 to 55 months and a PFS ranging from 4.4 to 14.7 months.[126] The authors noted that results from mature phase III RCTs are needed to fully determine the benefits and risks of SBRT for oligometastatic NSCLC.

In 2019, the Canadian Agency for Drugs and Technology in Health (CADTH) published a rapid response report addressing the clinical effectiveness and cost-effectiveness of SBRT for oligometastatic cancer.[127] Four publications met inclusion criteria, including three retrospective cohort studies and one economic evaluation. None of the included studies of clinical effectiveness found a significant difference in overall survival or progression-free survival following SBRT compared with other treatments. One study reported that local control of adrenal metastases was superior following real-time tumor-tracking radiotherapy compared to SBRT. The report concluded that the evidence was of limited quality and may not improve overall survival rates compared to other cancer treatments.

Zaorsky (2019) conducted a systematic review and meta-analysis of SBRT for oligometastatic renal cell carcinoma.[128] A total of 28 studies with 1602 unique patients were included. For extracranial disease, the summary effect size for one-year local control and the one-year survival rates were 89.1% (95% CI 83.6 to 93.7%, I^2=71%) and 86.8% (95% CI 62 to 99.8%, I^2=95%), respectively, and for intracranial disease were 90.1% (95% CI 83.5 to 95.3%, I^2=74%) and 49.7% (95% CI 41.1 to 58.3%, I^2=74%), respectively. For extracranial and intracranial disease, incidence of grade 3 to 4 toxicity was 0.7% (95% CI 0 to 2.1%, I^2=0%) and 1.1% (95% CI 0 to 7.4%, I^2=53%), respectively.

Spencer (2019) reported a systematic review of outcomes following SBRT for bone metastases.[129] A total of 57 studies met inclusion criteria. No meta-analysis was conducted due to clinical and methodological diversity and risk of bias present in the included studies. The majority of studies addressed spinal metastases, while eight included other sites of disease. A wide range of median OS was reported in the included studies, from 8 to 34 months. The authors concluded that this suggested a high risk of selection bias in the included observational studies. The measurement and definitions of pain response varied across studies, and only 10.5% of studies used the international consensus endpoint definitions of pain response. For the studies that addressed tumors in a location other than the spine, the total treated population pain response rates were 60 to 88% and local control rates were 70 to 96%.

Vilela (2018) performed a systematic review of the safely and effectiveness of SBRT for oligometastatic recurrent prostate cancer.[130] Fourteen studies met inclusion criteria and included 661 patients. A total of 899 lesions were treated, 561 nodal, 336 bone, 2 liver. Androgen deprivation therapy-free survival and median progression free survival were between one and three years. Using the GRADE system, the quality of evidence was assessed as low. Among the studies with a low risk of bias, local control varied between 82 to 100%. Acute and late grade 2 toxicity were reported in 2.4% and 1.1% of patients, respectively. One case of acute and two cases of late grade 3 toxicity were reported.

In 2020, Viani published a systematic review on the same topic as the above Vilela systematic review, SBRT for oligometastatic recurrent prostate cancer.[131] The 2020 systematic review included six studies not included in the Vilela publication. Two were identified during the Vilela search and excluded and five were published after the Vilela search dates. Overall, Viani identified 23 observational studies that met the inclusion criteria. According to the meta-analysis, the proportional rates of local control and progression-free survival were 0.976 (95% CI 0.96 to 0.98) and 0.413 (95% CI 0.378 to 0.477), respectively. The androgen deprivation-free survival was 20.1 months. There was a linear relationship between biologically effective dose and local control (p=0.017). Acute and late grade 2 or higher toxicity were reported in 1.3 and 1.2%, respectively.

In a 2018 systematic review, Petrelli analyzed the efficacy of SBRT to treat colorectal cancer liver oligometastases.[132] Eighteen studies met inclusion criteria. A total of 656 patients were included in the random-effect model pooled-analysis. Pooled one- and two-year survival were 67.18% (95% CI 42.1 to 92.2) and 56.5% (95% CI 36.7 to 76.2), respectively. Median PFS was 11.5 months and median OS was 31.5 months. The pooled one-year and two-year LC were 67% (95% CI 43.8 to 90.2) and 59.3% (95% CI 37.2 to 81.5), respectively. Reported mild to moderate and severe liver toxicity were 30.7% and 8.7%.

Kobiela (2018) published a systematic review of local control in colorectal cancer liver and lung oligometastases following treatment with SBRT.[133] A total of 15 studies met inclusion criteria. One-year LC ranged from 50% to 100% for liver metastases and 62% to 92% for lung metastases. Two-year LC ranged from 32% to 91% for liver metastases and 53% to 92% for lung metastases.

Comparative Studies

Ryu (2023) performed an RCT comparing SRS to cEBRT for localized vertebral metastases of the spine.[134] The study involved 339 adult patients with treatment naïve vertebral metastases and a baseline pain score of at least 5/10. The primary end point was pain response at three months. Patients were randomized to receive SRS or cEBRT. Complete response was defined as pain score of 0, no increase in narcotic pain medication, and no progressive pain at the other treated spine. Partial response was an improvement of at least three points from baseline pain score and no increase in narcotic medication. There was not a significant difference in pain response at three months (p=0.99). At 12 months, 46.6% of the patients were alive and pain response differences were still not significant (p=0.49). There were no significant differences in adverse events at three months (p=0.99) or at one year (p=0.38).

Ito (2022) published a single-center, single-arm, phase 2 study aimed to prospectively evaluate the outcomes of separation surgery and SBRT for metastatic epidural spinal cord compression (MESCC).[135] Patients with symptomatic MESCC due to a solid carcinoma were enrolled. The protocol for treatments comprised preoperative embolization, separation surgery, and spine SBRT. Surgical procedures were performed via the posterior approach, with decompression and a fixation procedure. The prescribed dose for spine SBRT was 24 Gy in 2 fractions. The primary endpoint was the 12-month local failure rate. The secondary endpoints were ambulatory functions and adverse effects. A total of 33 patients were registered between November 2017 and October 2019. All patients met the inclusion criteria, and all but one completed the protocol treatment. Of the included patients, 23 (70%) had radioresistant lesions. The Bilsky grade at registration was 1c in 3 patients, 2 in 8 patients, and 3 in 21 patients. The median follow-up duration after registration was 15 months (range, 3-35 months). Three months after the administration of treatments according to the protocol, 90% of patients (26 of 29) had disease of Bilsky grade $\leq$1. The 12-month local failure rate was 13%. Twenty patients could walk normally or with a cane 12 months after registration. Radiation-induced myelopathy, radiculopathy, and vertebral compression fracture were observed in 0, 1, and 6 patients, respectively. Separation surgery with SBRT for MESCC was effective in decompression and long-term local control.

McBride reported a randomized, phase II trial assessing nivolumab with vs. without SBRT.[136] A total of 62 patients with metastatic or recurrent head and neck squamous cell carcinoma were randomly assigned to receive nivolumab (n=30) or nivolumab plus SBRT (n=32). No statistically significant differences between groups were identified for ORR (34.5% [95% CI,

19.9% to 52.7%] v 29.0% [95% CI, 16.1% to 46.6%]; p=0.86), overall survival (p=0.75), progression-free survival (p=0.79), response duration (p= .26), or grade 3 to 5 toxicities (13.3% v 9.7%; p=0.70).

Phillips (2020) conducted the phase 2, randomized Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) study, which enrolled 54 men with recurrent hormone-sensitive prostate cancer and one to three metastases detectable by conventional imaging who had not received ADT within six months of enrollment or three or more years total.[137] These men were randomly assigned to stereotactic ablative radiotherapy or observation in a 2:1 ratio; 36 to treatment and 18 to observation. Results revealed that progression at six months was observed significantly more frequently in patients in the observation group versus active treatment (61% versus 19%; p=0.005). Stereotactic ablative radiotherapy was also associated with significant improvement in median PFS (not reached versus 5.8 months; HR, 0.30; 95% CI 0.11 to 0.81; p=0.002). No adverse effects of grade 3 or greater were reported.

Palma (2019) compared SBRT versus standard of care palliative treatment in patients with oligometastatic cancers in the randomized, phase 2, open-label Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial.[138] This multicenter study enrolled 99 adults with a controlled primary tumor and one to five metastatic lesions. After stratification by the number of metastases, patients were randomly assigned in a 1:2 ratio to either palliative standard of care or standard of care plus SBRT to all metastatic lesions. Results revealed a median OS of 28 months (95% CI, 19 to 33) in the control group versus 41 months (95% CI, 26 to not reached) in the SBRT group (HR, 0.57; 95% CI 0.30 to 1.10; p=0.09). Grade 2 or worse adverse events occurred more frequently in the SBRT group (29% versus 9%; p=0.026) and treatment-related deaths were reported in 3 patients in the SBRT group versus 0 in the control group. In a subsequent publication of long-term results of the SABR-COMET trial, the five-year OS rate was 17.7% in the standard of care arm versus 42.3% in the SBRT arm (p=0.006).[139] The five-year PFS was not reached in the standard of care group but was 17.3% in the SBRT group (p=0.001). No new grade 2 to 5 adverse events were reported and there were no differences in QOL between the groups.

Harrow (2022) published a follow-up study of outcomes beyond five years from the SABR-COMET trial.[140] OS after eight years was 27.2% in the SABR arm and 13.6% in the control arm (p=0.008). Patients in the SABR arm experienced more grade $\geq$2 toxic effects (30.3% vs. 9.1%; (p=0.019; however there were no new grade 3 to 5 toxic effects. Differences in quality of life and overall use of systemic therapy were not significant, but people in the SABR arm were less likely to be treated with chemotherapy (33.3% vs. 54.6%, p=0.043).

A number of studies were published in 2018 that evaluated the safety and efficacy of SBRT of oligometastases. Most addressed lung[141-145] or liver[146-148] metastases, although some addressed both[149] and others addressed adrenal[150, 151], bone[152-154], and other sites[155, 156]. The largest and those that are prospective or comparative are discussed below.

A 2018 retrospective study published by Franzese compared SBRT with microwave ablation.[157] Data from 135 patients with liver metastases were extracted and analyzed. Median follow-up time was 24.5 months (2.4 to 95.8). The one-year freedom from local progression was significantly longer in the SBRT group than the microwave ablation group (SBRT group 91%; 95% CI 81 to 95; versus the microwave ablation group 84%; 95% CI 0.72

to 0.91). The likelihood of local relapse was lower in the SBRT-treated group (adjusted hazard ratio 0.31; 95% CI 0.13 to 0.70, p=0.005).

Lung Oligometastases

Virbel (2021) performed a systematic review of the evidence regarding the use of SBRT for the treatment of oligometastatic lung disease.[158] The search dates were limited to January 1, 2015 to December 31, 2020. A total of 18 studies met inclusion criteria. No meta-analysis was completed. Oligometastatic disease was defined differently between articles, with eight studies defining it as one to five, one article as one to four, three articles as one to three, and six articles with no definition. The median number of treated metastases was between one and two in the included studies. Of the four included studies that evaluated the relationship between tumor size and LC, three reported that size impacted LC, with larger size associated with worse outcomes, and one reported no relationship. Overall, the authors concluded that SBRT is safe and effective in patients with oligometastases limited to one to three organs.

Choi (2020) published a systematic review and meta-analysis of tumor control and OS following SBRT for pulmonary oligometastases from colorectal cancer.[159] Fourteen studies including a total of 495 colorectal cancer patients with pulmonary oligometastases met inclusion criteria. The pooled estimate LC rate at one, two, three, four, and five years after SBRT was 81.0%, 71.5%, 56.0%, and 61.8%. The OS rate was 86.9%, 70.1%, 57.9%, and 43.0%, respectively, at the same time points. Two studies reported rates of grade 3 or higher pulmonary toxicity, and those rates were 2.2% and 10.8%.

Londero (2020) compared surgery versus SBRT for the treatment of pulmonary metastases in a systematic review of 79 studies (61 on surgical treatment and 18 on SBRT).[160] Results revealed no difference in short-term survival when comparing pulmonary metastasectomy and SBRT; however, survival rates were improved in the long-term among patients who underwent surgery. Mortality and morbidity after treatment were 0 to 4.7% and 0 to 23% for surgery and 0 to 2% and 4% to 31% for SBRT. The authors concluded that surgical metastasectomy remains the treatment of choice for pulmonary oligometastases.

A systematic review by Siva (2010) on the use of SBRT for pulmonary oligometastases estimated from the largest studies included in the review a two-year weighted OS rate of 54.5%,[161] ranging from higher rates in a study by Norisha (2008) of 84%[162] to lower rates, such as 39%, reported from a multi-institutional trial.[163]

Liver Oligometastases

The liver is the most common site of metastatic spread of colorectal cancer (CRC). Data show that surgical resection of limited liver metastases can result in long-term survival in select patients. However, only 10% to 20% of patients with metastatic CRC to the liver are surgical candidates. In patients who are not considered to be candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are RFA and transarterial chemoembolization. Retrospective analyses of RFA for liver metastases from CRC have shown wide variability in five-year OS rates, ranging from 14% to 55%.[164]

Retrospective series on the use of SBRT have reported LC rates ranging from 57% to 100% (median follow-up ranged 10 months – 4.3 years), as reported in a review by Alongi.[164] Prospective studies have reported one-year OS rates ranging from 61% to 85% and two-year OS rates ranging from 30% to 62%.[164] Another systematic review by Tree concluded similar

findings evaluating similar studies.[165] In addition, the review concluded that the rate of adverse events was low with less than 5% of patients experiencing severe toxicity (grade three or more).

In one of the larger series, Méndez Romero (2021) reported outcomes of 515 patients based on a web-based registry.[166] A total of 668 liver metastases were registered, with 80.3% coming from colorectal cancer, 8.9% from lung cancer, and 4% from breast cancer. Actuarial one-year local control and OS were 87% and 84%, respectively. The rate of grade 3 or higher toxicity was 3.9%.

McPartlin (2017) assessed 60 patients, of whom 82% received previous chemotherapy, 23% previously underwent focal liver treatment, and 38% had extrahepatic disease at the time of SBRT.[167] Only one acute toxicity greater than grade 2 was reported. Median overall survival was 16.0 months and local control rate per lesion at one and four years was 49.8% and 26.2%, respectively.

Chang (2011) studied outcomes of SBRT for colorectal liver metastases in a pooled patient cohort from three institutions with colorectal liver metastases.[168] Patients were included if they had one to four lesions, received one to six fractions of SBRT, and had radiologic imaging three months or more posttreatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had one or more chemotherapy regimens before stereotactic body radiotherapy, and 27 (42%) patients had two or more regimens. The median follow-up was 1.2 years (range, 0.3-5.2 years). The median dose was 42 Gy (range, 22-60 Gy). One- and two-year LC rates were 67% and 55%, respectively. One- and two-year OS rates were 72% and 38%, respectively.

In 2012, Lanciano reported on the single-center experience with SBRT to treat patients with metastases from multiple primary sites.[169] The patients were heavily pretreated with 87% having had prior systemic chemotherapy for treatment of liver metastases or liver tumor and 37% having had prior liver-directed therapy. These therapies included surgical resection, chemoembolization, RFA, photodynamic therapy, or previous external-beam radiation. There were four patients who had more than one prior liver-directed treatment. In 2014, Yuan reported on the single-site experience of a cohort of patients with liver metastases from multiple primary sites; 56% of whom had received prior systemic therapy.[32] Patients were considered to have a favorable prognosis with primary tumors originating from the colon, breast, or stomach, as well as sarcomas. In this group, the median overall survival was not reached and the one-year and two-year overall survival rates were 89.6% and 72.2%, respectively.

These studies have had relatively short follow-up times, typically less than two years. They are also limited by relatively small numbers of patients in the studies and differences in the systemic therapies administered, which may affect treatment outcomes.

Adrenal Gland Oligometastases

The most frequent primary tumor that metastasizes to the adrenal glands is NSCLC. Longer OS times have been reported with resection of clinically isolated adrenal metastases when compared with nonsurgical therapy, which has included locally ablative techniques, embolization and EBRT. A recent multicenter analysis reported one- and two-year OS of 72.3% and 53.5% one- and two-year LC of 85.4% and 79.2% following treatment of adrenal metastases of lung primary tumor with SBRT.[170]

Bone Oligometastases

Pielkenrood (2022) reported results of a randomized controlled trial comparing conventional radiotherapy versus SBRT (the VERTICAL trial).[171] A total of 110 patients with painful bone metastases were randomized 1:1 to receive conventional radiotherapy or SBRT. Intention-to-treat (ITT) and per-protocol (PP) linear mixed model analysis adjusting for baseline scores were used to assess changes in quality of life (QoL) over time. According to both analyses, QL scores improved over time comparably between groups with the exception of functional interference and psychological aspects in the ITT. At 12 weeks, the improvement in functional interference was significantly greater in the conventional radiotherapy group than that in the SBRT group (25.5 vs 14.1 points, respectively; p=0.04). At eight weeks, the improvement in psychosocial aspects scores was significantly greater in the conventional radiotherapy group than that in the SBRT group (12.2 vs 7.3; p=0.04).

Mazzola (2022) reported outcomes of a multiinstitutional study of SBRT for the treatment of bone oligometastatic prostate cancer.[172] Patients undergoing androgen deprivation therapy were excluded. A total of 40 patients were included, of whom 70% had a single oligometastatic lesion, 22.5% had two lesions, 5% had three lesions, and 2.5% had four lesions. SBRT was delivered in three to five fractions for a total of 24 to 40 Gy (median 30 Gy). The median follow-up was 22 months. One- and two-year rates of local control (LC) rates were 96.3% and 93.9%, and distant progression-free survival (DPFS) rates were 45.3% and 27%. A second SBRT course was proposed with concurrent ADT in seven patients and ADT alone was delivered in 11 patients due to polymetastatic spread. One- and two-year ADT-free survival rates were 67.5% and 61.8%.

Ito (2021) published a multicenter prospective noncomparative study on palliative SBRT for painful non-spine bone metastases.[173] A total of 38 patients with 41 osseous lesions from primarily lung (22%), prostate (15%), uterine (15%), and renal (12%) cancers. Median follow-up after registration was eight months. The three- and six-month pain responses for evaluable lesions was 78% and 75%, respectively. The six-month LC was 92%. Post-radiation bone fracture occurred in 17% of patients and grade 2 limb edema in 7%.

Sahgal (2021) published an RCT of SBRT versus conventional EBRT for painful spinal metastases.[174] Eligibility criteria were age 18 years and older, painful (defined as ≥2 points with the Brief Pain Inventory) MRI-confirmed spinal metastasis, no more than three consecutive vertebral segments to be included in the treatment volume, Eastern Cooperative Oncology Group performance status of 0 to 2, a Spinal Instability Neoplasia Score of less than 12, and no neurologically symptomatic spinal cord or cauda equina compression. A total of 229 patients were randomized to receive conventional EBRT (n=115) or SBRT (n=114). An intention-to-treat analysis was performed including all patients. Median follow-up was 6.7 months. Complete response for pain was achieved at three months in 35% of the SBRT group and 14% of the EBRT group (p=0.0002; multivariable adjusted analysis: OR=3.47, 95% CI 1.77 to 6.80, p=0.0003). Grade 3 pain occurred in five [4%] of 115 patients in the conventional EBRT group and five (5%) of 110 patients in the SBRT group. No treatment-related deaths were reported.

Napieralska (2014) reported a series 48 cases of prostate cancer bone metastases (in 32 patients) treated with SBRT primarily for pain control.[175] The size of the treated lesions ranged from 0.7 to 5.5 cm (mean, three dimension), and 31 (65%) of the treated metastases were located in the spine. At three-month follow-up, 17 patients had complete pain relief, two had

partial pain relief, and two had no pain reduction. At the end of the follow-up period, complete pain relief was observed in 28 patients and partial pain relief in 16 patients.

Section Summary

The evidence for the use of SBRT to treat oligometastases primarily consists of relatively small, noncomparative studies that confirm clinically important rates of local control. However, the evidence consistently reports a high rate of tumor control for isolated or few metastases (≤ 3 or ≤ 5). The local tumor control is good and reported at one-year to be in the range of 70% to 100%. The overall survival varied widely after two-years (21% to 84%) among the studies. Although some adverse events were reported, the overall rates for adverse events were low.

Other Indications

SBRT has been investigated for the treatment of additional conditions, including cardiac arrhythmias[176] and ventricular tachycardia[177]. The evidence for these other indications is limited in volume and in quality.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Network (NCCN) provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers.[178]

Cancer Site	Tumor Type	Recommendation	Version
Bone	Osteosarcoma	For primary treatment of resectable pulmonary, visceral, or skeletal metastases. In general, SRS/SBRT should be considered as clinically indicated to deliver high radiation dose and maximize normal tissue sparing.	**3.2023**
Bone	Ewing sarcoma	Consider use of SRS/SBRT, especially for oligometastases.	**3.2023**
Bone	Chondroma/ chondrosarcoma	Consider specialized techniques, which include SRS for resectable and unresectable chondromas and chondrosarcomas.	**3.2023**
CNS	Recurrent spinal ependymoma	Consider stereotactic radiosurgery (SRS) if geometrically favorable.	**1.2023**
CNS	Primary spinal cord tumors	In some instances focal SRS/SBRT to spinal tumors like hemangioblastoma may be appropriate, with care to respect normal tissue constraints of spinal cord and surrounding structures Meningioma: Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures.	**1.2023**
CNS	Metastatic spine tumors	Stereotactic radiation approaches (SRS/stereotactic body radiotherapy [SBRT]) for spinal cases may be preferred for patients with life expectancy ≥3 months where tumor ablation is a goal of treatment, in tumors considered radioresistant (eg, renal cell, melanoma, sarcoma, hepatocellular, some colorectal and NSCLC cases), and in select patients for optimal pain relief. Stereotactic radiation approaches may also be preferred in the setting of tumor recurrence after	**1.2023**

		prior radiation as a strategy to limit radiation dose to the spinal cord or other critical structures.	
CNS	Leptomeningeal metastases	SRS or RT to bulky disease and neurologically symptomatic or painful sites.	**1.2023**
Colorectal	Metastatic to liver or lung	Colon and Rectal: In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic sites can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or SBRT.	**2.2023** **3.3023**
Head and Neck	Palliative radiation for advanced cancer, or reirradiation	**Palliative radiation** using CD-CRT, IMRT, and SBRT should be considered in the advanced cancer setting when curative intent is not appropriate. **Reirradiation** with 3D-CRT, SBRT, PBT, or IMRT If the area in consideration overlaps with the previously radiated volume, the prior radiotherapy should have been more than 6 months from the appearance of new disease. In certain rare circumstances, reirradiation with intraoperative RT (IORT) or brachytherapy may be considered in high-volume centers with expertise in these techniques. Before reirradiation, the patient should have a reasonable ECOG performance status of 0–1. Patients who are more than 2 years from prior radiation, who have surgery to remove gross disease prior to reirradiation, and who are free of organ dysfunction (eg, laryngectomy, feeding tube) have better outcomes. The incidence of myelopathy is thought to increase after a cumulative biologically effective dose (BED) of 120 Gy, 53 but this risk is increased if large fraction sizes (≥2.5 Gy/fraction) are used. Radiation volumes should include known disease only to minimize the volume of tissue receiving very high doses in regions of overlap. Prophylactic treatment of subclinical disease (eg, elective nodal irradiation) is therefore not routinely indicated. When using SBRT techniques for reirradiation, careful selection of patients is advised. The best outcomes are seen in patients with smaller tumors and no skin involvement. Caution should be exercised in cases of circumferential carotid artery involvement.	**2.2023**
Hepatobiliary Cancer	Hepatocellular carcinoma	• All unresectable tumors irrespective of the location may be amenable to RT (3D conformal RT, intensity-modulated RT [IMRT], or stereotactic body RT [SBRT]). Image-guided RT is strongly recommended when using RT, IMRT, and SBRT to improve treatment accuracy and reduce treatment related toxicity. • There is growing evidence for the usefulness of SBRT in the management of HCC.SBRT can be considered as an alternative to ablation/	**1.2023**

		embolization techniques or when these therapies have failed or are contraindicated. • SBRT (typically 3–5 fractions) is often used for patients with 1 to 3 tumors.	
Hepatobiliary Cancer	Biliary Tract Cancers	Image-guided RT (IGRT) is strongly recommended when using RT, intensity-modulated RT (IMRT), and stereotactic body RT (SBRT) to improve treatment accuracy and reduce treatment-related toxicity. All unresectable tumors irrespective of the location may be amenable to RT (3D-CRT, IMRT, or SBRT).	**2.2023**
Kidney	Non-clear cell and clear cell renal cell carcinoma	• Metastasectomy or SBRT or ablative techniques for oligometastatic disease (category 2A). • SBRT may be considered for medically inoperable patients with Stage I (category 2B) or Stage II/III kidney cancer (category 3)	**1.2024**
Lung	Non-small-cell lung cancer; Initial treatment	Medically inoperable Stage I -Stage IIB: Definitive radiation therapy, preferably SABR	**3.2023**
Lung	Non-small-cell lung cancer – Stage IV; Treatment of thoracic disease T1-3, N0	Surgical resection or SABR	**3.2023**
Lung	NSCLC: Resectable recurrence	Reresection (preferred) and/or external-beam RT or SABR.	**3.2023**
Lung	Small cell lung cancer (SCLC)	SABR/SBRT is effective for patients with clinical limited stage I to IIA (T1-2, N0) SCLC, especially if medically inoperable or patient refuses surgery. Principles of SABR for SCLC are similar to those for NSCLC.	**3.2023**
Lung	Progression on biomarker directed therapy	Asymptomatic or symptomatic with limited progression (3-5 sites, excluding brain): Consider definitive local therapy (e.g., SABR or surgery) for limited lesions.	**3.2023**
Pancreas	Pancreatic adenocarcinoma – Locally advanced	• If good or intermediate performance status, in selected patients, locally advanced without systemic metastases, induction chemotherapy followed by chemoradiation or SBRT; or chemoradiation or SBRT in patients who are not candidates for induction chemotherapy. . As second-line therapy following disease progression, SBRT is an option if not previously given and if primary site is the sole site of progression.	**2.2023**
Pancreas	Pancreatic adenocarcinoma - Local recurrence after resection in Pancreatic operative bed	• Clinical trial (preferred) or Systemic therapy +/- chemoradiation or SBRT (if not previously done) or SBRT or Palliative and best supportive care (category 2A)	**2.2023**
Prostate	Prostate cancer	• SBRT has acceptable efficacy and toxicity in the following risk groups: very low and low, favorable intermediate, unfavorable intermediate, and high and very high. • SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise • SBRT for patients with unfavorable intermediate risk or high risk, prophylactic nodal radiation can	**2.2023**

		be considered. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered when delivering longer courses of EBRT would present a medical or social hardship. • SBRT for metastases can be considered for patients with limited metastatic disease to the vertebra or paravertebral region when ablation is the goal, in patients with oligometastatic progression where progression-free survival is the goal, and in symptomatic patients where the lesion occurs in or immediately adjacent to a previously irradiated field	
Skin	Melanoma – metastatic	Ablative treatment for intact extracranial metastases – higher doses utilizing conformal techniques such as stereotactic body radiation therapy (SBRT) may offer more durable local control. SBRT may be considered for selected patients with oligometastasis. (category 2A)	**2.2023**
Soft tissue sarcoma – extremity, superficial trunk, head/neck	Sarcoma – synchronous or recurrent stage IV disease	• If single organ and limited tumor bulk amenable to local therapy, consider SBRT (category 2A) • If disseminated metastases, SBRT is a palliative option (category 2A)	**2.2023**
Thyroid	Papillary, follicular, or Hurthle cell carcinoma – structurally persistent/recurrent locoregional or distant metastatic disease not amenable to radioactive iodine	• Non-radioiodine-avid unresectable locoregional recurrent/persistent disease or non-radioiodine-avid soft tissue metastases (eg lung, liver, muscle) excluding CNS metastases: consider EBRT (SBRT/IMRT) • Soft tissue metastases, excluding CNS: Consider resection of distant metastases and/or EBRT (SBRT/IMRT)/ other local therapies when available to metastatic lesions if progressive and/or symptomatic • Bone metastases: For asymptomatic weight-bearing sites or if symptomatic, consider SBRT • CNS metastases: for solitary lesions, either neurosurgical resection or SRS is preferred (category 2A)	**2.2023**

NCCN Categories

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.

AMERICAN COLLEGE OF CHEST PHYSICIANS

Non-Small-Cell Lung Cancer

- In patients with stage I or II NSCLC with no medical contraindications to operative intervention, surgical resection is recommended (grade 1B-strong recommendation based on moderate evidence)[179]

- In patients with stage I NSCLC who cannot tolerate lobectomy or segmentectomy:[179]
  - SBRT and wedge resection are recommended over no treatment (Grade 2C).
  - SBRT is favored over wedge resection in these cases unless surgical resection may provide the benefit of definitive histologic analysis and nodal information that will result in a change in the patient's management.
  - SBRT is also favored in these patients if adequate surgical margin is unlikely with wedge resection.

- For high-risk stage I NSCLC tumors <5 cm, SBRT is preferred over conventional fractionated RT for definitive treatment when normal dose constraints can be respected.[180]
- For tumors within 2 cm of the proximal bronchial tree, a modified SBRT treatment schedule is suggested to decrease treatment-related toxicity.[180]
- For second primary lung cancer, SRS is an emerging technology, particularly when there is limited pulmonary reserve.[179]

Lung Cancer

- In lung cancer patients with 1-3 brain metastases, stereotactic radiosurgery (SRS) alone is the recommended initial therapy (Grade 1A).[181]

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Non-Small-Cell Lung Cancer

For patients with T1-2, N0 non-small cell lung cancer who are medically operable, ASTRO makes the following recommendations related to the use of SBRT:[182]

- "For patients with "standard operative risk" (i.e., with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial."
- "For patients with "high operative risk" (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a a potential alternative to surgery are encouraged. Patients should be informed that while SBRG may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established."

Small Cell Lung Cancer

For patients with stage I or II node negative limited stage small cell lung cancer (SCLC) who are medically inoperable, ASTRO recommends either SBRT or conventional fractionation (Strength of recommendation: Strong; Quality of evidence: Moderate).[183]

Pancreatic Cancer

For patients with pancreatic cancer, ASTRO makes the following recommendations related to the use of SBRT:[184]

- Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry. (Strength of recommendation: Strong; Quality of evidence: Very Low)
- For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy

regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended. (Strength of recommendation: Conditional; Quality of evidence: Low)
- For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended. (Strength of recommendation: Conditional; Quality of evidence: Low)

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer Brain Metastases

The American Society of Clinical Oncology (ASCO) makes the following recommendations for patients with brain metastases from HER2-positive advanced breast cancer:[185]

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (SRS), SRS (WBRT), and FSRT for metastases 3 to 4 cm.
- For metastases 3 to 4 cm, treatment options include resection with postoperative adiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.

Locally Advanced, Unresectable Pancreatic Cancer

ASCO makes the following recommendations for patients with locally advanced, unresectable pancreatic cancer:[186]

- “Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria: Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, a favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy. There is no clear evidence to support one regimen over another, and physicians may offer therapy on the basis of extrapolation from data derived from studies in the metastatic setting. For some patients, conformal radiation therapy (CRT) or stereotactic body radiotherapy (SBRT) may be offered up front on the basis of patient and physician preference.” (evidence quality intermediate)
- “A short course of palliative radiotherapy (conventional RT or SBRT) may be offered to patients with LAPC who meet the following criteria: prominent local symptoms, such as abdominal pain and/or worsening jaundice and/or gastrointestinal (GI) bleeding; local infiltration into the GI tract causing impending gastric outlet or duodenal obstruction; and patient preference.” (evidence quality intermediate)

Localized Prostate Cancer

In 2018, ASCO produced a guideline in collaboration with ASTRO and the American Urological Association addressing the use of hypofractionated radiation therapy for localized prostate cancer.[187] The guideline defines hypofractionation as EBRT delivered with a fraction size greater than or equal to 500 cGy. The guideline makes the following evidence-based recommendations:

- "In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation." (Conditional recommendation, moderate quality of evidence)
- "In men with intermediate-risk prostate cancer receiving EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation. The task force strongly encourages that these patients be treated as part of a clinical trial or multi-institutional registry." (Conditional recommendation, low quality of evidence)
- "In men with high-risk prostate cancer receiving EBRT, the task force does not suggest offering ultrahypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence." (Conditional recommendation, low quality of evidence)

Salivary Gland Malignancy

In 2021, ASCO published a guideline on the management of salivary gland malignancy. The only reference to SRS or SBRT is a recommendation stating that surgery (metastatectomy) or SBRT may be offered for adenoid cystic carcinoma and/or low-grade tumors with indolent biology with limited metastases (i.e., ≤ 5 metastases).

SUMMARY

Hepatic Tumors

There is enough evidence to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) improve health outcomes for patients with hepatic tumors including biliary tract cancer and cholangiocarcinoma. Therefore, the use of SRS and SBRT for the treatment of hepatic tumors (primary or metastatic) may be considered medically necessary when policy criteria are met.

For all other tumors or indications when policy criteria is not met, there is not enough research to show improved health outcomes with stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). Therefore, all other indications for the use of SRS or SBRT for hepatic tumors are considered investigational.

Hepatocellular and Hepatobiliary Carcinoma

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) and hepatobiliary cancer improve health outcomes in patients with less than five tumors and less than 6 centimeters in diameter. Therefore, SRS and SBRT for the treatment of HCC may be considered medically necessary when policy criteria are met.

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for hepatocellular carcinoma (HCC) or hepatobiliary cancer when the criteria are not met. Therefore, the use of SRS and SBRT for all other indications for HCC is considered investigational.

Lung Metastases

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) improve health outcomes for people with lung metastases (e.g., local control and acceptable treatment-related toxicity) in a select group of patients with a limited number of metastases. Therefore, the use of SRS or SBRT for lung metastases may be considered medically necessary when policy criteria are met.

Outside this subgroup, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with lung metastases. Therefore SRS and SBRT of lung metastases are considered investigational when policy criteria are not met.

Oligometastases

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with oligometastases with a limited number of metastases. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for oligometastatic disease in certain scenarios. Therefore, SRS and SBRT for the treatment of oligometastatic disease may be considered medically necessary when policy criteria are met.

Outside this subgroup when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with oligometastases. Therefore, the use of SRS and SBRT for oligometastases when policy criteria are not met are considered investigational.

Osteosarcoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with osteosarcoma. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for osteosarcoma metastatic disease. Therefore, SRS and SBRT for the treatment of osteosarcoma metastatic disease may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with osteosarcoma. Therefore, the use of SRS and SBRT for osteosarcoma when policy criteria are not met are considered investigational.

Pancreatic Adenocarcinoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with pancreatic adenocarcinoma that is locally advanced, borderline resectable, inoperable, or locally recurrent after resection. Current clinical practice guidelines recommend SRS or SBRT as a

treatment option for pancreatic adenocarcinoma in these scenarios. Therefore, SRS and SBRT for the treatment of pancreatic adenocarcinoma may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with pancreatic adenocarcinoma. Therefore, the use of SRS and SBRT for pancreatic adenocarcinoma when policy criteria are not met are considered investigational.

Primary Lung Cancer

Non-comparative studies have consistently shown that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for patients with lung cancer, node negative, tumor stage T1a, T1b, T2a, or T2b, have survival rates comparable to patients who have undergone surgical resection. In addition, clinical practice guidelines recommend the use of SRS or SBRT for primary lung cancer. Therefore, SRS and SBRT may be considered medically necessary for patients with primary lung cancer, when policy criteria are met.

When policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with primary lung cancer. Therefore, SRS and SBRT for primary lung cancer are considered investigational when policy criteria are not met.

Prostate Cancer

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) may improve health outcomes for people with prostate cancer. Clinical guidelines based on research cautiously recommend SRS or SBRT for people with prostate cancer. Therefore, the use of SRS or SBRT for prostate cancer may be considered medically necessary.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with prostate cancer. Therefore, SRS and SBRT for prostate cancer are considered investigational when policy criteria are not met.

Renal Cell Carcinoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with inoperable primary renal cell carcinoma. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for renal cell carcinoma in these scenarios. Therefore, SRS and SBRT for the treatment of renal cell carcinoma may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with renal cell carcinoma. Therefore, the use of SRS and SBRT for renal cell carcinoma when policy criteria are not met are considered investigational.

Spinal and Vertebral Body Tumors (Primary or Metastatic)

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) lead to improved net health outcomes in patients with spinal or vertebral body tumors and especially in patients that have received prior radiation therapy. In addition, there is expert clinical consensus on the benefits of SBRT in this population. Therefore, SRS and SBRT may be considered medically necessary for the treatment of primary and salvage treatment of local recurrence after previous irradiation when policy criteria are met.

Other Indications

For all other tumors or indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) leads to improved health outcomes. Therefore, SRS and SBRT are considered investigational when policy criteria are not met.

REFERENCES

1. NCI Dictionary of Cancer Terms [cited 7/21/2023]. 'Available from:' https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neoplasm.
2. (NCCN) NCCN. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma V2.2023. [cited 07/19/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
3. (NCCN) NCCN. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer V2.2023. [cited 07/19/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
4. Viani GA, Gouveia AG, Yan M, et al. Stereotactic body radiotherapy versus surgery for early-stage non-small cell lung cancer: an updated meta-analysis involving 29,511 patients included in comparative studies. *J Bras Pneumol.* 2022;48(3):e20210390. PMID: 35508065
5. Zhang R, Kang J, Ren S, et al. Comparison of stereotactic body radiotherapy and radiofrequency ablation for early-stage non-small cell lung cancer: a systematic review and meta-analysis. *Ann Transl Med.* 2022;10(2):104. PMID: 35282118
6. Alcibar OL, Nadal E, Romero Palomar I, et al. Systematic review of stereotactic body radiotherapy in stage III non-small cell lung cancer. *Transl Lung Cancer Res.* 2021;10(1):529-38. PMID: 33569334
7. Ijsseldijk MA, Shoni M, Siegert C, et al. Oncologic Outcomes of Surgery Versus SBRT for Non-Small-Cell Lung Carcinoma: A Systematic Review and Meta-analysis. *Clinical lung cancer.* 2021;22(3):e235-e92. PMID: 32912754
8. Li H, Shen Y, Wu Y, et al. Stereotactic Body Radiotherapy Versus Surgery for Early-Stage Non-Small-Cell Lung Cancer. *The Journal of surgical research.* 2019;243:346-53. PMID: 31277011
9. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *International journal of radiation oncology, biology, physics.* 2014;90(3):603-11. PMID: 25052562

10. Nguyen NP, Garland L, Welsh J, et al. Can stereotactic fractionated radiation therapy become the standard of care for early stage non-small cell lung carcinoma. *Cancer Treat Rev.* 2008;34(8):719-27. PMID: 18657910
11. Koto M, Takai Y, Ogawa Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol.* 2007;85(3):429-34. PMID: 18022720
12. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative nonsmall cell lung carcinoma with radiotherapy alone. *International journal of radiation oncology, biology, physics.* 1996;36(3):607-13. PMID: 8948345
13. Peng P, Gong J, Zhang Y, et al. EGFR-TKIs plus stereotactic body radiation therapy (SBRT) for stage IV Non-small cell lung cancer (NSCLC): A prospective, multicenter, randomized, controlled phase II study. *Radiother Oncol.* 2023;184:109681. PMID: 37105304
14. Altorki NK, McGraw TE, Borczuk AC, et al. Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial. *Lancet Oncol.* 2021;22(6):824-35. PMID: 34015311
15. Chi A, Fang W, Sun Y, et al. Comparison of Long-term Survival of Patients With Early-Stage Non-Small Cell Lung Cancer After Surgery vs Stereotactic Body Radiotherapy. *JAMA Netw Open.* 2019;2(11):e1915724. PMID: 31747032
16. Wu J, Bai HX, Chan L, et al. Sublobar resection compared with stereotactic body radiation therapy and ablation for early stage non-small cell lung cancer: A National Cancer Database study. *The Journal of thoracic and cardiovascular surgery.* 2020;160(5):1350-57.e11. PMID: 32033815
17. Lam A, Yoshida EJ, Bui K, et al. A National Cancer Database Analysis of Radiofrequency Ablation versus Stereotactic Body Radiotherapy in Early-Stage Non-Small Cell Lung Cancer. *Journal of vascular and interventional radiology : JVIR.* 2018;29(9):1211-17 e1. PMID: 30061058
18. von Reibnitz D, Shaikh F, Wu AJ, et al. Stereotactic body radiation therapy (SBRT) improves local control and overall survival compared to conventionally fractionated radiation for stage I non-small cell lung cancer (NSCLC). *Acta oncologica (Stockholm, Sweden).* 2018;57(11):1567-73. PMID: 29873277
19. Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. *Cancer.* 2015;121(14):2341-9. PMID: 25847699
20. Ezer N, Veluswamy RR, Mhango G, et al. Outcomes after Stereotactic Body Radiotherapy versus Limited Resection in Older Patients with Early-Stage Lung Cancer. *J Thorac Oncol.* 2015;10(8):1201-6. PMID: 26200275
21. Tubin S, Khan MK, Salerno G, et al. Mono-institutional phase 2 study of innovative Stereotactic Body RadioTherapy targeting PArtial Tumor HYpoxic (SBRT-PATHY) clonogenic cells in unresectable bulky non-small cell lung cancer: profound non-targeted effects by sparing peri-tumoral immune microenvironment. *Radiat Oncol.* 2019;14(1):212. PMID: 31771654
22. Jeppesen SS, Schytte T, Jensen HR, et al. Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: an updated retrospective study on local failure and survival rates. *Acta oncologica (Stockholm, Sweden).* 2013;52(7):1552-8. PMID: 23902274

23. Raman S, Yau V, Pineda S, et al. Ultracentral Tumors Treated With Stereotactic Body Radiotherapy: Single-Institution Experience. *Clinical lung cancer.* 2018;19(5):e803-e10. PMID: 30007498
24. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer.* 2017;123(16):3031-39. PMID: 28346656
25. Miyakawa A, Shibamoto Y, Baba F, et al. Stereotactic body radiotherapy for stage I non-small-cell lung cancer using higher doses for larger tumors: results of the second study. *Radiat Oncol.* 2017;12(1):152. PMID: 28893300
26. Nanda RH, Liu Y, Gillespie TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: A National Cancer Data Base analysis. *Cancer.* 2015;121(23):4222-30. PMID: 26348268
27. Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. *J Thorac Oncol.* 2007;2(7 Suppl 3):S101-12. PMID: 17603304
28. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *International journal of radiation oncology, biology, physics.* 2014;88(5):1092-9. PMID: 24661663
29. Hof H, Muenter M, Oetzel D, et al. Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer (NSCLC). *Cancer.* 2007;110(1):148-55. PMID: 17516437
30. Allibhai Z, Taremi M, Bezjak A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *International journal of radiation oncology, biology, physics.* 2013;87(5):1064-70. PMID: 24210082
31. Harkenrider MM, Bertke MH, Dunlap NE. Stereotactic Body Radiation Therapy for Unbiopsied Early-stage Lung Cancer: A Multi-Institutional Analysis. *American journal of clinical oncology.* 2014;37(4):337-42. PMID: 23660597
32. Yuan ZY, Meng MB, Liu CL, et al. Stereotactic body radiation therapy using the CyberKnife((R)) system for patients with liver metastases. *Onco Targets Ther.* 2014;7:915-23. PMID: 24959080
33. Wu G, Huang G, Huang J, et al. Comparison of External Beam Radiation Therapy Modalities for Hepatocellular Carcinoma With Macrovascular Invasion: A Meta-Analysis and Systematic Review. *Frontiers in oncology.* 2022;12:829708. PMID: 35242713
34. Bisello S, Camilletti AC, Bertini F, et al. Stereotactic radiotherapy in intrahepatic cholangiocarcinoma: A systematic review. *Mol Clin Oncol.* 2021;15(2):152. PMID: 34141431
35. Shanker MD, Moodaley P, Soon W, et al. Stereotactic ablative radiotherapy for hepatocellular carcinoma: A systematic review and meta-analysis of local control, survival and toxicity outcomes. *Journal of medical imaging and radiation oncology.* 2021. PMID: 34396706
36. Long Y, Liang Y, Li S, et al. Therapeutic outcome and related predictors of stereotactic body radiotherapy for small liver-confined HCC: a systematic review and meta-analysis of observational studies. *Radiat Oncol.* 2021;16(1):68. PMID: 33832536
37. Lee J, Shin IS, Yoon WS, et al. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: Meta-analyses and a systematic review. *Radiother Oncol.* 2020;145:63-70. PMID: 31923711

38. Dobrzycka M, Spychalski P, Rostkowska O, et al. Stereotactic body radiation therapy for early-stage hepatocellular carcinoma - a systematic review on outcome. *Acta oncologica (Stockholm, Sweden).* 2019;58(12):1706-13. PMID: 31464155
39. Frakulli R, Buwenge M, Macchia G, et al. Stereotactic body radiation therapy in cholangiocarcinoma: a systematic review. *The British journal of radiology.* 2019;92(1097):20180688. PMID: 30673295
40. Tao C, Yang LX. Improved radiotherapy for primary and secondary liver cancer: stereotactic body radiation therapy. *Anticancer research.* 2012;32(2):649-55. PMID: 22287758
41. Cardenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico.* 2010;12(3):218-25. PMID: 20231127
42. Meng MB, Cui YL, Lu Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol.* 2009;92(2):184-94. PMID: 19042048
43. Shi C, Li Y, Geng L, et al. Adjuvant stereotactic body radiotherapy after marginal resection for hepatocellular carcinoma with microvascular invasion: A randomised controlled trial. *Eur J Cancer.* 2022;166:176-84. PMID: 35303509
44. Yang JF, Lo CH, Lee MS, et al. Stereotactic ablative radiotherapy versus conventionally fractionated radiotherapy in the treatment of hepatocellular carcinoma with portal vein invasion: a retrospective analysis. *Radiat Oncol.* 2019;14(1):180. PMID: 31640728
45. Bettinger D, Pinato DJ, Schultheiss M, et al. Stereotactic Body Radiation Therapy as an Alternative Treatment for Patients with Hepatocellular Carcinoma Compared to Sorafenib: A Propensity Score Analysis. *Liver Cancer.* 2019;8(4):281-94. PMID: 31602371
46. Roman J, Vávra P, Ekrtová T, et al. Comparison of surgical intervention to Cyberknife® radiotherapy in the treatment of liver malignancies. *Rozhl Chir.* 2019;98(10):408-13. PMID: 31842571
47. Nakano R, Ohira M, Kobayashi T, et al. Hepatectomy versus stereotactic body radiotherapy for primary early hepatocellular carcinoma: A propensity-matched analysis in a single institution. *Surgery.* 2018;164(2):219-26. PMID: 29801728
48. Parikh ND, Marshall VD, Green M, et al. Effectiveness and cost of radiofrequency ablation and stereotactic body radiotherapy for treatment of early-stage hepatocellular carcinoma: An analysis of SEER-medicare. *Journal of medical imaging and radiation oncology.* 2018;62(5):673-81. PMID: 29877615
49. Su TS, Liang P, Liang J, et al. Long-Term Survival Analysis of Stereotactic Ablative Radiotherapy Versus Liver Resection for Small Hepatocellular Carcinoma. *International journal of radiation oncology, biology, physics.* 2017;98(3):639-46. PMID: 28581406
50. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(5):452-9. PMID: 26628466
51. Shin YJ, Kim MS, Yoo SY, et al. Pilot study of stereotactic body radiotherapy for huge hepatocellular carcinoma unsuitable for other therapies. *Tumori.* 2010;96(1):65-70. PMID: 20437860
52. Comito T, Loi M, Franzese C, et al. Stereotactic Radiotherapy after Incomplete Transarterial (Chemo-) Embolization (TAE\TACE) versus Exclusive TAE or TACE for

Treatment of Inoperable HCC: A Phase III Trial (NCT02323360). *Curr Oncol.* 2022;29(11):8802-13. PMID: 36421345
53. Shen PC, Chang WC, Lo CH, et al. Comparison of Stereotactic Body Radiation Therapy and Transarterial Chemoembolization for Unresectable Medium-Sized Hepatocellular Carcinoma. *International journal of radiation oncology, biology, physics.* 2019;105(2):307-18. PMID: 31175903
54. Sapir E, Tao Y, Schipper MJ, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. *International journal of radiation oncology, biology, physics.* 2018;100(1):122-30. PMID: 29066120
55. Cai Y, Chang Q, Xiao E, et al. Transcatheter arterial chemoembolization (TACE) combined with gamma-knife compared to TACE or gamma-knife alone for hepatocellular carcinoma. *Medicine (Baltimore).* 2018;97(22):e10890. PMID: 29851811
56. Jacob R, Turley F, Redden DT, et al. Adjuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non-resectable hepatocellular carcinoma tumours of >/= 3 cm. *HPB (Oxford).* 2015;17(2):140-9. PMID: 25186290
57. Su TS, Lu HZ, Cheng T, et al. Long-term survival analysis in combined transarterial embolization and stereotactic body radiation therapy versus stereotactic body radiation monotherapy for unresectable hepatocellular carcinoma >5 cm. *BMC Cancer.* 2016;16(1):834. PMID: 27809890
58. Zhong NB, Lv GM, Chen ZH. Stereotactic body radiotherapy combined with transarterial chemoembolization for huge (>/=10 cm) hepatocellular carcinomas: A clinical study. *Mol Clin Oncol.* 2014;2(5):839-44. PMID: 25054055
59. Sapisochin G, Barry A, Doherty M, et al. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *Journal of hepatology.* 2017;67(1):92-99. PMID: 28257902
60. Foerster R, Zwahlen DR, Buchali A, et al. Stereotactic Body Radiotherapy for High-Risk Prostate Cancer: A Systematic Review. *Cancers (Basel).* 2021;13(4). PMID: 33673077
61. Valle LF, Lehrer EJ, Markovic D, et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *European urology.* 2021;80(3):280-92. PMID: 33309278
62. Achard V, Bottero M, Rouzaud M, et al. Radiotherapy treatment volumes for oligorecurrent nodal prostate cancer: a systematic review. *Acta oncologica (Stockholm, Sweden).* 2020:1-11. PMID: 32536241
63. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *International journal of radiation oncology, biology, physics.* 2019;104(4):778-89. PMID: 30959121
64. Kishan AU, Dang A, Katz AJ, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. *JAMA Netw Open.* 2019;2(2):e188006. PMID: 30735235
65. Loi M, Wortel RC, Francolini G, et al. Sexual Function in Patients Treated With Stereotactic Radiotherapy For Prostate Cancer: A Systematic Review of the Current Evidence. *The journal of sexual medicine.* 2019;16(9):1409-20. PMID: 31303575
66. Poon DMC, Lam D, Wong KCW, et al. Prospective Randomized Phase II Study of Stereotactic Body Radiotherapy (SBRT) vs. Conventional Fractionated Radiotherapy (CFRT) for Chinese Patients with Early-Stage Localized Prostate Cancer. *Curr Oncol.* 2021;29(1):27-37. PMID: 35049677

67. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol.* 2019;20(11):1531-43. PMID: 31540791
68. Tree AC, Ostler P, van der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2022;23(10):1308-20. PMID: 36113498
69. Gogineni E, Rana Z, Soberman D, et al. Biochemical Control and Toxicity Outcomes of Stereotactic Body Radiation Therapy Versus Low-Dose-Rate Brachytherapy in the Treatment of Low- and Intermediate-Risk Prostate Cancer. *International journal of radiation oncology, biology, physics.* 2021;109(5):1232-42. PMID: 33171199
70. Patel SA, Switchenko JM, Fischer-Valuck B, et al. Stereotactic body radiotherapy versus conventional/moderate fractionated radiation therapy with androgen deprivation therapy for unfavorable risk prostate cancer. *Radiat Oncol.* 2020;15(1):217. PMID: 32933541
71. Yu JB, Cramer LD, Herrin J, et al. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(12):1195-201. PMID: 24616315
72. Katz A, Ferrer M, Suarez JF. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat Oncol.* 2012;7:194. PMID: 23164305
73. Boyer MJ, Papagikos MA, Kiteley R, et al. Toxicity and quality of life report of a phase II study of stereotactic body radiotherapy (SBRT) for low and intermediate risk prostate cancer. *Radiat Oncol.* 2017;12(1):14. PMID: 28086825
74. Jeong BK, Jeong H, Ha IB, et al. Stereotactic Body Radiation Therapy for Low- to Intermediate-risk Prostate Adenocarcinoma. *Journal of Korean medical science.* 2015;30(6):710-5. PMID: 26028922
75. McBride SM, Wong DS, Dombrowski JJ, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: Preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer.* 2011;118(15):3681-90. PMID: 22170628
76. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol.* 2013;109(2):217-21. PMID: 24060175
77. Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(15):2020-6. PMID: 21464418
78. Jabbari S, Weinberg VK, Kaprealian T, et al. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. *International journal of radiation oncology, biology, physics.* 2012;82(1):228-34. PMID: 21183287
79. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. *Radiat Oncol.* 2011;6:3. PMID: 21219625
80. King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *International journal of radiation oncology, biology, physics.* 2012;82(2):877-82. PMID: 21300474

81. Katz AJ, Santoro M, Ashley R, et al. Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urol.* 2010;10:1. PMID: 20122161
82. Katz AJ, Santoro M, Diblasio F, et al. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. *Radiat Oncol.* 2013;8(1):118. PMID: 23668632
83. Wiegner EA, King CR. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. *International journal of radiation oncology, biology, physics.* 2010;78(2):442-8. PMID: 20137864
84. Bolzicco G, Favretto MS, Satariano N, et al. A single-center study of 100 consecutive patients with localized prostate cancer treated with stereotactic body radiotherapy. *BMC Urol.* 2013;13:49. PMID: 24134138
85. Park Y, Park HJ, Jang WI, et al. Long-term results and PSA kinetics after robotic SBRT for prostate cancer: multicenter retrospective study in Korea (Korean radiation oncology group study 15-01). *Radiat Oncol.* 2018;13(1):230. PMID: 30470253
86. Meier RM, Bloch DA, Cotrutz C, et al. Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer: Survival and Toxicity Endpoints. *International journal of radiation oncology, biology, physics.* 2018;102(2):296-303. PMID: 30191864
87. Miszczyk L, Namysł-Kaletka A, Napieralska A, et al. Stereotactic Ablative Radiotherapy for Prostate Cancer-The Treatment Results of 500 Patients and Analysis of Failures. *Technology in cancer research & treatment.* 2019;18:1533033819870815. PMID: 31462169
88. Zelefsky MJ, Pinitpatcharalert A, Kollmeier M, et al. Early Tolerance and Tumor Control Outcomes with High-dose Ultrahypofractionated Radiation Therapy for Prostate Cancer. *European urology oncology.* 2019. PMID: 31668713
89. Zilli T, Franzese C, Bottero M, et al. Single fraction urethra-sparing prostate cancer SBRT: Phase I results of the ONE SHOT trial. *Radiother Oncol.* 2019;139:83-86. PMID: 31431369
90. Bruynzeel AME, Tetar SU, Oei SS, et al. A Prospective Single-Arm Phase 2 Study of Stereotactic Magnetic Resonance Guided Adaptive Radiation Therapy for Prostate Cancer: Early Toxicity Results. *International journal of radiation oncology, biology, physics.* 2019;105(5):1086-94. PMID: 31419510
91. Pasquier D, Martinage G, Janoray G, et al. Salvage Stereotactic Body Radiation Therapy for Local Prostate Cancer Recurrence After Radiation Therapy: A Retrospective Multicenter Study of the GETUG. *International journal of radiation oncology, biology, physics.* 2019;105(4):727-34. PMID: 31344433
92. Nakamura R, Hirata T, Suzuki O, et al. Stereotactic Body Radiotherapy Using CyberKnife® for Localized Low- and Intermediate-risk Prostate Cancer: Initial Report on a Phase I/II Trial. *Anticancer research.* 2020;40(4):2053-57. PMID: 32234896
93. Francolini G, Jereczek-Fossa BA, Di Cataldo V, et al. Stereotactic radiotherapy for prostate bed recurrence after prostatectomy, a multicentric series. *BJU international.* 2020;125(3):417-25. PMID: 31608534
94. Pasquier D, Peiffert D, Nickers P, et al. A Multicenter Phase 2 study of Hypofractionated Stereostatic Boost in Intermediate Risk Prostate Carcinoma: A 5-Year Analysis of the CKNO-PRO Trial. *International journal of radiation oncology, biology, physics.* 2020;106(1):116-23. PMID: 31604131
95. Kawakami S, Tsumura H, Satoh T, et al. A phase II trial of stereotactic body radiotherapy in 4 fractions for patients with localized prostate cancer. *Radiat Oncol.* 2022;17(1):67. PMID: 35379264

96. Magli A, Farneti A, Faiella A, et al. Toxicity at 1 Year After Stereotactic Body Radiation Therapy in 3 Fractions for Localized Prostate Cancer. *International journal of radiation oncology, biology, physics.* 2021;111(1):93-100. PMID: 33745951
97. Fuller D, Wurzer J, Shirazi R, et al. Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT. *International journal of radiation oncology, biology, physics.* 2020;106(2):291-99. PMID: 31629838
98. Chen LN, Suy S, Wang H, et al. Patient-reported urinary incontinence following stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer. *Radiat Oncol.* 2014;9:148. PMID: 24966110
99. Kim DW, Cho LC, Straka C, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *International journal of radiation oncology, biology, physics.* 2014;89(3):509-17. PMID: 24929162
100. King CR, Collins S, Fuller D, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *International journal of radiation oncology, biology, physics.* 2013;87(5):939-45. PMID: 24119836
101. Liu S, Liu Y, Yang J, et al. Survival outcome after stereotactic body radiotherapy for locally advanced and borderline resectable pancreatic cancer: A systematic review and meta-analysis. *Transl Oncol.* 2021;14(8):101139. PMID: 34091293
102. Zaorsky NG, Lehrer EJ, Handorf E, et al. Dose Escalation in Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Meta-Analysis. *American journal of clinical oncology.* 2019;42(1):46-55. PMID: 29965809
103. Buwenge M, Macchia G, Arcelli A, et al. Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. *J Pain Res.* 2018;11:2169-78. PMID: 30323651
104. Buwenge M, Arcelli A, Cellini F, et al. Pain Relief after Stereotactic Radiotherapy of Pancreatic Adenocarcinoma: An Updated Systematic Review. *Curr Oncol.* 2022;29(4):2616-29. PMID: 35448188
105. Petrelli F, Comito T, Ghidini A, et al. Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials. *International journal of radiation oncology, biology, physics.* 2017;97(2):313-22. PMID: 28068239
106. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. *HPB (Oxford).* 2017;19(2):83-92. PMID: 28065427
107. Ma T, Bai X, Wei Q, et al. Adjuvant therapy with gemcitabine and stereotactic body radiation therapy versus gemcitabine alone for resected stage II pancreatic cancer: a prospective, randomized, open-label, single center trial. *BMC Cancer.* 2022;22(1):865. PMID: 35941566
108. Arcelli A, Buwenge M, Macchia G, et al. Stereotactic body radiotherapy vs conventionally fractionated chemoradiation in locally advanced pancreatic cancer: A multicenter case-control study (PAULA-1). *Cancer Med.* 2020;9(21):7879-87. PMID: 32910549
109. Wu G, Baine MJ, Zhao N, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy compared to conventional fractionated radiation therapy in patients with locally advanced pancreatic cancer. *BMC Cancer.* 2019;19(1):977. PMID: 31640607

110. Park JJ, Hajj C, Reyngold M, et al. Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer. *Acta oncologica (Stockholm, Sweden).* 2017:1-8. PMID: 28661823
111. Zhong J, Patel K, Switchenko J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer.* 2017;123(18):3486-93. PMID: 28493288
112. Cheung P, Patel S, North SA, et al. Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study. *European urology.* 2021;80(6):693-700. PMID: 34399998
113. Correa RJM, Louie AV, Zaorsky NG, et al. The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. *European urology focus.* 2019;5(6):958-69. PMID: 31248849
114. Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer.* 2018;124(5):934-42. PMID: 29266183
115. Prins FM, Kerkmeijer LGW, Pronk AA, et al. Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for Small Renal Masses, a Systematic Review. *Journal of endourology.* 2017;31(10):963-75. PMID: 28741377
116. Yamamoto T, Kadoya N, Takeda K, et al. Renal atrophy after stereotactic body radiotherapy for renal cell carcinoma. *Radiat Oncol.* 2016;11:72. PMID: 27229710
117. Ranck MC, Golden DW, Corbin KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. *American journal of clinical oncology.* 2013;36(6):589-95. PMID: 22868242
118. Campbell JC, Lee JW, Ledbetter L, et al. Systematic Review and Meta-analysis for Surgery Versus Stereotactic Radiosurgery for Jugular Paragangliomas. *Otol Neurotol.* 2023;44(3):195-200. PMID: 36728610
119. Ong V, Bourcier AJ, Florence TJ, et al. Stereotactic Radiosurgery for Glomus Jugulare Tumors: Systematic Review and Meta-Analysis. *World Neurosurg.* 2022;162:e49-e57. PMID: 35189418
120. Conti A, Starnoni D, Barges-Coll J, et al. Radiosurgery for Benign Vertebral Body Hemangiomas of the Spine: A Systematic Review and Meta-Analysis. *World Neurosurg.* 2022;164:97-105. PMID: 35378316
121. Ito K, Saito T, Nakamura N, et al. Stereotactic body radiotherapy versus conventional radiotherapy for painful bone metastases: a systematic review and meta-analysis of randomised controlled trials. *Radiat Oncol.* 2022;17(1):156. PMID: 36100905
122. Viani GA, Gouveia AG, Louie AV, et al. Stereotactic body radiotherapy to treat breast cancer oligometastases: A systematic review with meta-analysis. *Radiother Oncol.* 2021;164:245-50. PMID: 34624408
123. Deodato F, Macchia G, Buwenge M, et al. Systematic review of stereotactic body radiotherapy for nodal metastases. *Clin Exp Metastasis.* 2021;38(1):11-29. PMID: 33452954
124. Yan M, Moideen N, Bratti VF, et al. Stereotactic body radiotherapy (SBRT) in metachronous oligometastatic prostate cancer: a systematic review and meta-analysis on the current prospective evidence. *The British journal of radiology.* 2020;93(1116):20200496. PMID: 32822547
125. Yegya-Raman N, Cao CD, Hathout L, et al. Stereotactic body radiation therapy for oligometastatic gynecologic malignancies: A systematic review. *Gynecol Oncol.* 2020;159(2):573-80. PMID: 32917412

126. Tsao MN, Ven LI, Cheung P, et al. Stereotactic Body Radiation Therapy for Extracranial Oligometastatic Non-small-cell Lung Cancer: A Systematic Review. *Clinical lung cancer.* 2020;21(2):95-105.e1. PMID: 31959533
127. Stereotactic Body Radiotherapy for Oligometastatic Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottowa: CADTH; 2019 Feb. (CADTH Rapid Response Report). [cited 7/22/2022]. 'Available from:' https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1071%20Stereotactic%20Body%20Radiotherapy%20Final.pdf.
128. Zaorsky NG, Lehrer EJ, Kothari G, et al. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *European urology oncology.* 2019;2(5):515-23. PMID: 31302061
129. Spencer KL, van der Velden JM, Wong E, et al. Systematic Review of the Role of Stereotactic Radiotherapy for Bone Metastases. *J Natl Cancer Inst.* 2019;111(10):1023-32. PMID: 31119273
130. Vilela RA, Navarro NF, Faria ET, et al. Use of stereotactic body radiation therapy for oligometastatic recurrent prostate cancer: A systematic review. *Journal of medical imaging and radiation oncology.* 2018;62(5):692-706. PMID: 29808571
131. Viani GA, Arruda CV, Hamamura AC, et al. Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Recurrence: A Meta-analysis. *American journal of clinical oncology.* 2020;43(2):73-81. PMID: 31809327
132. Petrelli F, Comito T, Barni S, et al. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. *Radiother Oncol.* 2018;129(3):427-34. PMID: 29997034
133. Kobiela J, Spychalski P, Marvaso G, et al. Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review. *Critical reviews in oncology/hematology.* 2018;129:91-101. PMID: 30097241
134. Ryu S, Deshmukh S, Timmerman RD, et al. Stereotactic Radiosurgery vs Conventional Radiotherapy for Localized Vertebral Metastases of the Spine: Phase 3 Results of NRG Oncology/RTOG 0631 Randomized Clinical Trial. *JAMA Oncol.* 2023;9(6):800-07. PMID: 37079324
135. Ito K, Sugita S, Nakajima Y, et al. Phase 2 Clinical Trial of Separation Surgery Followed by Stereotactic Body Radiation Therapy for Metastatic Epidural Spinal Cord Compression. *International journal of radiation oncology, biology, physics.* 2022;112(1):106-13. PMID: 34715257
136. McBride S, Sherman E, Tsai CJ, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2021;39(1):30-37. PMID: 32822275
137. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(5):650-59. PMID: 32215577
138. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet.* 2019;393(10185):2051-58. PMID: 30982687
139. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2020;38(25):2830-38. PMID: 32484754

140. Harrow S, Palma DA, Olson R, et al. Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes. *International journal of radiation oncology, biology, physics.* 2022;114(4):611-16. PMID: 35643253
141. Khadige M, Salleron J, Marchesi V, et al. Cyberknife((R)) stereotactic radiation therapy for stage I lung cancer and pulmonary metastases: evaluation of local control at 24 months. *J Thorac Dis.* 2018;10(8):4976-84. PMID: 30233872
142. Mihai A, Mu Y, Armstrong J, et al. Patients with colorectal lung oligometastases (L-OMD) treated by dose adapted SABR at diagnosis of oligometastatic disease have better outcomes than patients previously treated for their metastatic disease. *Journal of radiosurgery and SBRT.* 2017;5(1):43-53. PMID: 29296462
143. Dohopolski MJ, Horne Z, Clump D, et al. Stereotactic Body Radiation Therapy for Pulmonary Oligometastases Arising from Non-lung Primaries in Patients Without Extrapulmonary Disease. *Cureus.* 2018;10(2):e2167. PMID: 29644155
144. Osti MF, Agolli L, Valeriani M, et al. 30 Gy single dose stereotactic body radiation therapy (SBRT): Report on outcome in a large series of patients with lung oligometastatic disease. *Lung cancer (Amsterdam, Netherlands).* 2018;122:165-70. PMID: 30032826
145. Mazzola R, Fersino S, Ferrera G, et al. Stereotactic body radiotherapy for lung oligometastases impacts on systemic treatment-free survival: a cohort study. *Med Oncol.* 2018;35(9):121. PMID: 30076479
146. Gandhidasan S, Ball D, Kron T, et al. Single Fraction Stereotactic Ablative Body Radiotherapy for Oligometastasis: Outcomes from 132 Consecutive Patients. *Clinical oncology (Royal College of Radiologists (Great Britain)).* 2018;30(3):178-84. PMID: 29224900
147. He X, Zhang P, Li Z, et al. Curative-intent radiotherapy in patients with oligometastatic lesions from colorectal cancer: A single-center study. *Medicine (Baltimore).* 2018;97(40):e12601. PMID: 30290630
148. Scorsetti M, Comito T, Clerici E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. *Radiat Oncol.* 2018;13(1):234. PMID: 30477560
149. Nakamura M, Hashimoto N, Mayahara H, et al. Additional chemotherapy improved local control and overall survival after stereotactic body radiation therapy for patients with oligo-recurrence. *Radiat Oncol.* 2018;13(1):75. PMID: 29688858
150. Buergy D, Rabe L, Siebenlist K, et al. Treatment of Adrenal Metastases with Conventional or Hypofractionated Image-guided Radiation Therapy - Patterns and Outcomes. *Anticancer research.* 2018;38(8):4789-96. PMID: 30061250
151. Celik E, Semrau R, Baues C, et al. Robot-assisted Extracranial Stereotactic Radiotherapy of Adrenal Metastases in Oligometastatic Non-small Cell Lung Cancer. *Anticancer research.* 2017;37(9):5285-91. PMID: 28870966
152. Erler D, Brotherston D, Sahgal A, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. *Radiother Oncol.* 2018;127(2):304-09. PMID: 29706460
153. Fanetti G, Marvaso G, Ciardo D, et al. Stereotactic body radiotherapy for castration-sensitive prostate cancer bone oligometastases. *Med Oncol.* 2018;35(5):75. PMID: 29671075
154. Loi M, Klass ND, De Vries KC, et al. Pain flare, complexity and analgesia in bone oligometastases treated with stereotactic body radiation therapy. *European journal of cancer care.* 2018;27(6):e12915. PMID: 30246916

155. Loi M, Duijm M, Baker S, et al. Stereotactic body radiotherapy for oligometastatic soft tissue sarcoma. *Radiol Med.* 2018;123(11):871-78. PMID: 29923086
156. Iftode C, D'Agostino GR, Tozzi A, et al. Stereotactic Body Radiation Therapy in Oligometastatic Ovarian Cancer: A Promising Therapeutic Approach. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* 2018;28(8):1507-13. PMID: 30036231
157. Franzese C, Comito T, Toska E, et al. Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy. *Radiother Oncol.* 2018. PMID: 30414754
158. Virbel G, Le Fèvre C, Noël G, et al. Stereotactic Body Radiotherapy for Patients with Lung Oligometastatic Disease: A Five-Year Systematic Review. *Cancers (Basel).* 2021;13(14). PMID: 34298836
159. Choi HS, Jeong BK, Kang KM, et al. Tumor Control and Overall Survival after Stereotactic Body Radiotherapy for Pulmonary Oligometastases from Colorectal Cancer: A Meta-Analysis. *Cancer Res Treat.* 2020;52(4):1188-98. PMID: 32718145
160. Londero F, Grossi W, Morelli A, et al. Surgery versus stereotactic radiotherapy for treatment of pulmonary metastases. A systematic review of literature. *Future Sci OA.* 2020;6(5):Fso471. PMID: 32518686
161. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol.* 2010;5(7):1091-9. PMID: 20479693
162. Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. *International journal of radiation oncology, biology, physics.* 2008;72(2):398-403. PMID: 18374506
163. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(10):1572-8. PMID: 19255321
164. Alongi F, Arcangeli S, Filippi AR, et al. Review and uses of stereotactic body radiation therapy for oligometastases. *The oncologist.* 2012;17(8):1100-7. PMID: 22723509
165. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol.* 2013;14(1):e28-37. PMID: 23276369
166. Méndez Romero A, Schillemans W, van Os R, et al. The Dutch-Belgian Registry of Stereotactic Body Radiation Therapy for Liver Metastases: Clinical Outcomes of 515 Patients and 668 Metastases. *International journal of radiation oncology, biology, physics.* 2021;109(5):1377-86. PMID: 33451857
167. McPartlin A, Swaminath A, Wang R, et al. Long-Term Outcomes of Phase 1 and 2 Studies of SBRT for Hepatic Colorectal Metastases. *International journal of radiation oncology, biology, physics.* 2017;99(2):388-95. PMID: 28871989
168. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer.* 2011;117(17):4060-9. PMID: 21432842
169. Lanciano R, Lamond J, Yang J, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. *Frontiers in oncology.* 2012;2:23. PMID: 22645716
170. Franzese C, Nicosia L, Facondo G, et al. Stereotactic body radiation therapy for adrenal gland metastases: outcome and predictive factors from a multicenter analysis. *Clin Exp Metastasis.* 2021;38(6):511-18. PMID: 34651241
171. Pielkenrood BJ, Gal R, Kasperts N, et al. Quality of Life After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone

Metastases. *International journal of radiation oncology, biology, physics.* 2022;112(5):1203-15. PMID: 35017007
172. Mazzola R, Cuccia F, Pastorello E, et al. PSMA-guided metastases directed therapy for bone castration sensitive oligometastatic prostate cancer: a multi-institutional study. *Clin Exp Metastasis.* 2022;39(3):443-48. PMID: 35266063
173. Ito K, Nakajima Y, Onoe T, et al. Phase 2 Clinical Trial of Stereotactic Body Radiation Therapy for Painful Nonspine Bone Metastases. *Practical radiation oncology.* 2021;11(2):e139-e45. PMID: 33068791
174. Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *Lancet Oncol.* 2021;22(7):1023-33. PMID: 34126044
175. Napieralska A, Miszczyk L, Tukiendorf A, et al. The results of treatment of prostate cancer bone metastases after CyberKnife radiosurgery. *Ortopedia, traumatologia, rehabilitacja.* 2014;16(3):339-49. PMID: 25058109
176. Munshi A. Ablative radiosurgery for cardiac arrhythmias - A systematic review. *Cancer Radiother.* 2021;25(4):373-79. PMID: 33589330
177. Blanck O, Buergy D, Vens M, et al. Radiosurgery for ventricular tachycardia: preclinical and clinical evidence and study design for a German multi-center multi-platform feasibility trial (RAVENTA). *Clin Res Cardiol.* 2020;109(11):1319-32. PMID: 32306083
178. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Treatment of Cancer by Site. [cited 7/22/2022]. 'Available from:' http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
179. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e278S-313S. PMID: 23649443
180. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest.* 2012;142:1620-35. PMID: 23208335
181. Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e455S-97S. PMID: 23649452
182. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Practical radiation oncology.* 2017. PMID: 28596092
183. Simone CB, 2nd, Bogart JA, Cabrera AR, et al. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. *Practical radiation oncology.* 2020;10(3):158-73. PMID: 32222430
184. Palta M, Godfrey D, Goodman KA, et al. Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. *Practical radiation oncology.* 2019;9(5):322-32. PMID: 31474330
185. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. [cited 19]. 'Available from:'

186. Balaban EP, Mangu PB, Khorana AA, et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(22):2654-68. PMID: 27247216
187. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. *Journal of Clinical Oncology.* 2018;36(34):3411-30. PMID:

CODES

NOTE: Coding for stereotactic radiosurgery typically consists of a series of CPT codes describing the individual steps required; medical radiation physics, clinical treatment planning, attachment of stereotactic head frame, treatment delivery and clinical treatment management.

The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the treatment planning.

Treatment Planning Services:

Treatment delivered with LINAC based MLC may involve planning with the following codes.

Codes	Number	Description
CPT	77301	Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

NOTE: Treatment delivery:

The codes used for treatment delivery will depend on the energy source used, typically either photons or protons.

Codes	Number	Description
CPT	32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
	77371	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
	77372	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
	77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fraction
	77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

NOTE: Codes for treatment delivery primarily reflects the cost related to the energy source used, and not physician work.

Clinical treatment management:

Codes	Number	Description
CPT	77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.)
	61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
	61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
	61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
	61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
	61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
	63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
	63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
		Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance and real-time positron emissions-based delivery adjustments to 1 or more lesions, entire course not to exceed 5
	G0339	Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment.
	G0340	Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

Date of Origin: *July 2019*

Regence

Medical Policy Manual Surgery, Policy No. 215

Hypoglossal Nerve Stimulation

Effective: January 1, 2024

Next Review: June 2024
Last Review: August 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

When patients with obstructive sleep apnea cannot tolerate positive airway pressure, or when continuous positive airway pressure (CPAP) treatment has failed, hypoglossal nerve stimulation may be considered.

MEDICAL POLICY CRITERIA

Note: Contract language takes precedent over medical policy. Some member contracts have specific benefit limitations for orthognathic surgery.

I. Hypoglossal nerve stimulation may be considered **medically necessary** in adults with obstructive sleep apnea when all of the criteria below (A.-E.) are met:

A. Has an AHI greater than or equal to 15 and less than or equal to 100 with less than 25% central apneas (see Policy Guidelines); and

B. Has PAP failure (residual AHI greater than or equal to 20 or failure to use CPAP greater than or equal to 4 hr per night for greater than or equal to 5 nights per week) or the patient is not an appropriate PAP candidate (see Policy Guidelines); and

C. Has a body mass index less than 35 kg/m^2; and

D. Has non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration.

E. One of the following is met:

1. Patient is 22 years of age or older; or
2. Patient is between 18 and 22 years of age and one of the following is met:
    a. Patient has had an adenotonsillectomy; or
    b. An adenotonsillectomy is contraindicated for the patient.

II. Hypoglossal nerve stimulation may be considered **medically necessary** in adolescents or young adults with Down syndrome and obstructive sleep apnea when all of the criteria below (A.-E.) are met:

A. Patient is age 10 to 21 years; and

B. Has an AHI greater than 10 and less than 50 with less than 25% central apneas after prior adenotonsillectomy (see Policy Guidelines); and

C. Have either tracheotomy or be ineffectively treated with PAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device; and

D. Has a body mass index less than or equal to 95th percentile for age; and

E. Has non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration.

III. Revisions to an existing hypoglossal nerve stimulator may be considered **medically necessary** after the device has been placed.

IV. The replacement of all or part of an existing hypoglossal nerve stimulator and/or generator is considered **medically necessary** when the existing hypoglossal nerve stimulator and/or generator is malfunctioning, cannot be repaired, or is no longer under warranty.

V. Hypoglossal nerve stimulation is considered **not medically necessary** in adults with obstructive sleep apnea when Criterion I.C. is not met, including PAP refusal.

VI. The replacement of all or part of an existing hypoglossal nerve stimulator and/or generator is considered **not medically necessary** when Criterion IV. is not met.

VII. Hypoglossal nerve stimulation is considered **investigational** for all other indications including but not limited to when policy Criteria I. or II. are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

There is divergence on scoring rules for hypopneas between the recommendations of the American Academy of Sleep Medicine (AASM) and the Center for Medicare Services (CMS), the latter being more restrictive.[1] Policy Criteria are based on apnea-hypopnea index (AHI)

scored with either the AASM or the CMS scoring rules,[2, 3] either of which are acceptable in this medical policy.

The most recent (2012) AASM rules define apnea in adults as a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor, for ≥ 10 seconds. Hypopnea in adults is scored when the peak signal excursions drop by ≥ 30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal.

The Center for Medicare Services (CMS) scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation.

POSITIVE AIRWAY PRESSURE (PAP) – Continuous (CPAP), Bi-Level (BiPAP) or auto adjusting (APAP)

PAP failure: defined as AHI greater than 20 events per hour while using PAP.

Not an appropriate PAP candidate: defined as being unable to use PAP therapy for at least 4 hours per night for 5 nights or more per week, with reasonable attempts having been made to address any medical, mechanical, or psychological problems associated with PAP, e.g., adjustment of pressure settings, appropriate medication and humidification, refitting of the mask, trial of alternative pressure delivery systems such as auto-adjusting positive airway pressure or bi-level positive airway pressure.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Current symptomology
- Conservative medical therapies failed
- CPAP trial results
- Documentation that the patient is not an appropriate PAP candidate with clinical rationale, if applicable (See policy guidelines)
- Sleep Study results, including apnea-hypopnea index (AHI) scored either by the American Academy of Sleep Medicine (AASM) scoring rules or the Center for Medicare Services (CMS) scoring rules.
- Drug-induced sleep endoscopy (DISE) results
- If a replacement is being requested, documentation that the stimulator and/or generator is malfunctioning, cannot be repaired, or is no longer under warranty

CROSS REFERENCES

1. Prefabricated Oral Appliances for Obstructive Sleep Apnea, Allied Health, Policy No. 36
2. Orthognathic Surgery, Surgery, Policy No. 137

3. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166
4. Absorbable Nasal Implant for Treatment of Nasal Valve Collapse, Surgery, Policy No. 209
5. Phrenic Nerve Stimulation for Central Sleep Apnea, Surgery, Policy No. 212

BACKGROUND

OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep. The hallmark symptom of OSA is excessive daytime sleepiness, and the typical clinical sign of OSA is snoring, which can abruptly cease and be followed by gasping associated with a brief arousal from sleep. The snoring resumes when the patient falls back to sleep, and the cycle of snoring/apnea/arousal may be repeated as frequently as every minute throughout the night.

Sleep fragmentation associated with the repeated arousal during sleep can impair daytime activity. For example, adults with OSA-associated daytime somnolence are thought to be at higher risk for accidents involving motorized vehicles (i.e., cars, trucks, heavy equipment). OSA in children may result in neurocognitive impairment and behavioral problems. In addition, OSA affects the cardiovascular and pulmonary systems. For example, apnea leads to periods of hypoxia, alveolar hypoventilation, hypercapnia, and acidosis. This, in turn, can cause systemic hypertension, cardiac arrhythmias, and cor pulmonale. Systemic hypertension is common in patients with OSA. Severe OSA is associated with decreased survival, presumably related to severe hypoxemia, hypertension, or an increase in automobile accidents related to overwhelming sleepiness.

There are racial and ethnic health disparities seen for OSA impacting the prevalence of disease and accessibility to treatment options, particularly affecting children. Black children are 4 to 6 times more likely to have OSA than white children.[4] Among young adults younger than 26 years, African American individuals are 88% more likely to have OSA compared to white individuals. Another study found that African American individuals 65 years of age and older were 2.1 times more likely to have severe OSA than white individuals of the same age group. These health disparities may affect accessibility of treatment for OSA and impact health outcomes. One analysis of insurance claims data, including over 500,000 patients with a diagnosis of OSA, found that increased age above the 18- to 29- year range ($p<0.001$) and Black race ($p=0.020$) were independently associated with decreased likelihood for receiving surgery for sleep apnea.[5] Lee (2022) found that Black men had a continuous mortality increase specifically related to OSA over the study period (1999 to 2019; annual percentage change 2.7%; 95% confidence interval, 1.2 to 4.2) compared to any other racial group.[6]

A polysomnogram performed in a sleep laboratory and, in adults, home sleep apnea testing with a technically adequate device, are considered the gold standard test used to diagnose OSA.[7] Objective measures of OSA are compiled using polysomnography monitors, which document the number of apneic (cessation or near cessation of airflow) and hypopneic (reductions in airflow associated with certain physiologica consequences) events per hour and combine them into the apnea-hypopnea index (AHI). AHI is a measure of severity of OSA. The American Academy of Sleep Medicine (AASM) provided an updated set of scoring rules in 2012.[2] Based on the 2012 AASM rules, apnea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative

apnea sensor, for ≥ 10 seconds. Hypopnea in adults is scored when the peak signal excursions drop by ≥ 30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal. The Center for Medicare Services (CMS) also published a set of scoring rules.[3] The CMS scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. The respiratory disturbance index (RDI) may be defined as the number of apneas, hypopneas and respiratory effort-related arousals (RERAs) per hour of sleep.

The final diagnosis of OSA rests on a combination of objective and subjective criteria (e.g. AHI or RDI and excessive daytime sleepiness) that seek to identify those levels of obstruction which are clinically significant. When sleep onset and offset are unknown (e.g., in home sleep studies) the AHI or RDI may be calculated based on the number of apneas, hypopneas, and/or RERAs per hour of recording time.

An increase in mortality is associated with an AHI greater than 15. More difficult to evaluate is the clinical significance of patients with mild sleep apnea. Mortality has not been shown to be increased in these patients, and frequently the most significant manifestations reported by the patient are snoring, excessive daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, nocturia, morning headaches, memory loss, irritability, or hypertension.[8, 9] The hallmark clinical symptom of OSA is excessive snoring, although it is important to note that snoring can occur in the absence of OSA. Isolated snoring in the absence of medical complications, while troubling to the patient's bed partner, is not considered a medical problem requiring surgical intervention.

Table 1. Definitions of Terms for Obstructive Sleep Apnea

Terms	Definition
Apnea	The frequency of apneas and hypopneas is measured from channels assessing oxygen desaturation, respiratory airflow, and respiratory effort. In adults, apnea is defined as a drop in airflow by ≥90% of pre-event baseline for at least 10 seconds. Due to faster respiratory rates in children, pediatric scoring criteria define an apnea as ≥2 missed breaths, regardless of its duration in seconds.
Hypopnea	Hypopnea in adults is scored when the peak airflow drops by at least 30% of pre-event baseline for at least 10 seconds in association with either at least 3% oxygen desaturation or an arousal or at least 4% oxygen desaturation (depending on the scoring criteria). Hypopneas in children are scored by a ≥50% drop in nasal pressure and either a ≥3% decrease in oxygen saturation or an associated arousal.
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Obstructive sleep apnea (OSA)	Repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep
Mild OSA	In adults: AHI of 5 to <15 In children: AHI ≥1 to <5
Moderate OSA	In adults: AHI of 15 to <30 In children: AHI ≥5 to <10
Severe OSA	Adults: AHI ≥30 Children: AHI of ≥10
Continuous	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP)

Terms	Definition
positive airway pressure (CPAP)	or Bi-level (Bi-PAP). CPAP is a more familiar abbreviation and will refer to all types of PAP devices.
CPAP Failure	Usually defined as an AHI greater than 20 events per hour while using CPAP.
CPAP Intolerance	CPAP use for less than 4 h per night for 5 nights or more per week, or refusal to use CPAP. CPAP intolerance may be observed in patients with mild, moderate, or severe OSA

IMPLANTABLE HYPOGLOSSAL NERVE STIMULATORS

Hypoglossal nerve stimulation involves the surgical implantation of a subcutaneous generator in the upper chest and an electrode tunneled from the generator to the hypoglossal nerve. The patient uses a hand-held remote to activate the device just prior to sleep and to turn it off upon waking. Some have sensors detect inspiratory efforts and the hypoglossal nerve is stimulated in a synchronized fashion. This stimulation is intended to maintain muscle tone of the tongue base to prevent airway occlusion.

Stimulation systems such as the Inspire II Upper Airway Stimulation System include respiratory sensing leads that permit intermittent stimulation during inspiration. Stimulation parameters are titrated during an in-laboratory polysomnography and can be adjusted by the patient during home use. The device is turned on only during sleep periods.

REGULATORY STATUS

The Inspire® II Upper Airway Stimulation System (Inspire Medical Systems) received FDA approval in 2014 (P130008) for a subset of patients age 22 years and older with moderate to severe obstructive sleep apnea. Product code: MNQ. The original approval was for patients with an Apnea Hypopnea Index (AHI) of greater or equal to 20 and less than or equal to 65. In 2017, approval was granted to expand the AHI range to 15 to 65 events per hour (S021). In 2020, Inspire received approval to expand the indications to include adolescent patients age 18 to 21 with moderate to severe OSA (15≤ AHI ≤65) who:

- Do not have complete concentric collapse at the soft palate level
- Are contraindicated for, or not effectively treated by, adenotonsillectomy
- Have been confirmed to fail, or cannot tolerate, PAP therapy despite attempts to improve compliance
- Have followed standard of care in considering all other alternative/adjunct therapies

For this approval, existing adult clinical data and interim data from a pediatric feasibility study in patients with Down's syndrome were leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in the pediatric sub-population of adolescents age 18 to 21.

In 2023 the FDA approved an expanded AHI for the Inspire Medical System for patients (18 and older) with an upper limit baseline AHI to 100 (increase from less than or equal to 65 to less than or equal to 100). Also, the FDA approved increasing the body mass index (BMI) warning to 40 kg/m^2 (increase from less than and equal to 32 to less than or equal to 40).[10]

There are hypoglossal nerve stimulation devices which have received an investigational device exemption (IDE) from the FDA. IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data, however, the device is still in the developmental phase and not considered to be in commercial distribution.

- In 2014, ImThera™ Medical received FDA approval for an IDE trial with the aura6000® hypoglossal nerve stimulator system.
- In 2011, Apnex Medical received FDA approval to conduct a randomized investigational device exemption (IDE) trial for the Hypoglossal Nerve Stimulation (HGNS®) System. The trial was terminated and Apnex Medical has ceased operations.
- In June 2020, the FDA approved an Investigational Device Exemption (IDE) trial for the Genio® system from Nyxoah. This is a battery-free, leadless and minimally invasive implanted hypoglossal nerve stimulator.

EVIDENCE SUMMARY

Continuous positive airway pressure (CPAP) is the most widely accepted medical therapy for treatment of obstructive sleep apnea (OSA) and improvement of primary health outcomes such as cardiovascular disease, type 2 diabetes, and overall mortality associated with OSA. Hypoglossal nerve stimulation (HNS), sometimes referred to as upper airway stimulation, is being proposed as a second line treatment for patients who have failed CPAP.

SYSTEMATIC REVIEWS

A systematic review (SR) with meta-analysis comparing outcomes of upper airway stimulation and other upper airway surgical procedures in the treatment of obstructive sleep apnea (OSA) was published by Neruntarat (2021).[11] Five articles (n= 990) were included in the review and analysis. Patients in the "Stim" group underwent hypoglossal nerve stimulation (HNS, n=660) with the Inspire implant, and patients in the surgical intervention "Surg" group (n=330) underwent various surgical interventions including uvulopalatoplasty (UPPP), transoral robotic surgery, expansion sphincter pharyngoplasty, and palatal or tongue base surgery. Studies by Huntley,[12-14] Shah,[15] and Yu[16] were included in the analysis. The follow-up time ranged from 2 to 13 months. The mean cure rates in the Stim group and the Surg group were 63% and 22%, respectively, and the mean success rates were 86% and 51% ($p < 0.001$). The apnea-hypopnea index (AHI) was significantly more reduced in the Stim group, -23.9 events/ hour (MD, 95% CI -25.53, -22.29) compared to the Surg group, -15.5 events/hour (MD, 95% CI -17.50, -13.45), $p < 0.001$. Oxygen saturation nadir improvement was 8.5% (MD 95% CI 7.05%, 9.92%) in the Stim group and 2.2% (MD 95% CI-0.22%, 4.58%) in the Surg group, which is significantly higher in the Stim group ($p < 0.001$). No significant difference in Epworth Sleepiness Scale (ESS) between groups was found. High risk of bias in multiple domains, including selective outcome reporting, incomplete outcome data, blinding, and participant selection was found for all included studies. Noted limitations in available data include retrospective study designs, limited follow-up times, and heterogeneity in patient characteristics.

Costantino (2020) published a SR with meta-analysis of studies evaluating the clinical outcomes of HNS in the treatment of moderate to severe OSA.[17] The SR included 12 prospective studies, excluding redundant cohorts of the same studies with varied follow-up lengths such as the STAR Trial[18-21] and the German Post-Market studies[22, 23] No randomized controlled trials comparing HNS to CPAP or other surgical interventions were identified. Of the 350 patients (median age 54.3 [IQR 53-56.25] years), 239 were implanted with the Inspire® system, 59 were implanted with the ImThera™ system, and 52 were implanted with the Apnex system. All of the studies were considered to be of generally high quality, having satisfied at least six of the eight NICE quality assessment tool items. In all studies, the American Academy of Sleep Medicine (AASM) apnea and hypopnea definitions[2] were used, except that a 4%

oxygen desaturation was required for a hypopnea to determine AHI. Analyses of long-term outcomes were conducted with data from the nine studies which had follow-up timepoints of six- and 12-months separately from the STAR trial data, which reported longer-term follow-up timepoints of 18-, 36-, and 60-months. At 12 months, the mean AHI difference was - 17.50 (Inspire; 95% CI: - 20.01 to - 14.98, p < 0.001), - 24.20 (ImThera™; 95% CI: - 37.39 to 11.01, p < 0.001), and - 20.10 (Apnex; 95% CI: - 29.62 to - 10.58, p < 0.001). The mean AHI reduction after five years was - 18.00 (Inspire®, - 22.38 to - 13.62, p < 0.001). The Epworth sleepiness scale (ESS) mean reduction was - 5.27 (Inspire®), - 2.90 (ImThera™), and - 4.20 (Apnex) at 12 months and - 4.40 (Inspire) at 60 months, respectively. Five-year serious device-related adverse events requiring surgical intervention in the STAR trial were 6% (8/126 patients), and the other studies included in the meta-analysis (n=195) reported a comparable complication rate at six and 12 months. Among the nine studies included in the meta-analysis, the overall success rate at 12 months (defined as a 50% reduction in AHI and overall AHI less than 20), was 72.4% (Inspire®, n=211), 76.9% (ImThera™, n=13), and 55% (Apnex, n=31).

A 2015 SR identified six case series with a total of 200 patients treated with HNS.[24] No controlled trials were identified. Two series were identified on the Inspire II System and included the STAR trial described below. Three series were identified with the HGNS system and included the study of 31 patients described above. One series of 13 patients was identified with the aura6000 System (ImThera Medical). When data were combined for meta-analysis, AHI and Oxygen Desaturation Index (ODI) improved by 50% (eg, AHI from 44 to 20, ODI from 21 to 10), and the ESS improved from 12 to 7. All of the included studies described minor complications such as tongue weakness, tongue soreness, pain/swelling at the neck incision, fever, and lack of tongue response to stimulation. Of the 200 patients, nine (4.5%) had serious device-related adverse events that led to removal of the stimulator.

RANDOMIZED CONTROLLED TRIALS

Schwartz (2023) published results from the ImThera Medical Targeted Hypoglossal Neurostimulation Study #3 (THN3), which investigated the efficacy and safety of targeted HNS of the proximal hypoglosal nerve in patients with moderate-to-severe OSA (AHI 20-60 events per hour).[25] This was a multicenter, randomized, open-label trial where all patients (n=138) were implanted with the HNS system (aura6000; ImThera Medical), and randomly assigned 2:1 to HNS device activation at 1 or 4 months after implant for the treatment and control groups, respectively. Efficacy was measured at month 4, as well as after 11 months of therapy (study months 12 and 15 for treatment and control groups, respectively). The study included mostly males (86.2%) and White individuals (91.3%). The results demonstrated that at month 4, the treatment group had significantly better outcomes compared to the control group for AHI and ODI scores. However, after 11 months of active therapy, the difference between the treatment and control groups was not statistically significant for AHI (relative risk [RR], -7.5; 95% CI, -16.0 to 1.4) but remained significant for ODI (RR, 10.4; 95% CI, 1.6 to 18.8). Limitations include homogeneity of the study population and difference in starting points for treatment between groups.

Heiser (2021) published the results of a multicenter, double-blind, randomized, sham-controlled, crossover trial to examine the effect of implanted hypoglossal nerve stimulation (Stim, n=45) or sham stimulation (Sham, n=44) using the Inspire HNS.[26] Inclusion criteria were moderate-to-severe OSA (AHI ≥ 15), CPAP intolerance, and the absence of complete concentric retropalatal collapse during drug-induced sleep endoscopy. The UAS devices implanted in the participants were programmed to the setting assigned to their respective

groups, i.e., Stim (continued therapeutic stimulation, average amplitude 1.6 V ± 0.7) and Sham (stimulation voltage set at 0.1 V as a subtherapeutic stimulation level and a deception for the patient). All participants received therapeutic stimulation during the first visit (baseline visit), and once randomized, the Stim–Sham group received therapeutic stimulation while the Sham–Stim group received sham stimulation for one week. Crossover occurred during the second week, in which the Stim–Sham group received sham stimulation while the Sham–Stim group received therapeutic stimulation. Primary outcome measures were the proportion of AHI responders (defined as AHI ≤ 15/h) between parallel randomized groups and self-reported sleepiness measure using the ESS questionnaire at the one-week visit. At one week, the AHI response rate was 76.7% with Stim and 29.5% with Sham, a difference of 47.2% (95% CI: 24.4 to 64.9, p < 0.001). The average ESS change from the Stim–Sham group was 0.4 ± 2.3 and from the Sham–Stim group was 5.0 ± 4.6, with a significant difference of 4.6 (95% CI of 3.1 to 6.1, p = 0.001). The change of AHI and ESS from the baseline to the one-week and two-week visits between the Stim–Sham and Sham–Stim groups and found no statistical evidence of a carryover effect for AHI (p = 0.55) or ESS (p = 0.23). The homogenous study population (81% male, 100% Caucasian) limits the generalizability of the study findings. In addition, the authors note that most participants randomized to the sham arm became aware of the group allocation, which may impact study outcomes. Longer-term outcomes are not reported. This study was funded by the device manufacturer (Inspire Medical Systems, Inc) and study authors received fees and/or other funding from the device manufacture and no clear attempt to mitigate potential bias is provided.

NONRANDOMIZED STUDIES

Observational Comparative Studies

Heiser (2023) published a study comparing HNS with positive airway pressure (PAP) treatment in 126 propensity matched patients in a real-world setting.[27] A clinically important symptom improvement was seen at 12 months in both cohorts, though there was a greater difference in the Epworth Sleepiness Scale (ESS) improvement in patients treated with HNS (8.0 ± 5.1 points vs. 3.9 ± 6.8 points; p = 0.042). In both groups, mean posttreatment AHI was significantly reduced (HNS: 8.1 ± 6.3/hour [h]; PAP: 6.6 ± 8.0/h; p < 0.001). Adherence after 12 months among patients treated with HNS was higher than in those receiving PAP therapy (5.0 ± 2.6 h/night; 4.0 ± 2.1 h/night) but not with statistical significance. Several of the study authors received fees and/or other funding from the device manufacture and no clear attempt to mitigate potential bias is provided.

Nonrandomized evidence consists of comparative studies that compared HNS with historical controls treated with UPPP or a variant of UPPP (expansion sphincter pharyngoplasty, see Table 2) and a study that compared HNS with transoral robotic surgery. AHI success by the Sher criteria ranged from 87% to 100% in the HNS group compared with 40% to 64% in the UPPP group (see Table 3). Posttreatment ESS was below 10 in both groups. It is not clear from some studies whether the patients in the historical control group were similar to the subset of patients in the HNS group, particularly in regard to the pattern of palatal collapse and from patients who did not return for postoperative PSG (see Tables 4 and 5).

Several comparative studies have addressed these concerns by only including patients who meet the criteria for HNS in the control group. Yu (2019) compared outcomes for patients who met the criteria for both HNS (non-concentric collapse on drug-induced sleep endoscopy) and transoral robotic surgery (retroglossal obstruction).[16] When patients with similar anatomic

criteria were compared, HNS led to significantly better improvements in AHI, cure rate (defined as AHI < 5), and the percentage of time that oxygen saturation fell below 90%. Huntley (2021) selected patients in the control group who met criteria for HNS (non-concentric collapse on drug-induced sleep endoscopy and body mass index [BMI] criteria) but had been treated at their institutions by single or multi-level palatal and lingual surgery.[12] There was no explanation of why the different treatments were given during the overlap period of 2010 to 2019, but the HNS patients were older and heavier. HNS resulted in a modestly greater decrease in AHI (HNS: -21.4 vs -15.9. p <.001), but not in ESS (HNS: -4.7 vs -5.8, p =.06). More patients in the HNS group achieved success by the Sher criteria (70% vs 48 to 49%) suggesting that there might be a clinical benefit for some patients.

Another report from the ADHERE registry investigators (Mehra 2020) compared outcomes from HNS patients with patients who met criteria but had been denied insurance coverage.[28] In a post-hoc multivariate analysis, previous use of PAP and prior surgical procedures were predictors of insurance approval. In the group of patients who received HNS, the average use downloaded from the device was 5.6 h/night and 92% of patients had usage greater than 20 h/week. Most of the comparator group (86%) were not using any therapy at follow-up. The remaining 14% were using PAP, an oral appliance, or underwent OSA surgery. The AHI decreased to 15 events/h (moderate OSA) on the night of the sleep test in patients with HNS, with only modest improvement in patients who did not receive HNS. The hours of use on the night of the post-operative sleep study was not reported, and the HNS patients may have been more likely to use their device on the test night. In addition, the use of a home sleep test for follow-up may underestimate the AHI. The ESS improved in the HNS group but worsened in the controls. This suggests the possibility of bias in this subjective measure in patients who were denied coverage.

Table 2. Summary of Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	HNS	Traditional Surgery	Follow-Up
Mehra (2020)[28]	ADHERE registry	US, EU	2017-2019	OSA patients who were intolerant to CPAP and met HNS criteria of AHI 15 to 65, BMI < 35, and favorable pattern of palatal collapse[a]	250 registry patients treated with HNS	100 patients who qualified for HNS but were denied insurance coverage	6 to 24 months
Huntley (2021)[12]	ADHERE registry compared to retrospective controls	US, EU	• HNS 2010-2019 • Modified UPPP 2003-2019	OSA patients who were intolerant to CPAP and met HNS criteria of AHI 15 to 65, BMI < 35, and favorable pattern of palatal collapse[a]	465 registry patients treated with HNS who had 12 mo follow-up	233 patients who would have qualified for HNS and were treated by single level (68%) or multilevel (31%) surgery	173 days after surgery 383 days after HNS
Yu (2019)[16]	Retrospective series with historical controls	US	• HNS 2014-2016 • TORS 2011-NR	OSA patients with AHI >20 and <65, BMI ≤32, failed CPAP, favorable pattern of palatal collapse[a]	27 patients age 62 with retroglossal collapse amenable to TORS	20 patients age 53 y who would have qualified for HNS and were treated by TORS	NR
Shah (2018)[15]	Retrospective series with historical controls	US	HNS 2015-2016 UPPP 2003-2012	40 OSA patients with AHI >20 and <65, BMI ≤32, failed CPAP, favorable pattern of palatal collapse[a]	35% had previously had surgery for OSA	UPPP 50% of patients had additional surgical procedures	2-13 mo
Huntley (2018)[14]	Retrospective series with historical controls	US	HNS2014-2016 Modified UPPP 2011-2016	Retrospective review included treated patients who had a postoperative PSG	75 patients age 61.67 y with a favorable pattern of palatal collapse	33 patients age 43.48 y treated by ESP	To post-operative PSG

BMI: body mass index; CPAP: continuous positive airway pressure; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; OSA: obstructive sleep apnea; PSG: polysomnography; UPPP: uvulopalatopharyngoplasty.

[a] A favorable pattern of palatal collapse is not concentric retropalatal obstruction on drug-induced sleep endoscopy.

Table 3. Summary of Key Observational Comparative Study Results

Header Row	Baseline AHI (SD)	Posttreatment AHI (SD)	AHI Success (%) Sher Criteria	Baseline ESS (SD)	Posttreatment ESS (SD)
Huntley (2021)[12]					
HNS	35.5 (15.0)	14.1 (14.4)	70	11.9 (5.5)	7.3 (4.7)
Single or multi-level UPPP	35.0 (13.1)	19.3 (16.3)	48 to 49	11.3 (5.1)	5.9 (4.0)
p-Value	0.88	<0.001	<0.001	0.22	0.06
Mehra (2020)[28]					
HNS	33.7 (13.4)	14.7 (13.8)		12.3 (5.5)	7.2 (4.8)
No HNS	34.9 (16.4)	26.8 (17.6)		10.9 (5.4)	12.8 (5.2)
p-value	0.95	<0.001		0.06	<0.001
Yu (2019)[16]		Average AHI Reduction	% Cure Rate	Change in SaO2 <90%	
HNS		33.3	70.4%	14.1	
TORS		12.7	10.0%	1.3	
p-value		0.002	<0.001	0.02	
Shah (2018)[15]					
HNS	38.9 (12.5)	4.5 (4.8)[b]	20 (100%)	13 (4.7)	8 (5.0)[b]
UPPP	40.3 (12.4)	28.8 (25.4)[a]	8 (40%)	11 (4.9)	7 (3.4)[b]
Huntley (2018)[14]					
HNS	36.8 (20.7)	7.3 (11.2)	86.7	11.2 (4.2)	5.4 (3.4)
ESP	26.7 (20.3)	13.5 (19.0)	63.6	10.7 (4.5)	7.0 (6.0)
p	0.003	0.003	0.008	0.565	*NS*

AHI: Apnea/Hypopnea Index; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; NS: not significant; Sher criteria: 50% decrease in AHI and final AHI <20; SD; standard deviation; UPPP: uvulopalatopharyngoplasty.
[a] Baseline vs posttreatment p<0.05.
[b] Baseline vs posttreatment p<0.001.

Table 4. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Huntley (2021)[12]	4. Study populations not comparable				1. The timing of follow-up was different (173 days after surgery and 383 days after HNS)
Mehra (2020)[28]	4. Study populations not comparable		3. Hours of use on the test night was not reported. This may not represent the normal use of the device.		1. The timing of follow-up was different
Yu (2019)[16]					1, 2. Duration of follow-up unclear
Shah (2018)[15]			2. UPPP may not be preferred treatment for patients with primarily lingual obstruction		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Huntley (2018)[14]	4. Study populations not comparable		1. Not clearly defined, few ESP patients had follow-up PSG		
Steffen (2018)[22]			2.No comparator		
STAR trial[18-21, 29, 30]			2.No comparator		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. ESP: expansion sphincter pharyngoplasty; PSG: polysomnography; STAR: Stimulation Therapy for Apnea Reduction; UPPP: uvulopalatopharyngoplasty.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[d]	Power[d]	Statistical[f]
Huntley (2021)[12]	1. Not randomized (retrospective)	1.-3. No blinding				
Mehra (2020)[28]	1. Not randomized	1.-3. No blinding			1. Power calculations not reported	
Yu (2019)[16]	1. Not randomized (retrospective)					
Shah (2018)[15]	1. Not randomized (retrospective) 4. Inadequate control for selection bias	1.-3. No blinding				4. Comparative treatment effects not calculated
Huntley (2018)[14]	1. Not randomized (retrospective)	1.-3. No blinding				
Steffen (2018)[22]	1. Not randomized	1.-3. No blinding				
STAR trial[18-21, 29, 30]	1. Not randomized	1.-3. No blinding				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. STAR: Stimulation Therapy for Apnea Reduction.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Prospective Single Arm Studies

Results of prospective single-arm studies show success rates in 66% to 68% of patients who had moderate-to-severe sleep apnea and a favorable pattern of palatal collapse (see Tables 6 and 7). Mean AHI was 31 to 32 at baseline, decreasing to 14 to 15 at 12 months. ESS scores decreased to 6.5 to 7.0. All improvements were maintained through 5 years of follow-up. Discomfort due to the electrical stimulation and tongue abrasion were initially common but were decreased when stimulation levels were reduced (see Table 8). In the post-market study, a normal ESS score (< 10) was obtained in 73% of patients. A FOSQ score of at least 19 was observed in 59% of patients compared to 13% at baseline. At the 12- month follow-up, 8% of bed partners regularly left the room due to snoring, compared to 75% of bed partners at baseline. The average use was 5.6 + 2.1 h per night. Use was correlated with the subjective outcomes, but not with AHI response. Two- and three-year follow-up of this study were reported by Steffen (2020)[31] but the percentage of patients at follow-up was only 68% at two years and 63% at 3 years, limiting conclusions about the longer-term efficacy of the procedure. A comparison of the populations who had 12-month versus two- or three-year results showed several differences between the patients who followed up and those who dropped out, including higher baseline AHI, higher baseline ODI, and trends towards lower usage per night and a lower responder rate at 12 months.

Table 6. Summary of Prospective Single-Arm Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
STAR trial[18-21, 29, 30]	EU, US	126 patients with AHI >20 and <50, BMI ≤32 kg/m^2, failed CPAP, favorable pattern of palatal collapse[a]	Stimulation parameters titrated with full PSG	5 y
Postmarket studies: Heiser (2017)[23] Steffen (2018, 2020)[22, 31] Hasselbacher (2018)[32] Withrow (2019)[33]	3 sites in Germany Thirteen US hospitals and 3 German hospitals	60 patients with AHI ≥15 and ≤65 on home sleep study, BMI ≤35 kg/m^2, failed CPAP; favorable pattern of palatal collapse[a] 600 adults with moderate to severe OSA (AHI, 15-65), <25% central and mixed apneas, CPAP nonadherence or intolerance, absence of concentric collapse		12 mo 12 mo

AHI: apnea/hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; STAR: Stimulation Therapy for Apnea Reduction.
[a] A favorable pattern of palatal collapse is non-concentric retropalatal obstruction on drug-induced sleep endoscopy.

Table 7. Summary of Prospective Single-Arm Study Results

Study	N	Percent of Patients with AHI Success (Sher criteria)	Mean AHI Score (SD)	Mean ODI Score (SD)	FOSQ Score (SD)	ESS Score (SD)
STAR trial[18-21, 29, 30]						
Baseline	126		32.0 (11.8)	28.9 (12.0)	14.3 (3.2)	11.6 (5.0)
12 months	124	66%	15.3 (16.1)[d]	13.9 (15.7)[d]	17.3 (2.9)[d]	7.0 (4.2)[d]
3 years	116[a]	65%	14.2 (15.9)	9.1 (11.7)	17.4 (3.5)[b]	7.0 (5.0)[b]
5 years	97[c]	63%	12.4 (16.3)	9.9 (14.5)	18.0 (2.2)	6.9 (4.7)
Postmarket studies: Heiser (2017)[23] Steffen (2018, 2020)[22, 31] Hasselbacher (2018)[32]						
Baseline	60		31.2 (13.2)	27.6 (16.4)	13.7 (3.6)	12.8 (5.3)
12 months	56[f]	68%	13.8 (14.8)[e]	13.7 (14.9)[e]	17.5 (3)[e]	6.5 (4.5)[e]
2 years	41	76%[h]				
3 years	38	68%[h]				
Withrow (2019)[33]						
age < 65	365					
Baseline			36.2 (34.6-37.8)[f]			12.3 (11.7-12.9)[f]
12 months			11.9 (9.9-13.9)[f]			7.1 (6.4-7.8)
age ≥ 65	235					
Baseline			36.1 (34.2-38.0)[f]			10.7 (9.9-11.5)[f]
12 months			7.6 (6.1-9.1)[f]			6.3 (5.4-7.2)[f]

AHI: Apnea/Hypopnea Index; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; ODI: Oxygen Desaturation Index; PSG: polysomnography; SD: standard deviation; STAR: Stimulation Therapy for Apnea Reduction.

[a] Ninety-eight participants agreed to undergo PSG at 36 months, of the 17 participants who did not undergo PSG at 36 months, 54% were nonresponders and their PSG results at 12 or 18 months were carried forward.

[b] The change from baseline was significant at p<0.001.

[c] Seventy-one participants agreed to a PSG.

[d] p<0.001.

[e] p< 0.05.

[f] Four patients lost to follow-up were analyzed as treatment failures.

[g] Range

[h] defined as AHI below 15/h

Table 8. Device-Related Adverse Events from Prospective Single-Arm Studies

Header Row	N	Discomfort due to Electrical Stimulation[a]	Tongue Abrasion	Dry Mouth	Mechanical Pain from Device	Internal Device Usability	External Device Usability
STAR trial[21]							

Header Row	N	Discomfort due to Electrical Stimulation[a]	Tongue Abrasion	Dry Mouth	Mechanical Pain from Device	Internal Device Usability	External Device Usability
0 to 12 months	126	81	28	10	7	12	11
12 to 24 months	124	23	12	5	2	8	11
24 to 36 months	116	26	4	2	3	1	8
36 to 48 months	97	7	3	0	1	3	9
> 48 months		5	3	3	1	1	6
Participants with event, n of 126 (%)		76 (60.3)	34 (27.0)	19 (15.1)	14 (11.1)	21 (16.7)	33 (26.2)

STAR: Stimulation Therapy for Apnea Reduction.
[a] Stimulation levels were adjusted to reduce discomfort

Down Syndrome

Liu (2022) published a systematic review investigating HNS in adolescents with Down Syndrome and OSA.[34] A total of nine studies were included with a follow up period ranging from two to 58 months; six studies had sample sizes fewer than 10 patients. The largest of the included studies was a prospective cohort study published by Yu (2022), which is summarized below. In an analysis that included 104 patients, AHI scores were significantly reduced in patients after HNS (mean AHI reduction, 17.43 events/h; 95% CI, 13.98 to 20.88 events/h; p<0.001). Similarly, in an analysis that included 88 patients, OSA-18 survey scores were significantly reduced after HNS (mean OSA-18 reduction, 1.67; 95% CI, 1.27 to 2.08; p<0.001).

Yu (2022) reported on the safety and effectiveness of HNS in 42 adolescents with Down Syndrome and severe OSA (AHI of 10 events/h or greater).[35] This was a single-group, multicenter, cohort study with a one-year follow-up that included non-obese (BMI <95%) children and adolescents aged 10 to 21 years who were refractory to adenotonsillectomy and unable to tolerate CPAP. Patients who were included had an AHI between 10 and 50 on baseline PSG; the mean baseline AHI was 23.5 (SD, 9.7). All patients included tolerated HNS without any intraoperative complications. The most common complication was tongue or oral discomfort or pain, which occurred in 5 (11.9%) patients and was temporary, lasting weeks or rarely, months. Four patients (9.5%) had device extrusion resulting in readmissions to replace the extruded device. At 12 months, there was a mean decrease in AHI of 12.9 (SD, 13.2) events per hour (95% CI, -17.0 to -8.7 events/h). At the 12-month PSG, 30 of 41 patients (73.2%) had an AHI of less than 10 events/h, 14/41 patients (34.1%) had an AHI of less than five events/h, and 3/41 patients (7.3%) had an AHI of less than two events/h. There was also a significant improvement in quality-of-life outcomes. The mean improvement in the OSA-18 total score was 34.8 (SD, 20.3; 95% CI, -42.1 to -27.5) and the ESS improved by 5.1 (SD, ,6.9; 95% CI, -7.4 to -2.8).

Caloway (2020) reported a safety study of HNS in 20 children with Down Syndrome and severe OSA (AHI of 10 or greater) treated at three tertiary care centers.[36] Included were non-obese (BMI < 95%) children and adolescents aged 10 - 21 years who were refractory to tonsillectomy and either unable to tolerate CPAP or dependent on a tracheostomy. Patients who were included had an AHI between 10 and 50 on baseline PSG; the median baseline AHI

was 24.15 (interquartile range [IQR] of 19.88 to 35.10). All of the patients tolerated the stimulation, and at two months after implantation, the median AHI was 3.56 (IQR 2.61 to 4.40). Success, defined as an AHI of 5 or less (mild) with HNS, was achieved in 14 of 20 patients (70%). The median percent reduction in AHI was 85% with a median usage of 9.21 h (IQR: 8.29 to 9.50) per night. The OSA-18 score improved by 1.15 (IQR: 0.02 to 1.97), indicating a moderate but clinically significant change. There were two adverse events related to extrusion or connectivity of the stimulation or sensation leads, which were both corrected with wound exploration surgery. Study in a larger population of children with Down Syndrome is ongoing.

Registry

A retrospective review of the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database, a publicly available voluntary reporting system, was published by Bellamkonda in 2021.[37] This search was specific to the Inspire system and for adverse events reported between May 2014 and September 2019. Over the five-year period, 132 patient reports containing 134 adverse events were identified, including 32 device revision procedures and 17 device explantations. Complications noted to have not been reported in large-scale clinical trials included pneumothorax, pleural effusion, and lead migration into the pleural space.

Kent (2019) pooled data from the ADHERE registry plus data from three other studies to evaluate factors predicting success.[38] Over 80% of the 584 patients were men, and most were overweight. Seventy-seven percent of patients achieved treatment success, defined as a decrease in AHI by at least 50% and below 20 events/per hour. AHI decreased to below 5 in 41.8% of patients. Greater efficacy was observed in patients with a higher preoperative AHI, older patient age, and lower BMI. A report of data from the ADHERE registry by Thaler (2020) included 640 patients with 6-month follow-up and 382 with 12-month follow-up.[39] AHI was reduced from 35.8 at baseline to 14.2 at 12 months ($p < 0.001$), although the number of hours of use during the sleep test was not reported and home sleep studies may underestimate AHI. ESS was reduced from 11.4 at baseline to 7.2 at 12 months ($p < 0.001$), and patient satisfaction was high. In a multivariate model, only female sex (odds ratio: 3.634, $p = 0.004$) and lower BMI (odds ratio: 0.913, $p = 0.011$) were significant predictors of response according to the Sher criteria. In sensitivity analysis, higher baseline AHI was also found to be a negative predictor of success.

Boon (2018) reported results from 301 patients in the multicenter Adherence and Outcome of Upper Airway Stimulation for OSA International Registry (ADHERE).[40] The ADHERE registry included both retrospective and prospectively collected data from the U.S. and Germany between October 2016 and September 2017. Data were collected from PSG prior to implantation and between 2 and 6 months after implantation, or from home sleep tests which were often performed at 6 and 12 months after implantation as part of routine care. Mean AHI decreased from 35.6 (SD: 15.3) to 10.2 (SD: 12.9) post-titration with 48% of patients achieving an AHI of 5 or less. ESS decreased from 11.9 (5.5) to 7.5 (4.7) ($p < 0.001$).

Body Mass Index

Apublication by Sarber (2020) reported on outcomes of 18 patients implanted with HNS as a salvage procedure despite being outside of FDA trial data.[41] Of these patients, 12 had a BMI >32 kg/m^2 (range 32.1–39.1). Positive outcomes across the 18 subjects were found, with (83.3%) patients achieving surgical success (decrease in AHI >50% and AHI <20 events/hour). This study is limited by the retrospective design and very small sample size. In addition, a

retrospective analysis by Huntley (2018) found patients with a BMI of greater than 32 (n=40) did not have lower success rates than patients with a BMI less than 32 (n=113).[13] Only patients who had palpable cervical landmarks and carried most of their weight in the waist and hips were offered HNS.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY

In a position statement, the American Academy of Otolaryngology - Head and Neck Surgery (2019) supported hypoglossal nerve stimulation as an effective second-line treatment of moderate-to-severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy.[42]

AMERICAN ACADEMY OF SLEEP MEDICINE

The American Academy of Sleep Medicine (AASM, 2021) published practice guideline on when to refer patients for surgical modifications of the upper airway for OSA.[43] These guidelines replaced the 2010 practice parameters for surgical modifications.[44] The AASM guidelines note that positive airway pressure (PAP) is the most efficacious treatment for OSA, but effectiveness can be compromised when patients are unable to adhere to therapy or obtain adequate benefit, which is when surgical management may be indicated. The AASM guideline recommendations are based on a systematic review and meta-analysis of 274 studies of surgical interventions, including procedures such as uvulopalatopharyngoplasty (UPPP), modified UPPP, MMA, tongue base suspension, and hypoglossal nerve stimulation.[45] The systematic review deemed most included data of low quality, consisting of mostly observational data. The AASM strongly recommend that clinicians discuss referral to a sleep surgeon with adults with OSA and body mass index (BMI) <40 kg/m^2 who are intolerant or unaccepting of PAP. Clinically meaningful and beneficial differences in nearly all critical outcomes, including decrease in excessive sleepiness, improved quality of life (QOL), improved Apnea/Hypopnea Index (AHI) or respiratory disturbance index (RDI), and sleep quality, were demonstrated with surgical management in patients who are intolerant or unaccepting of PAP. The AASM makes a conditional recommendation that clinicians discuss referral to a sleep surgeon with adults with OSA, BMI <40 kg/m^2, and persistent inadequate PAP adherence due to pressure-related side effects, as available data (very low-quality) suggests that upper airway surgery has a moderate effect in reducing minimum therapeutic PAP level and increasing PAP adherence. In adults with OSA and obesity (class II/III, BMI >35) who are intolerant or unaccepting of PAP, the AASM strongly recommends discussion of referral to a bariatric surgeon, along with other weight loss strategies.

SUMMARY

Evidence for hypoglossal nerve stimulation (HNS) as a treatment of obstructive sleep apnea (OSA) is limited. However, HNS has become generally accepted in medical practice, and is recommended as an effective second-line treatment in a consensus statement by the American Academy of Otolaryngology - Head and Neck Surgery. Therefore, hypoglossal nerve stimulation may be considered medically necessary for some patients with OSA when policy criteria are met.

A hypoglossal nerve stimulation device may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing hypoglossal nerve stimulation device may be considered medically necessary after the device has been placed.

In certain situations, a hypoglossal nerve stimulation device may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a hypoglossal nerve stimulation device and/or generator may be considered medically necessary when device replacement Criteria are met.

When a hypoglossal nerve stimulation device is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a hypoglossal nerve stimulation device and/or generator is considered not medically necessary when device replacement Criteria are not met.

Clinical practice guidelines recommend positive airway pressure (PAP) as the most efficacious treatment for obstructive sleep apnea (OSA) and hypoglossal nerve stimulation (HNS) may be considered in some patients who are unable to adhere to therapy or obtain adequate benefit. Therefore, HNS is considered **not medically necessary** when there is PAP therapy refusal in adults with OSA.

There is not enough research to know if or how well hypoglossal nerve stimulation (HNS) works to treat people when policy criteria are not met. This does not mean that it does not work, but more research is needed to know. No clinical guidelines based on research address HNS for indications other than for those listed in the policy criteria. Therefore, hypoglossal nerve stimulation is considered investigational when policy criteria are not met.

REFERENCES

1. Korotinsky A, Assefa SZ, Diaz-Abad M, et al. Comparison of American Academy of Sleep Medicine (AASM) versus Center for Medicare and Medicaid Services (CMS) polysomnography (PSG) scoring rules on AHI and eligibility for continuous positive airway pressure (CPAP) treatment. *Sleep & breathing = Schlaf & Atmung.* 2016;20:1169-74. PMID: 26969658
2. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2012;8(5):597-619. PMID: 23066376
3. Centers for Medicare & Medicaid Services. Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093N). [cited 8/9/2023]. 'Available from:' https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=19&fromdb=true.
4. Dudley KA, Patel SR. Disparities and genetic risk factors in obstructive sleep apnea. *Sleep Med.* 2016;18:96-102. PMID: 26428843

5. Cohen SM, Howard JJM, Jin MC, et al. Racial Disparities in Surgical Treatment of Obstructive Sleep Apnea. *OTO Open.* 2022;6(1):2473974X221088870. PMID: 35321423
6. Lee YC, Chang KY, Mador MJ. Racial disparity in sleep apnea-related mortality in the United States. *Sleep Med.* 2022;90:204-13. PMID: 35202926
7. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2017;13:479-504. PMID: 28162150
8. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2009;5(3):263-76. PMID: 19960649
9. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep.* 1999;22(5):667-89. PMID: 10450601
10. (FDA) FaDA. Inspire Upper Airway Stimulation System (P130008/S090). [cited 08/15/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130008S090A.pdf.
11. Neruntarat C, Wanichakorntrakul P, Khuancharee K, et al. Upper airway stimulation vs other upper airway surgical procedures for OSA: a meta-analysis. *Sleep & breathing = Schlaf & Atmung.* 2021. PMID: 33999362
12. Huntley C, Boon M, Tschopp S, et al. Comparison of Traditional Upper Airway Surgery and Upper Airway Stimulation for Obstructive Sleep Apnea. *The Annals of otology, rhinology, and laryngology.* 2021;130(4):370-76. PMID: 32862654
13. Huntley C, Steffen A, Doghramji K, et al. Upper Airway Stimulation in Patients With Obstructive Sleep Apnea and an Elevated Body Mass Index: A Multi-institutional Review. *The Laryngoscope.* 2018;128(10):2425-28. PMID: 30098035
14. Huntley C, Chou DW, Doghramji K, et al. Comparing Upper Airway Stimulation to Expansion Sphincter Pharyngoplasty: A Single University Experience. *The Annals of otology, rhinology, and laryngology.* 2018;127(6):379-83. PMID: 29707958
15. Shah J, Russell JO, Waters T, et al. Uvulopalatopharyngoplasty vs CN XII stimulation for treatment of obstructive sleep apnea: A single institution experience. *American journal of otolaryngology.* 2018;39(3):266-70. PMID: 29540289
16. Yu JL, Mahmoud A, Thaler ER. Transoral robotic surgery versus upper airway stimulation in select obstructive sleep apnea patients. *The Laryngoscope.* 2019;129(1):256-58. PMID: 30208225
17. Costantino A, Rinaldi V, Moffa A, et al. Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis. *Sleep & breathing = Schlaf & Atmung.* 2020;24:399-411. PMID: 31418162
18. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *The New England journal of medicine.* 2014;370(2):139-49. PMID: 24401051
19. Strollo PJ, Jr., Gillespie MB, Soose RJ, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. *Sleep.* 2015;38:1593-8. PMID: 26158895
20. Woodson BT, Soose RJ, Gillespie MB, et al. Three-Year Outcomes of Cranial Nerve Stimulation for Obstructive Sleep Apnea: The STAR Trial. *Otolaryngology--head and*

neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2016;154:181-8. PMID: 26577774
21. Woodson BT, Strohl KP, Soose RJ, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2018;159(1):194-202. PMID: 29582703
22. Steffen A, Sommer JU, Hofauer B, et al. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. *The Laryngoscope.* 2018;128(2):509-15. PMID: 28561345
23. Heiser C, Maurer JT, Hofauer B, et al. Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2017;156(2):378-84. PMID: 28025918
24. Certal VF, Zaghi S, Riaz M, et al. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: A systematic review and meta-analysis. *The Laryngoscope.* 2015;125(5):1254-64. PMID: 25389029
25. Schwartz AR, Jacobowitz O, Eisele DW, et al. Targeted Hypoglossal Nerve Stimulation for Patients With Obstructive Sleep Apnea: A Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg.* 2023;149(6):512-20. PMID: 37022679
26. Heiser C, Steffen A, Hofauer B, et al. Effect of Upper Airway Stimulation in Patients with Obstructive Sleep Apnea (EFFECT): A Randomized Controlled Crossover Trial. *J Clin Med.* 2021;10(13). PMID: 34209581
27. Heiser C, Steffen A, Strollo PJ, Jr., et al. Hypoglossal nerve stimulation versus positive airway pressure therapy for obstructive sleep apnea. *Sleep & breathing = Schlaf & Atmung.* 2023;27(2):693-701. PMID: 35779166
28. Mehra R, Steffen A, Heiser C, et al. Upper Airway Stimulation versus Untreated Comparators in Positive Airway Pressure Treatment-Refractory Obstructive Sleep Apnea. *Ann Am Thorac Soc.* 2020;17(12):1610-19. PMID: 32663043
29. Soose RJ, Woodson BT, Gillespie MB, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Self-Reported Outcomes at 24 Months. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2016;12:43-8. PMID: 26235158
30. Gillespie MB, Soose RJ, Woodson BT, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Patient-Reported Outcomes after 48 Months of Follow-up. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2017;156(4):765-71. PMID: 28194999
31. Steffen A, Sommer UJ, Maurer JT, et al. Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea. *Sleep & breathing = Schlaf & Atmung.* 2020;24(3):979-84. PMID: 31485853
32. Hasselbacher K, Hofauer B, Maurer JT, et al. Patient-reported outcome: results of the multicenter German post-market study. *Eur Arch Otorhinolaryngol.* 2018;275:1913-19. PMID: 29808422
33. Withrow K, Evans S, Harwick J, et al. Upper Airway Stimulation Response in Older Adults with Moderate to Severe Obstructive Sleep Apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2019;161(4):714-19. PMID: 31084350
34. Liu P, Kong W, Fang C, et al. Hypoglossal nerve stimulation in adolescents with down syndrome and obstructive sleep apnea: A systematic review and meta-analysis. *Front Neurol.* 2022;13:1037926. PMID: 36388229

35. Yu PK, Stenerson M, Ishman SL, et al. Evaluation of Upper Airway Stimulation for Adolescents With Down Syndrome and Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg.* 2022;148(6):522-28. PMID: 35446411
36. Caloway CL, Diercks GR, Keamy D, et al. Update on hypoglossal nerve stimulation in children with down syndrome and obstructive sleep apnea. *The Laryngoscope.* 2020;130(4):E263-E67. PMID: 31219619
37. Bellamkonda N, Shiba T, Mendelsohn AH. Adverse Events in Hypoglossal Nerve Stimulator Implantation: 5-Year Analysis of the FDA MAUDE Database. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2021;164(2):443-47. PMID: 32957866
38. Kent DT, Carden KA, Wang L, et al. Evaluation of Hypoglossal Nerve Stimulation Treatment in Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg.* 2019;145(11):1044-52. PMID: 31556927
39. Thaler E, Schwab R, Maurer J, et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *The Laryngoscope.* 2020;130(5):1333-38. PMID: 31520484
40. Boon M, Huntley C, Steffen A, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2018;159(2):379-85. PMID: 29557280
41. Sarber KM, Chang KW, Ishman SL, et al. Hypoglossal Nerve Stimulator Outcomes for Patients Outside the U.S. FDA Recommendations. *The Laryngoscope.* 2020;130(4):866-72. PMID: 31291013
42. American Academy of Otolaryngology-Head and Neck Surgery. Position Statement: Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnea (OSA). . 2019 [cited 08/09/2023]. 'Available from:' https://www.entnet.org/resource/position-statement-hypoglossal-nerve-stimulation-for-treatment-of-obstructive-sleep-apnea-osa/.
43. Kent D, Stanley J, Aurora RN, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine clinical practice guideline. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2021;17(12):2499-505. PMID: 34351848
44. Aurora RN, Casey KR, Kristo D, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep.* 2010;33(10):1408-13. PMID: 21061864
45. Kent D, Stanley J, Aurora RN, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2021;17(12):2507-31. PMID: 34351849

CODES

Codes	Number	Description
CPT	64568	Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64582	Hypoglossal nerve neurostimulator implantation; open
	64583	Hypoglossal nerve neurostimulator revision or replacement
	64584	Hypoglossal nerve neurostimulator removal

Codes	Number	Description
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable

Date of Origin: *June 2019*

Regence

Medical Policy Manual Surgery, Policy No. 216

Responsive Neurostimulation

Effective: March 1, 2024

Next Review: September 2024
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Responsive neurostimulation (RNS) provides cortical stimulation in response to detection of specific seizure-related electrical signals. RNS shares some features with deep brain stimulation but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. RNS is used in individuals with refractory focal epilepsies to provide a treatment option that is an alternative to or an improvement on existing therapies.

MEDICAL POLICY CRITERIA

I. Responsive neurostimulation may be considered **medically necessary** for patients with focal epilepsy who meet ALL of the following criteria:

   A. 18 years or older; and

   B. Device is FDA approved (PMA or 510k only); and

   C. Diagnosis of focal seizures with 1 or 2 localized seizure foci identified; and

   D. Average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month for 3 consecutive months; and

   E. Failed greater than or equal to 2 antiepileptic medications; and

F. Not a candidate for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); and

G. Do not have any of the following contraindications for responsive neurostimulation device placement:

1. 3 or more specific seizure foci
2. Presence of primary generalized epilepsy
3. Presence of a rapidly progressive neurologic disorder

II. Responsive neurostimulator revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.

III. Responsive neurostimulation is considered **investigational** for all other indications, including but not limited to patients with focal epilepsy who do not meet the above Criteria.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical exam, including requirements as outlined by the policy criteria
- Number of seizure foci
- Documentation of seizure occurrence over the prior 3 months
- Clinical documentation demonstrating medicine-refractory symptoms
- Clinical documentation demonstrating that the patient is not a candidate for focal resective epilepsy surgery
- Presence of other conditions, such as a neurological disorder

CROSS REFERENCES

1. Vagus Nerve Stimulation, Surgery, Policy No. 74
2. Deep Brain Stimulation, Surgery, Policy No. 84
3. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213

BACKGROUND

Focal seizures (previously referred to as partial seizures) arise from a discrete area of the brain and can cause a range of symptoms, depending on the seizure type and the brain area involved.

Note that the term focal seizure in older literature may be referred to as “partial seizure.” A position paper from the International League Against Epilepsy (2017) outlined updated terminology for seizure and epilepsy subtypes.[1] For example, focal-onset seizures are subdivided based on the associated level of consciousness, and subsequently into whether they are motor or non-motor-onset.

Seizure disorders may be grouped into epileptic syndromes based on a number of factors, including the types of seizures that occur and their localization, the age of onset, patterns on electroencephalogram, associated clinical or neuroimaging findings, and genetic factors. Temporal lobe epilepsy is the most common syndrome associated with focal seizures. Of those with focal seizures, 30% to 40% have intractable epilepsy, defined as a failure to control seizures after two seizure medications have been appropriately chosen and used.[2]

EPILEPSY TREATMENT

Medical Therapy for Seizures

Standard therapy for seizures, including focal seizures, includes treatment with one or more of various antiepileptic drugs (AEDs), which include newer AEDs, like oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide.[2] Currently, response to AEDs is less than ideal: one systematic review comparing newer AEDs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%.[2] As a result, a substantial number of patients do not achieve good seizure control with medications alone.

Surgical Therapy for Seizures

When a discrete seizure focus can be identified, seizure control may be achieved through resection of the seizure focus (epilepsy surgery). For temporal lobe epilepsy, a randomized controlled trial has demonstrated that surgery for epilepsy was superior to prolonged medical therapy in reducing seizures associated with impaired awareness and in improving quality of life.[3] Surgery for refractory focal epilepsy (excluding simple focal seizures) is associated with five-year freedom from seizure rates of 52%, with 28% of seizure-free individuals able to discontinue AEDs.[4] Selection of appropriate patients for epilepsy surgery is important, because those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional temporal lobe epilepsy.[5] Some patients are not candidates for epilepsy surgery if the seizure focus is located in an eloquent area of the brain or other region that cannot be removed without risk of significant neurologic deficit.

Neurostimulation for Neurologic Disorders

Electrical stimulation at one of several locations in the brain has been used as therapy for epilepsy, either as an adjunct to or as an alternative to medical or surgical therapy. Vagus nerve stimulation (VNS) has been widely used for refractory epilepsy, following Food and Drug Administration (FDA) approval of a VNS device in 1997 and two randomized controlled trials evaluating VNS in epilepsy.[6] Although the mechanism of action for VNS is not fully understood, VNS is thought to reduce seizure activity through activation of vagal visceral afferents with diffuse central nervous system projections, leading to a widespread effect on neuronal excitability.

Stimulation of other locations in the neuroaxis has been studied for a variety of neurologic disorders. Electrical stimulation of deep brain nuclei (deep brain stimulation [DBS]) involves the use of chronic, continuous stimulation of a target. It has been most widely used in the treatment of Parkinson disease and other movement disorders, and has been investigated for treating epilepsy. DBS of the anterior thalamic nuclei was studied in a randomized control trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial, but DBS is not currently approved by FDA for stimulation of the anterior thalamic nucleus.[7] Stimulation of the

cerebellar and hippocampal regions and the subthalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy.[6]

Responsive Neurostimulation for Epilepsy

Responsive neurostimulation (RNS) shares some features with DBS but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. The RNS system provides stimulation in response to detection of specific epileptiform patterns, while DBS provides continuous or intermittent stimulation at preprogrammed settings.

Development of the RNS system arose from observations related to the effects of cortical electrical stimulation for seizure localization. It has been observed that electrical cortical stimulation can terminate induced and spontaneous electrographic seizure activity in humans and animals.[8] Patients with epilepsy may undergo implantation of subdural monitoring electrodes for the purposes of seizure localization, which at times have been used for neurostimulation to identify eloquent brain regions. Epileptiform discharges that occur during stimulation for localization can be stopped by a train of neighboring brief electrical stimulations.[9]

In tandem with the recognition that cortical stimulation can stop epileptiform discharges was development of fast pre-ictal seizure prediction algorithms. These algorithms interpret electrocorticographic data from detection leads situated over the cortex. The RNS process thus includes electrocorticographic monitoring via cortical electrodes, analysis of data through a proprietary seizure detection algorithm, and delivery of electrical stimulation via both cortical and deep implanted electrodes in an attempt to halt a detected epileptiform discharge.

One device, the NeuroPace RNS System, is currently approved by FDA and is commercially available.

RNS FOR SEIZURE MONITORING

Although the intent of the electrocorticography component of the RNS system is to provide input as a trigger for neurostimulation, it also provides continuous seizure mapping data (chronic unlimited cortical electrocorticography) that may be used by practitioners to evaluate patients' seizures. In particular, the seizure mapping data have been used for surgical planning of patients who do not experience adequate seizure reduction with RNS placement. Several studies have described the use of RNS in evaluating seizure foci for epilepsy surgery[10] or for identifying whether seizure foci are unilateral.[11, 12]

This review does not further address use of RNS exclusively for seizure monitoring.

REGULATORY STATUS

In November 2013, the NeuroPace RNS® System (NeuroPace) was approved by FDA through the premarket approval process for the following indication[13]:

"The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average three or more

disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures."

FDA product code: PFN.

EVIDENCE SUMMARY

RNS FOR TREATMENT OF REFRACTORY FOCAL EPILEPSY

The body of evidence addressing whether RNS is associated with improved health outcomes for patients with focal epilepsy includes an industry-sponsored RCT, which was used for the device's U.S. Food and Drug Administration (FDA) approval, as well as several published follow-up analyses.

Pivotal Trial

RNS for epilepsy was evaluated in the RNS System Pivotal Trial, a multicenter, double-blinded, sham-controlled trial that served as the basis of FDA's approval of the device.[14] Published by Morrell (2011), this RCT included 191 patients with medically intractable focal epilepsy who were implanted with the RNS device and randomized to treatment or sham control after a one-month postimplant period during which time no subjects had the device activated. Eligible patients were adults with focal seizures whose epilepsy had not been controlled with at least two trials of antiepileptic drugs (AEDs), who had at least three disabling seizures (motor focal seizures, complex focal seizures, or secondary generalized seizures) per month on average, and who had standard diagnostic testing that localized one or two epileptogenic foci. Thirty-two percent of those implanted had prior epilepsy surgery, and 34% had a prior vagal nerve stimulator.

Patients were randomized to active stimulation (n=97) or sham stimulation (n=94). After the four-week postoperative period, patients received either sham or active stimulation according to group assignment. There was a four-week stimulation optimization period, followed by a three-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a nonblinded physician. One patient in each group did not complete the stimulus optimization period (one due to subject preference in the active stimulation group; one due to death in the sham stimulation group). An additional patient in each group did not complete the blinded evaluation phase due to emergent explant of the device. After the three-month blinded evaluation period, all patients received active stimulation during an open-label follow-up period. At the time of the Morrell publication, 98 subjects had completed the open-label period and 78 had not. Eleven patients did not complete the open-label follow-up period (five due to death, two to emergent explant, four to study withdrawal).

The trial's primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the treatment group compared with the sham group during the blinded evaluation period relative to baseline (preimplant). The mean preimplant seizure frequency per month in the treatment group was 33.5 (range 3 to 295) and 34.9 (range, 3-338) in the sham group.[13] Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group compared with the sham group (p=0.012). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range 0.0 to 227) and 29.8 (range 0.3 to 447) in the sham group. The treatment group experienced a -37.9% change in seizure frequency (95% confidence

interval [CI] -46.7% to -27.7%), while the sham group experienced a -17.3% change in seizure frequency (95% CI -29.9% to -2.3%).

By the third month of the blinded evaluation period, the treatment group had 27% fewer days with seizures while the sham group experienced 16% fewer days (p=0.048). There were no significant differences between groups over the blinded evaluation period for secondary end points of responder rate (proportion of subjects who experienced a ≥50% reduction in mean disabling seizure frequency vs the preimplant period), change in average frequency of disabling seizures, or change in seizure severity.

During the open-label period, subjects in the sham group demonstrated significant improvements in mean seizure frequency compared with the preimplant period (p=0.04). For all subjects (treatment and sham control), the responder rate at one-year postimplant was 43%. Overall quality of life scores improved for both groups compared with baseline at one year (p=0.001) and two years postimplant (p=0.016).

For the study's primary safety end point, the significant adverse event rate over the first 28 days postimplant was 12%, which did not differ significantly from the prespecified literature-derived comparator of 15% for implantation of intracranial electrodes for seizure localization and epilepsy surgery. During the implant period and the blinded evaluation period, the significant adverse event rate was 18.3%, which did not differ significantly from the prespecified literature-derived comparator of 36% for implantation and treatment with deep brain stimulation for Parkinson disease. The treatment and sham groups did not differ significantly in terms of mild or serious adverse events during the blinded evaluation period. Intracranial hemorrhage occurred in 9 (4.7%) of 191 subjects; implant or incision site infection occurred in 10 (5.2%) of 191 subjects, and the devices were explanted from 4 of these subjects.

Follow-Up Analyses to the Pivotal Trial Subjects

In a follow-up to the RNS System Pivotal Trial, Heck (2014) compared outcomes at one and two years postimplant with baseline for patients in both groups (sham and control) who had the RNS stimulation device implanted during the RNS System Pivotal Trial.[15] Of the 191 subjects implanted, 182 subjects completed follow-up to one year postimplant and 175 subjects completed follow-up to two years postimplant. Six patients withdrew from the trial, four underwent device explantation due to infection, and five died, with one due to sudden unexplained death in epilepsy. During the open-label period, at two years of follow-up, median percent reduction in seizures was 53% compared with the preimplant baseline (p<0.001), and the responder rate was 55%.

Loring (2015) analyzed one of the trial's prespecified safety end points (neuropsychologic function) during the trial's open-label period.[16] Neuropsychological testing focused on language and verbal memory, measured by the Boston Naming Test and the Rey Auditory Verbal Learning Test. One hundred seventy-five subjects had cognitive assessment scores at baseline and at one or two years or both and were included in this analysis. The authors used reliable change indices (RCIs) to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% RCIs used for classification. Overall, no significant group-level declines in any neuropsychological outcomes were detected. On the Boston Naming Test, 23.5% of subjects demonstrated RCI improvements while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated RCI improvements and 1.4% demonstrated declines.

Meador (2015) reported on quality of life and mood outcomes for individuals in the RNS pivotal trial.[17] At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those with follow-up to two years post-enrollment, implanted patients had statistically significant improvements in QOLIE-89 scores from enrollment to one- and two-year follow-up. Mood, as assessed by the Beck Depression Inventory and the Profile of Mood States, did not worsen over time.

Nair (2020) published a long-term prospective open-label study that included patients who participated in the two-year feasibility or pivotal studies of the RNS® System between 2004 and 2018.[18] Patients were followed for an additional seven years. Overall, 230 patients enrolled in the study and 162 completed all nine years of follow-up, providing a total of 1,895 patient-implantation years. Among 68 patients who discontinued the study, four experienced emergent explant, five were lost to follow up, nine were deceased, and 50 withdrew (five transferred care to a non-study center, seven were noncompliant, eight experienced insufficient efficacy, 10 pursued other treatments, and 20 chose not to replace neurostimulator). The mean follow-up period was 7.5 years. At nine years, the median percent reduction in seizure frequency was 75% ($p<0.0001$), 73% of patients were considered responders, and 35% had a ≥90% reduction in seizure frequency. Overall, 18.4% of patients experienced at least one year free of seizures. Overall scores for quality of life and epilepsy-targeted and cognitive domains of the Quality of Life in Epilepsy-89 (QOLIE-89) inventory remained significantly improved at year nine ($p<0.05$). The only device-related serious adverse events that were reported in ≥ 5% of patients were implantation site infection and elective explantation of the neurostimulator, leads, or both. Overall, serious device-related implantation site infection occurred in 12.1% of patients. No serious adverse events occurred related to stimulation.

Section Summary: RNS for Treatment of Refractory Focal Epilepsy

The most direct and rigorous evidence related to the effectiveness of RNS in the treatment of refractory focal seizures is from the RNS System Pivotal Trial, in which patients who had focal epilepsy refractory to at least two medications and received RNS treatment demonstrated a significantly greater reduction in their rates of seizures compared with sham-control patients. Although this single RCT was relatively small (97 patients in the treatment group), it was adequately powered for its primary outcome and all patients were treated with the device during the open-label period (97 in the original treatment group, 94 in the original sham group) and demonstrated a significant improvement in seizure rates compared with baseline. However, there were no differences in the percentage of patients who responded to RNS, and no difference on most of the other secondary outcomes. Follow-up has been reported to five years postimplantation, without major increases in rates of adverse events.

Adverse Events with the RNS System

As a surgical procedure, implantation of the RNS system is associated with the risks that should be balanced against the risks of alternative treatments, including AEDs and other invasive treatments (vagal nerve stimulator and epilepsy surgery), and the risks of uncontrolled epilepsy. During the RNS System Pivotal Trial, rates of serious adverse events were relatively low: 3.7% of patients had implant site infections, 6% had lead revisions or damage, and 2.1% percent had intracranial hemorrhages during initial implantation.[15]

FDA's summary of safety and effectiveness data for the RNS system summarized deaths and adverse events. As reported in the safety and effectiveness data, as of October 24, 2012, there were 11 deaths in the RNS System trials, including the pivotal trial and the ongoing long-term treatment study. Two of the deaths were suicides (one each in the pivotal and LTT studies), one due to lymphoma and another to complications of status epilepticus, and seven were attributed to possible, probable, or definite sudden unexplained death in epilepsy. With 1195 patient implant years, the estimated sudden unexplained death in epilepsy rate is 5.9 per 1000 implant years, which is comparable with the expected rate for patients with refectory epilepsy.[13]

The Long-Term Treatment (LTT) Study was a seven-year, multicenter, prospective, open-label study to evaluate the RNS system's long-term efficacy and safety in individuals who participated in device's feasibility or pivotal trials. Bergey (2015) reported on follow-up for 191 participants in the LTT Study (of a total of 230 originally enrolled in the LTT Study) for a median 5.4 years.[19] Of those who discontinued, three were lost to follow-up, 28 patients withdrew (nine to pursue other treatments, five due to insufficient efficacy, five decided not to replace the RNS system after expected battery depletion, five after infection resolved, three for noncompliance, one for elective explant, one due to ongoing suicidality/noncompliance), four underwent emergent explant, and four died. For follow-up at years three and six, the median percent reductions in seizures were 60% and 66%, respectively. Statistically significant quality of life improved at four years, with a trend toward improvement at five years. The most common adverse events were implant site infection (n=24 [9.4%]) and increase in complex focal seizures (n=20 [7.8%]).

Summary of Evidence

For individuals who have refractory focal epilepsy who receive RNS, the evidence includes an industry-sponsored RCT, which was used for Food and Drug Administration approval of the NeuroPace RNS System, as well as case series. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. The pivotal trial was well-designed and well-conducted; it reported that RNS is associated with improvements in mean seizure frequency in patients with refractory focal epilepsy, with an absolute difference in change in seizure frequency of about 20% between groups, though the percentage of treatment responders with at least a 50% reduction in seizures did not differ from sham control. Overall, the results suggested a modest reduction in seizure frequency in a subset of patients. The number of adverse events reported in the available studies is low, although the data on adverse events were limited because of small study samples. Generally, patients who are candidates for RNS are severely debilitated and have few other treatment options, so the benefits are likely high relative to the risks. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

The American Academy of Neurology has published guidelines on specific treatments for epilepsy, which were reaffirmed in 2019.[20] It has not published any guidelines with recommendations regarding responsive neurostimulation.

SUMMARY

It appears that in patients with refractory focal epilepsy, responsive neurostimulation (RNS) may improve health outcomes, including a reduction in seizure frequency in some patients. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. Therefore, RNS may be considered medically necessary in patients with medication-refractory focal epilepsy when criteria are met.

In certain situations, a responsive neurostimulation device may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, responsive neurostimulator revision(s) or replacement(s) may be considered medically necessary after the device has been placed.

There is not enough research to show that responsive neurostimulation (RNS) improves health outcomes for all other indications not meeting the criteria, including but not limited to patients with focal epilepsy who do not meet the criteria. Therefore, RNS is considered investigational when criteria are not met.

REFERENCES

1. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58(4):522-30. PMID: 28276060
2. Costa J, Fareleira F, Ascencao R, et al. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia.* 2011;52(7):1280-91. PMID: 21729036
3. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England journal of medicine.* 2001;345(5):311-8. PMID: 11484687
4. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet.* 2011;378:1388-95. PMID: 22000136
5. Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. *JAMA Neurol.* 2013;70:1003-8. PMID: 23732844
6. Fridley J, Thomas JG, Navarro JC, et al. Brain stimulation for the treatment of epilepsy. *Neurosurgical focus.* 2012;32(3):E13. PMID: 22380854
7. Fisher RS. Therapeutic devices for epilepsy. *Annals of neurology.* 2012;71(2):157-68. PMID: 22367987
8. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia.* 2004;45:1560-7. PMID: 15571514
9. Anderson WS, Kossoff EH, Bergey GK, et al. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. *Neurosurgical focus.* 2008;25(3):E12. PMID: 18759613
10. DiLorenzo DJ, Mangubat EZ, Rossi MA, et al. Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced

fidelity in seizure focus localization with improved surgical efficacy. *Journal of neurosurgery.* 2014;120(6):1402-14. PMID: 24655096
11. King-Stephens D, Mirro E, Weber PB, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. *Epilepsia.* 2015;56(6):959-67. PMID: 25988840
12. Spencer D, Gwinn R, Salinsky M, et al. Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. *Epilepsy Res.* 2011;93:221-5. PMID: 21256715
13. US Food and Drug Administration. Summary of Safety and Effectiveness Data: RNS System [cited 1/2/2024]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100026b.pdf.
14. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology.* 2011;77:1295-304. PMID: 21917777
15. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia.* 2014;55(3):432-41. PMID: 24621228
16. Loring DW, Kapur R, Meador KJ, et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia.* 2015;56(11):1836-44. PMID: 26385758
17. Meador KJ, Kapur R, Loring DW, et al. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. *Epilepsy & behavior : E&B.* 2015;45:242-7. PMID: 25819949
18. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology.* 2020;95(9):e1244-e56. PMID: 32690786
19. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology.* 2015;84:810-7. PMID: 25616485
20. Morris GL, 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81:1453-9. PMID: 23986299

CODES

Codes	Number	Description
CPT	61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	;each additional array (List separately in addition to primary procedure)
	61880	Revision or removal of intracranial neurostimulator electrodes
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	;with connection to 2 or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver

Codes	Number	Description
	61889	Insertion of skull-mounted cranial neurostimulator pulse generator or receiver, including craniectomy or craniotomy, when performed, with direct or inductive coupling, with connection to depth and/or cortical strip electrode array(s)
	61891	Revision or replacement of skull-mounted cranial neurostimulator pulse generator or receiver with connection to depth and/or cortical strip electrode array(s)
	95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
	95971	;simple spinal cord, or peripheral (ie, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming
HCPCS	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8680	Implantable neurostimulator electrode, each
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

Date of Origin: *September 2019*

Regence

Medical Policy Manual Surgery, Policy No. 217

Leadless Cardiac Pacemakers

Effective: January 1, 2024

Next Review: September 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. Conventional pacemakers consist of two components: a pulse generator and electrodes (or leads). Some patients are medically ineligible for conventional pacemakers due to lack of venous access and recurrent infection. Leadless pacemakers are single-unit devices that are implanted in the heart via femoral access.

MEDICAL POLICY CRITERIA

Notes: See Policy Guidelines for contraindications for leadless pacemaker systems.

I. A single-chamber transcatheter leadless cardiac pacing system may be considered **medically necessary** in patients when all the Criteria (A. – C.) . below are met:

   A. The device is approved by the Food and Drug Administration (FDA).

   B. The patient has one or more of the following:

      1. Symptomatic paroxysmal or permanent high-grade atrioventricular (AV) block; or

      2. Symptomatic bradycardia-tachycardia syndrome; or

3. Sinus node dysfunction (sinus bradycardia or sinus pauses).

C. The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads, including but not limited to a history or high risk of infection, limited venous access, or presence of a bioprosthetic tricuspid valve.

II. A single-chamber transcatheter leadless pacing system is considered **investigational** for all other indications when Criterion I. is not met.

III. The initial insertion or replacement of a dual chamber leadless pacemaker is considered **investigational.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

MICRA™ SYSTEM CONTRAINDICATIONS[1]

Devices

As per the FDA label, the Micra™ Model MC1VR01 pacemaker is contraindicated for patients who have the following types of devices implanted:

- An implanted device that would interfere with the implant of the Micra™ device in the judgment of the implanting physician
- An implanted inferior vena cava filter
- A mechanical tricuspid valve
- An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra™ device

Conditions

As per the FDA label, the Micra™ Model MC1VR01 pacemaker is also contraindicated for patients who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within <12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin or sensitivity to contrast medical which cannot be adequately premedicated

Other Contraindications

As per the FDA label, the Micra™ Model MC1VR01 pacemaker should not be used in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated because the device contains a molded and cured mixture of dexamethasone acetate with the target dosage

of 272 µg dexamethasone acetate. It is intended to deliver the steroid to reduce inflammation and fibrosis.

For the MRI contraindications for patients with a Micra™ MRI device, refer to the Medtronic MRI Technical Manual.

AVEIR™ SYSTEM CONTRAINDICATIONS[2]

Aveir™ DR Leadless System

As per the FDA label, the Aveir™ Leadless Pacemaker System is contraindicated in the following situations:

- Use of any pacemaker is contraindicated in patients with a co-implanted ICD because high-voltage shocks damage the pacemaker, and the pacemaker could reduce shock effectiveness.
- Single-chamber ventricular demand pacing is relatively contraindicated in patients who have demonstrated pacemaker syndrome, have retrograde VA conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing.
- Programming of rate-responsive pacing is contraindicated in patients with intolerance of high sensor-driven rates.
- Use is contraindicated in patients with an implanted vena cava filter or mechanical tricuspid valve because of interference between these devices and the delivery system during implantation.
- Persons with known history of allergies to any of the components of this device may suffer an allergic reaction to this device. Prior to use on the patient, the patient should be counseled on the materials (listed in IFU Product Materials) contained in the device and a thorough history of allergies must be discussed.
- For the MRI contraindications for patients implanted with Aveir™ Leadless Pacemaker, refer to the MRI Procedure Manual.
- There are no contraindications for use of the Aveir™ Link Module.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments
- Name of FDA-approved leadless device
- Documentation that supports contraindication of placement of conventional single-chamber ventricular pacemaker leads

CROSS REFERENCES

1. Implantable Cardioverter Defibrillator, Surgery, Policy No. 17
2. Intracardiac Ischemia Monitoring, Surgery, Policy No. 208

BACKGROUND

CONVENTIONAL PACEMAKERS

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. By providing an appropriate heart rate and heart rate response, cardiac pacemakers can reestablish effective circulation and more normal hemodynamics that are compromised by a slow heart rate. Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and the ventricles.

Transvenous pacemakers or pacemakers with leads (hereinafter referred as conventional pacemakers) consist of two components: a pulse generator (i.e., battery component) and electrodes (i.e., leads). The pulse generator consists of a power supply and electronics that can provide periodic electrical pulses to stimulate the heart. The generator is commonly implanted in the infraclavicular region of the anterior chest wall and placed in a pre-pectoral position; in some cases, a subpectoral position is advantageous. The unit generates an electrical impulse, which is transmitted to the myocardium via the electrodes affixed to the myocardium to sense and pace the heart as needed.

Conventional pacemakers are also referred to as single-chamber or dual-chamber systems. In single-chamber systems, only one lead is placed, typically in the right ventricle. In dual-chamber pacemakers, tow leads are placed: one in the right atrium and the other in the right ventricle. Single-chamber ventricular pacemakers are more common.

As of 2015, approximately 200,000 pacemakers are implanted in the United States and one million worldwide, annually.[3] Implantable pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of bradyarrhythmias. Pacemaker systems have matured over the years with well-established, acceptable performance standards. As per the Food and Drug Administration (FDA), the early performance of conventional pacemaker systems from implantation through 60 to 90 days has usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance (90 days through more than five years) has usually demonstrated the reliability of the pulse generator and lead technology. Chronic performance (5 to 10 years) includes a predictable decline in battery life and mechanical reliability, but a vast majority of patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers comes from registries from Europe, particularly from Denmark where all pacemaker implants are recorded in a national registry. These data are summarized in Table 1. It is important to recognize that valid comparison of complication rates is limited by differences in definitions of complications, which results in a wide variance of outcomes, as well as by the large variance in follow-up times, use of single-chamber or dual-chamber systems, and data reported over more than two decades.[4] As such, the following data are contemporary and limited to single-chamber systems when reported separately.

In many cases when conventional pectoral approach is not possible, alternate approaches such as epicardial pacemaker implantation and trans-iliac approaches have been used[5]. Cohen (2001) reported outcomes from a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations[6]. Congenital heart disease was present in 103 (84%) of the patients. Epicardial leads were followed for 29 months (range 1 to 207 months). Lead failure was defined as the need for replacement or abandonment due to pacing or sensing problems, lead fracture, or phrenic/muscle stimulation. The one-, two-, and five-year lead survival was

96%, 90%, and 74%, respectively. Epicardial lead survival in those placed by a subxiphoid approach was 100% at one year and at 10 years, by the sternotomy approach (93.9% at one year and 75.9% at 10 years) and lateral thoracotomy approach (94.1% at one year and 62.4% at 10 years).

Doll (2008) reported results of a randomized trial comparing epicardial implantation to conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy.[7] The authors reported that the conventional pacemaker group had significantly shorter intensive care unit stay, less blood loss, and shorter ventilation times while the epicardial group had less exposure to radiation and less use of contrast medium. The left ventricular pacing threshold was similar in the two groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the two groups. The following events were experienced by one (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, acute respiratory distress syndrome, and hospital mortality.

As a less invasive alternate to epicardial approach, trans-iliac approach has also been utilized. Data using trans-iliac approach is limited. Multiple other studies with smaller sample size report a wide range of lead longevity.

Harake (2018) reported a retrospective analysis of five patients who underwent a transvenous iliac approach (median age 26.9 years)[8]. Pacing indications included AV block in three patients and sinus node dysfunction in two patients. After a median follow-up of 4.1 years (range 1.0 -16.7 years), outcomes were reported for four patients. One patient underwent device revision for lead position-related groin discomfort; a second patient developed atrial lead failure following a Maze operation and underwent lead replacement by the iliac approach. One patient underwent heart transplantation six months after implant with only partial resolution of pacing-induced cardiomyopathy.

Tsutsumi (2010) reported a case series of four patients from Japan in whom conventional pectoral approach was precluded due to recurrent lead infections (n=1), superior vena cava obstruction following cardiac surgery (n=2) and a postoperative dermal scar (n=1). The mean follow-up was 24 months and authors concluded iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that incidence of atrial lead dislodgement using this approach in the literature ranged from 7% to 21%. Experts who provided clinical input reported that trans-iliac or surgical epicardial approach require special expertise and long term performance is suboptimal.[9]

Table 1. Reported Complication Rates with Conventional Pacemakers

Complications	Rates, %[10-12]a
Traumatic complications	
RV perforation	0.2-0.8
RV perforation with tamponade	0.07-0.4
Pneumo(hemo)thorax	0.7-2.2
Pocket complications	
Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion	4.75
Including only those requiring invasive correction or reoperation	0.66-1.0
Lead-related complications	
Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other	1.6-3.8

Complications	Rates, %[10-12]a
All system related infections requiring reoperation or extraction	0.5-0.7

Adapted from Food and Drug Administration executive summary memorandum (2016).[13]

[a] Rates are for new implants only and ventricular single-chamber devices when data were available. Some rates listed in this column are for single- and dual-chamber devices when data were not separated in the publication. Note that Micra™ transcatheter pacing system is a single-chamber device.

POTENTIAL ADVANTAGES OF LEADLESS CARDIAC PACEMAKERS OVER CONVENTIONAL PACEMAKERS

The potential advantages of leadless pacemakers fall into three categories: avoidance of risks associated with intravascular leads in conventional pacemakers, avoidance of risks associated with pocket creation for placement of conventional pacemakers, and an additional option for patients who require a single-chamber pacer.[14]

Lead complications include lead failure, lead fracture, insulation defect, pneumothorax, infections requiring lead extractions and replacements that can result in a torn subclavian vein or tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (e.g., dialysis, chemotherapy).

Pocket complications include infections, erosions, and pain that can be eliminated with leadless pacemakers. Further, a leadless cardiac pacemaker may be more comfortable and appealing because, unlike conventional pacemakers, patients are unable to see or feel the device or have an implant scar on the chest wall.

Leadless pacemakers may also be a better option than surgical endocardial pacemakers for patients with no vascular access due to renal failure or congenital heart disease.

SINGLE CHAMBER LEADLESS CARDIAC PACEMAKERS IN CLINICAL DEVELOPMENT

Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses a battery and electronics to operate the system. Similar to most pacing leads, the tip of the capsule includes a fixation mechanism and a monolithic controlled-release device. The controlled-release device elutes glucocorticosteroid to reduce acute inflammation at the implantation site. Leadless pacemakers have rate-responsive functionality, and current device longevity estimates are based on bench data. Estimates have suggested that these devices may last over 10 years, depending on the programmed parameters.[13]

Three systems are currently being evaluated in clinical trials: (1) the Micra™ Transcatheter Pacing System (Medtronic), (2) the Aveir™ VR leadless pacemaker (Abbot; formerly Nanostim, St. Jude Medical); and (3) the WiCS Wireless Cardiac Stimulation System (EBR Systems). The first two devices are free-standing capsule-sized devices that are delivered via femoral venous access using a steerable delivery sheath. However, the fixing mechanism differs between the two devices. In the Micra™ Transcatheter Pacing System, the fixation system consists of four self-expanding nitinol tines, which anchor into the myocardium; for the Aveir™ device, there is a screw-in helix that penetrates into the myocardium. In both devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The third device, WiCS system differs from the other devices; this system requires implanting a pulse generator subcutaneously near the heart, which then wirelessly transmits ultrasound energy to a receiver electrode implanted in the left ventricle. The receiver electrode

converts the ultrasound energy and delivers electrical stimulation to the heart sufficient to pace the left ventricle synchronously with the right.[13]

Of these three, only the Micra™ and Aveir™ single-chamber transcatheter pacing systems are approved by FDA and commercially available in the United States. Multiple clinical studies of the Aveir™ predecessor device, the Nanostim, have been published[3, 15-19] but trials have been halted due to the migration of the docking button in the device and premature battery depletion. These issues have since been addressed with the Aveir™ device.[20] Aveir™ has a unique mapping capability to assess correct positioning prior to placement and is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced.[21]

The Micra™ is about 26 mm in length and introduced using a 23 French catheter via the femoral vein to the right ventricle. It weighs about two grams and has an accelerometer-based rate response.[22]

The Aveir™ is about 42 mm in length and introduced using a 25 French catheter to the right ventricle. It also weighs about three grams and uses a temperature-based rate response sensor.[23]

REGULATORY STATUS

Micra™ leadless pacing system (Medtronic)

In April 2016, the Micra™ transcatheter pacing system (Medtronic) was approved by FDA through the premarket approval process for use in patients who have experienced one or more of the following conditions:

- symptomatic paroxysmal or permanent high-grade AV block in the presence of atrial fibrillation
- paroxysmal or permanent high-grade AV block in the absence of atrial fibrillation, as an alternative to dual-chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual-chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.

In January 2020, the Micra AV Transcatheter Pacing System Model MC1AVR1 and Application Software Model SW044 were approved as a PMA supplement (S061) to the Micra system described above. The Micra AV includes an enhanced algorithm to provide AV synchronous pacing.

In November 2021, the U.S. FDA issued a letter to health care providers regarding the risk of major complications related to cardiac perforation during implantation of leadless pacing systems.[24] Specifically, the FDA states that "real-world use suggests that cardiac perforations associated with Micra leadless pacemakers are more likely to be associated with serious complications, such as cardiac tamponade or death, than with traditional pacemakers."

Aveir™ DR Leadless Pacemaker system (Abbott)

In March 2022, the Aveir™ VR Leadless Pacemaker was approved by the U.S. FDA through the premarket approval process for use in patients with bradycardia and:

- normal sinus rhythm with only rare episodes of A-V block or sinus arrest
- chronic atrial fibrillation
- severe physical disability.

Rate-modulated pacing is indicated for patients with chronotropic incompetence, and for those would benefit from increased stimulation rates concurrent with physical activity.

In June 2023, the Aveir™ DR Leadless Pacemaker system was approved by the FDA through the premarket approval process. The device is indicated for management of one or more of the following permanent conditions:

- syncope
- pre-syncope
- fatigue
- disorientation.

The device has multiple pacing functions including rate-modulated pacing, atrial pacing, ventricular pacing and dual chamber pacing. Each function has specific indications:

Rate-Modulated Pacing is indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity.

Atrial Pacing is indicated for patients with:

- Sinus node dysfunction and normal AV and intraventricular conduction systems

Ventricular Pacing is indicated for patients with:

- Significant bradycardia and normal sinus rhythm with only rare episodes of AV block or sinus arrest
- Chronic atrial fibrillation
- Severe physical disability

Dual-Chamber Pacing is indicated for patients exhibiting:

- Sick sinus syndrome
- Chronic, symptomatic second- and third-degree AV block
- Recurrent Adams-Stokes syndrome
- Symptomatic bilateral bundle branch block when tachyarrhythmia and other causes have been ruled out.

MR Conditional: The Aveir Leadless Pacemaker is conditionally safe for use in the MRI environment and according to the instructions in the MRI-Ready Leadless System Manual.

EVIDENCE SUMMARY

Conventional pacemaker systems have been in use for over 50 years and current technology has matured with significant similarities in designs across models. Extensive bench testing

data with conventional pacemakers and a good understanding of operative and early postimplant safety and effectiveness are available, which limits the need for clinical data collection to understand their safety and effectiveness with regard to implantation, tip fixation, electrical measures, and rate response. As such, a randomized controlled trial comparing the leadless pacemakers with conventional pacemakers was not required by the Food and Drug Administration (FDA).

VENTRICULAR PACING FOR INDIVIDUALS WHO ARE MEDICALLY ELIGIBLE FOR A CONVENTIONAL PACING SYSTEM

Micra™ Leadless Pacemaker

Pivotal Trial

The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolled 744 patients with a class I or II indications for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design[25], and results of the IDE trial have been published.[26-28] Trial characteristics and results at six months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published,[29] but results are not discussed further.

Of the 744 patients enrolled, implantation of the Micra™ transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U. S., with 42% being female and the average age was 76 years. Sixty-four percent had a pacing indication associated with persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n =199) without atrial fibrillation, 16.1% (n =32) had a primary indication of sinus bradycardia and 3.5% (n =7) had a primary indication of tachycardia-bradycardia.[28]

The IDE trial had two primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra™ transcatheter pacing system or implantation procedure exceeded 83% at six months. Major complications were defined as those resulting in any of the following; death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant).[1] The trial would meet its efficacy endpoint if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at six months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is influenced by physiologic and pharmacologic factors.[1] As per the FDA, demonstrating that “PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra™ system will have longevity similar to current pacing systems since Micra’s capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT.”[1]

Safety and efficacy results of the IDE trial are summarized in Table 3. At six months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI 96.1% to 99.5%), compared with a performance goal of 80%.[28]

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively.[27] The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD] 9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD 12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD 9.4, $p< 0.001$) and a mean Mental Component Scale score of 50.7 (SD 12.2, $p< 0.001$) compared with baseline.

IDE trial results were compared post hoc with a historical cohort of 2,667 patients generated from six previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at six months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra™ device was associated with fewer complications than the historical control (4.0% vs 7.4%, hazard ratio [HR], 0.49, 95% CI 0.33 to 0.75, p=0.001).[28] Because there were differences in baseline patient characteristics between the two cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR 0.46, 95% CI 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra™ device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing issues), and fixation events (there was no device or lead dislodgements in the Micra™ IDE trial).[13]

While the overall rate of complications was low, the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) was higher in the Micra™ IDE trial than in the six reference Medtronic pacemaker studies (1.6% vs. 1.1%, p=0.288).[13] Thus, there appears to be a trade-off between types of adverse events with the Micra™ transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra™ device, certain adverse events (e.g., groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (e.g., acute cardiac perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.[13]

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions.[30] There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra™ device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have only been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans,

it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely.[30] Current recommendations for end-of-device-life care for a Micra™ device may include the addition of a replacement device with or without explantation of the Micra™ device, which should be turned off.[31]

Grubman (2017) reported on system revisions including patients from the IDE study (n=720) and the Micra Transcatheter Pacing System Continued Access Study (n=269).[32] The Continued Access study was conducted to allow for continued access of the Micra™ in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and two months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI 0.7% to 2.6%) actuarial rate of revisions through 24 months. Micra™ was disabled and left in situ in 7 of 11 revisions including five patients in which there was no retrieval attempt, one patient in which retrieval was aborted because of fluoroscopy failure, and one patient in which retrieval was unsuccessful because of inability to dislodge the device. There were three percutaneous retrievals and one retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that there when a transvenous system was implanted with a deactivated Micra™, there were no reported interactions between the two systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actuarial rate 5.3%, 95% CI 4.4% to 6.4%). Using propensity score matching, the reduction in system revisions for Micra™ compared to historical controls was significant (HR 0.27, 95% CI 0.14 to 0.54, p<0.001).

Micra™ Post-approval Experience

Three year outcomes from the Micra Coverage with Evidence Development study were published by Crossley (2023).[33] Patients implanted with leadless pacemakers had a 32% lower rate of chronic complications (HR, 0.68; 95% CI, 0.59 to 0.78; p<.001) and a 41% lower rate of any reinterventions compared to patients receiving a transvenous pacemaker (HR, 0.59; 95% CI, 0.44 to 0.78; p=.0002). Use of a leadless system was also associated with a 49% lower rate (p=.01) of upgrades to a dual-chamber system and a 35% lower rate (p=.002) of upgrades to cardiac resynchronization therapy. Heart failure hospitalizations at three years were slightly, but significantly lower in adjusted time-to-event models (HR, 0.90; 95% CI, 0.83 to 0.97; p=.005) in patients receiving a leadless system. All-cause mortality rates at three years between leadless and transvenous systems were not significantly different after accounting for differences in baseline characteristics (HR, 0.97; 95% CI, 0.92 to 1.03; p=.32). No significant differences in the composite endpoint of time to heart failure hospitalization or death were observed for the original full cohort (p = 0.28) or in a subgroup of patients without a history of heart failure (p = 0.98).

Boveda (2023) published a study comparing clinical outcomes between leadless pacemakers (leadless-VVI) and transvenous ventricular pacemakers (transvenous ventricular permanent-VVI) in subgroups of patients at higher risk of pacemaker complications. [34] This study is based on the Micra Coverage with Evidence Development (CED) study. Patients from the Micra CED study were considered in a high-risk subgroup if they had a diagnosis of chronic kidney disease Stages 4-5 (CKD45), end-stage renal disease, malignancy, diabetes, tricuspid valve disease (TVD), or chronic obstructive pulmonary disease (COPD) 12 months prior to pacemaker implant. A pre-specified set of complications and reinterventions were identified using diagnosis and procedure codes. Competing risks models were used to compare

reinterventions and complications between leadless-VVI and transvenous-VVI patients within each subgroup; results were adjusted for multiple comparisons. A post hoc comparison of a composite outcome of reinterventions and device complications was conducted. Out of 27 991 patients, 9858 leadless-VVI and 12 157 transvenous-VVI patients have at least one high-risk comorbidity. Compared to transvenous-VVI patients, leadless-VVI patients in four subgroups [malignancy, HR 0.68 (0.48-0.95); diabetes, HR 0.69 (0.53-0.89); TVD, HR 0.60 (0.44-0.82); COPD, HR 0.73 (0.55-0.98)] had fewer complications, in three subgroups [diabetes, HR 0.58 (0.37-0.89); TVD, HR 0.46 (0.28-0.76); COPD, HR 0.51 (0.29-0.90)) had fewer reinterventions, and in four subgroups (malignancy, HR 0.52 (0.32-0.83); diabetes, HR 0.52 (0.35-0.77); TVD, HR 0.44 (0.28-0.70); COPD, HR 0.55 (0.34-0.89)] had lower rates of the combined outcome. ClinicalTrials.gov ID NCT03039712.

The FDA approval of the Micra™ transcatheter pacing system was contingent on multiple post-approval studies to provide reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multicenter study, enrolled 1,830 patients to collect data on 1,741 patients to estimate the acute complication rate within 30 days of the implant, 500 patients to estimate the nine-year complication-free survival rate, and a minimum of 200 patients with a Micra™ device revision for characterizing device end of service.[1] As per the protocol, if a subsequent device is placed and the Micra™ is deactivated or explanted, Medtronic would contact the implanting center and request the patient's clinical data concerning the revision. All such data would be summarized, including the type of system revision, how the extraction was attempted, success rate, and any associated complications.[30]

Study characteristics and results at one year (reported in the FDA documents and published) are summarized in Table 2 and 3, respectively. The post-approval study completed enrollment in early March 2018. The definition of a major complication in the post-approval study was the same as the Micra IDE trial. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore includes an independent population. Results summarized in Table 3 summarize the data at 30 days published by Roberts (2017)[35] and El-Chami (2018),[36, 37] with a mean follow-up of 6.8 months for 1,817 patients, of whom 465 patients had a follow-up for more than one year.

At 30 days, the major complication rate was 1.51% (95% CI 0.78 to 2.62%). The major complication rate was lower in the post-approval study than in the IDE trial (odds ratio, 0.58, 95% CI 0.27 to 1.25) although this did not reach statistical difference. The lower rate of major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the post-approval study compared with the IDE trial.[35] A subsequent subgroup analysis of patients who did not receive perioperative anticoagulation treatment, who received interrupted anticoagulation treatment, or who received continuous anticoagulation treatment did not find a significant difference in rates of acute major complications according to anticoagulation strategy (3.1%, 2.6%, and 1.5%, respectively, p=0.29). The most common major complication was pacing problems, including elevated threshold and device capturing issues.[38] A subgroup analysis of patients treated with and without atrioventricular node ablation (AVNA) at the time of Micra™ implantation identified a significantly higher risk of major complications at both 30 days (7.3% versus 2.0%, p<0.001) and 36 months (HR 3.81, 95% CI 2.33 to 6.23, p<0.001) in the AVNA group versus those without AVNA.[39]

After a mean follow-up of 6.8 months, the estimated major complication rate at 12 months was 2.7% (95% CI 2.0% to 3.7%), corresponding to 46 major complications in 41 patients, the majority of which (89%) occurred within 30 days of implantation. The major complications included 14 device pacing issue events, 11 events at the groin puncture site, eight cardiac effusion/perforation events, three infections, one cardiac failure event, one cardiomyopathy event, and one pacemaker syndrome event. Authors compared these results with the same historical cohort of 2,667 patients used in the IDE trial and reported a 63% reduction in the risk for major complications through 12 months with the Micra™ transcatheter pacing system relative to conventional pacemakers (HR 0.37, 95% CI 0.27 to 0.52). Additionally, the risk for major complications was lower in the Micra™ post-approval study than in the IDE trial but it was a statistically significant difference (HR 0.71, 95% CI 0.44 to 1.1).[36] The reduction in major complications compared to historical controls was primarily driven by a significant 74% (95% CI 54 to 85, p=0.0001) relative risk reduction in system revisions and 71% (95% CI 51 to 83, p=0.0001) relative risk reduction in hospitalizations. The reduction in risk compared to the IDE trial was driven by significantly lower pericardial effusion rates in the post-approval study.

Piccini (2021) published initial data from the ongoing Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED).[40] Patients implanted between March 2017 and December 2018 were identified and included from a fee-for-service population with at least 12 continuous months of Medicare enrollment prior to device implantation. A total of 5,746 patients with single-chamber leadless Micra™ pacemakers and 9,662 patients with transvenous pacemakers were analyzed. Patients with a Micra™ pacemaker were more likely to have end-stage kidney disease (p<0.001) and a higher mean Charlson Comorbidity Index score (5.1 versus 4.6, p<0.001). The unadjusted acute 30-day complication rate was higher in the Micra™ subgroup (8.4% versus 7.3%, p=0.02), but no significant difference was found following adjustment for patient characteristics (p=0.49). Pericardial effusion and/or perforation within 30 days of implantation was significantly higher in the Micra™ population in the adjusted model (0.8% versus 0.4%, p=0.004). Patients with Micra™ pacemakers had a 23% lower risk of complications at six months compared to patients receiving a transvenous pacemaker (HR 0.77, 95% CI 0.62 to 0.96, p=0.02) and a 37% reduction in rates of device revision after adjustment for patient baseline characteristics. The 30-day all-cause mortality rate was not significantly different between groups in both unadjusted (p=0.14) and adjusted analyses (p=0.61). The study is ongoing with an estimated study completion date of June 2025. Study characteristics and results are summarized in Tables 2 and 3.

El-Chami (2022) subsequently compared reinterventions, chronic complications, and all-cause mortality at two years in patients implanted with the Micra™ leadless pacemaker or a transvenous pacemaker in the Micra™ Coverage with Evidence Development study.[41] Patients implanted with leadless (n=6,219) or transvenous pacemakers (n=10,212) were identified from Medicare claims data and compared contemporaneously. Patients receiving leadless pacemakers had higher rates of end-stage renal disease (12.0% versus 2.3%) and a higher Charlson comorbidity index (5.1 versus 4.6). Patients with leadless pacemakers received 37% fewer reinterventions (adjusted HR 0.62, 95% CI 0.45 to 0.85, p =0.003), defined as system revision lead revision or replacement, system replacement, system removal, or system switch or upgrade to an alternative device. Patients implanted with leadless pacemakers also experienced fewer chronic complications (2.4% versus 4.8%, adjusted HR 0.69, 95% CI 0.60 to 0.81, p<0.0001). However, patients receiving leadless pacemakers experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% versus 0.8%, p<0.0001). Adjusted all-cause mortality at two years was not

significantly different between groups (adjusted HR 0.97, 95% CI 0.91 to 1.04, p=0.37) despite the higher comorbidity index in patients implanted with a Micra™ device. Study interpretation is limited by reliance on claims data. It is unclear whether all patients receiving leadless devices were considered medically eligible for transvenous devices. Study characteristics and results are summarized in Tables 2 and 3.

Hauser (2021) analyzed the Food and Drug Administration's Manufacturers and User Facility Device Experience (MAUDE) database to capture major adverse clinical events (MACE) associated with the Micra™ device compared to the Medtronic CapSureFix transvenous pacing system.[42] In a search of reports from 2016 through 2020, 363 MACE and 960 MACE were identified for the Micra™ and CapSureFix devices, respectively. For the Micra™ device, significantly higher rates of death (26.4% versus 2.4%, p<0.001)), cardiac tamponade (79.1% versus 23.4%; p<.001), and rescue thoracotomy (27.3% versus 5.2%; p<.001) were reported. Micra™ patients were more likely to require cardiopulmonary resuscitation (21.8% versus 1.1%) and to suffer hypotension or shock (22.0% versus 5.8%) compared to CapSureFix recipients (p<0.001). While the overall incidence of myocardial and vascular perforations and tears that may result in cardiac tamponade and death in Micra™ recipients is estimated to be low (<1%), the authors note that Micra™ patients were more likely to survive these events if they received surgical repair (p=0.014). In a subsequent analysis of the MAUDE database focused on rates of Micra™ perforations from 2016 to 2021, Hauser (2022) identified 563 perforations reported within 30 days of implant, resulting in 150 deaths (27%), 499 cardiac tamponades (89%), and 64 pericardial effusions (11%).[43] Emergency surgery was required in 146 patients (26%). Half all perforations were associated with 139 device problems (25%), 78 operator use problems (14%), and 62 combined device and operator use problems (11%). The most common device problem leading to redeployment were non-capture or inadequate electrical values that required implantable pulse generator recapture and reimplantation or replacement. No device or operator use problems were identified for the remaining 282 perforations (50%), but these were associated with 78 deaths, 245 tamponades, and 57 emergency surgeries. The authors concluded that Micra™ implantation should be confined to specialized centers capable of managing emergency complications and that a risk score for perforation should be developed and validated. Importantly, these analyses are limited by the passive nature of the FDA's post-market device surveillance system, which may not capture all voluntary reports from health care professionals, consumers, and patients. Such analyses carry a high risk of ascertainment bias which may lead to overestimation of the true prevalence of adverse events.

Three year outcomes from the Micra Coverage with Evidence Development study were published by Crossley (2023).[44] Patients implanted with leadless pacemakers had a 32% lower rate of chronic complications (HR, 0.68; 95% CI, 0.59 to 0.78; p<.001) and a 41% lower rate of any reinterventions compared to patients receiving a transvenous pacemaker (HR, 0.59; 95% CI, 0.44 to 0.78; p=.0002). Use of a leadless system was also associated with a 49% lower rate (p=.01) of upgrades to a dual-chamber system and a 35% lower rate (p=.002) of upgrades to cardiac resynchronization therapy. Heart failure hospitalizations at 3 years were slightly, but significantly lower in adjusted time-to-event models (HR, 0.90; 95% CI, 0.83 to 0.97; p=.005) in patients receiving a leadless system. All-cause mortality rates at 3 years between leadless and transvenous systems were not significantly different after accounting for differences in baseline characteristics (HR, 0.97; 95% CI, 0.92 to 1.03; p=.32). No significant differences in the composite endpoint of time to heart failure hospitalization or death were observed for the original full cohort (p=.28) or in a subgroup of patients without a history of

Aveir™ Leadless Pacemaker

Pivotal Trial

The pivotal investigational device exemption (IDE) trial of the Aveir™ leadless pacemaker (LEADLESS II - Phase 2) was a multicenter, prospective single cohort study enrolling 200 patients with a guidelines-based indication for single-chamber pacing.[23] Primary results from the IDE trial have been summarized in a published research correspondence[20] and FDA documents.[23] Trial characteristics and results through six months are summarized in Tables 2 and 3, respectively.

Implantation of the Aveir™ leadless pacing system was successful in 196/200 (98%) trial subjects (mean age 75.6 years, 37.5% female). The primary indication for pacing was chronic atrial fibrillation with 2nd or 3rd degree atrioventricular block (52.5%). The trial had two primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 97.5% CI for the complication-free rate exceeded 86% at six weeks. A complication was defined as a device-or-procedure-related serious adverse event, including those that prevented initial implantation. The trial would meet its efficacy endpoint if the lower bound of the 97.5% CI for the composite success rate exceeded 85% at six weeks. The confirmatory effectiveness endpoint was considered met if the pacing threshold voltage is ≤ 2.0 V at 0.4 ms and the sensed R-wave amplitude is either ≥ 5.0 mV at the six-week visit or ≥ the value at implant.

Safety and efficacy results of the Aveir™ IDE trial are summarized in Table 3. At six weeks, the trial met both of its confirmatory safety and efficacy endpoints, including freedom from device-or-procedure-related complications in 96% of patients (95% CI 92.2% to 98.2%), compared with a performance goal of 86%, and a composite success rate of 95.9% of patients (95% CI 92.1% to 98.2%), compared with a performance goal of 85%. The six-month complication-free rate was 94.9% (95% CI 90.0% to 97.4%). The most frequent complications included three cardiac tamponade events and three premature deployment events. The rate of cardiac perforation/tamponade/pericardial effusion was 1.5%. No dislodgement events were reported in the Aveir™ cohort.

Confirmatory secondary endpoints included assessment of an appropriate and proportional rate-response during a Chronotropic Assessment Exercise Protocol (CAEP) exercise protocol and an estimated two-year survival rate. The CAEP assessment was initiated in 23 subjects, of which 17 were considered analyzable. The rate-response slope was 0.93 (95%CI 0.78 to 1.08), which fell within the prespecified range of 65% to 135%. The estimated two-year survival rate based on the Nanostim Phase 1 cohort (n=917) was 85.3% (95% CI 82.7% to 87.4%), which exceeded the performance goal of 80%.[44]

Table 2. Summary of Key Nonrandomized Trial Characteristics

Study; Trial	Study; Type	Country	Dates	1. Participants	Treatment	Follow-Up, mo
Micra						
Reynolds (2016)[28] NCT02004873	Prospective single cohort	19 countries in North America, Europe,	2013-2015	Patients who met a class I or II guidelines-based indication for pacing and suitable	Micra™ pacemaker (n=744)	6

Study; Trial	Study; Type	Country	Dates	1. Participants	Treatment	Follow-Up, mo
		Asia, Australia, and Africa		candidates for single-chamber ventricular demand pacing		
Roberts (2017)[35] El-Chami (2018)[36, 37]	Prospective single cohort (Micra Post-Approval Study)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra™ device	Micra™ pacemaker (n=795[a] and 1830[b])	1.8[a] 6.8[b]
Piccini (2021)[40]	Prospective single cohort with contemporaneous control group (Micra CED study)	United States	2017-2018	Medicare beneficiaries implanted with a Micra™ device or transvenous device	Micra™ pacemaker (n=5,746) Transvenous pacemaker (n=9,662)	6
El-Chami (2022)[41]	Prospective Medicare registry	United States	2017-2018	Medicare beneficiaries implanted with a Micra™ device or transvenous device	Micra™ pacemaker (n=6,219) Transvenous pacemaker (n=10,212)	24
Aveir						
FDA SSED (2022), PMA P150035[23]	Prospective single cohort	43 sites in the United States, Canada, and Europe	2020-2021	Patients with a guidelines-based indication for single-chamber pacing	Aveir™ pacemaker (n=200)	6

[a] 30-day results reported by Roberts (2017).[35]

[b] Results after a mean follow-up of 6.8 months reported by El-Chami (2018)[36, 37]

Table 3. Summary of Key Nonrandomized Trial Results

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Micra IDE Trial				
	6 Months	**6 Months**	**6 Months**	**6 Months**
Reynolds (2016)[28]				
N	719[a];300[b]	719	725	725
Micra™	96.0%	98.3% (≤2.0 V)	Death: 1 (0.1)	TMCs: 28 in 25 patients (3.5%) • DVT: 1 (0.1)

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
			Loss of device function: 1 (0.1) Hospitalization: 13 (2.3) Prolonged hospitalization (≥48 h): 16 (2.6) System revision: 3 (0.4)	• Pulmonary TE: 1 (0.1) • Events at groin puncture site: 5 (0.7) • Cardiac perforation: 11 (1.6) • Pacing issues: 2 (0.3) • Others: 8 (1.7)
95% CI	93.9% to 97.3%	95.4% to 99.6%	NA	NA
	12 Months	**12 Months**	**12 Months**	**12 Months**
Duray (2017)[45]				
N	726	NA	726	726
Micra	96.0%	NR (93%)	Death: NR (0.1) Loss of device function: NR (0.1) Hospitalization: NR (2.3) Prolonged hospitalization (≥48 h): NR (2.2) System revision[c]: NR (0.7) Loss of device function: NR (0.3)	TMCs: 32 in 29 patients (4.0) • DVT: 1 (0.1) • Pulmonary TE: 1 (0.1) • Events at groin puncture site: 5 (0.7) • Cardiac perforation: 11 (1.6) • Pacing issues: 2 (0.3) • Others: 11 (1.7)
95% CI	94.2% to 97.2%	NA		
Micra Post-Approval Study				
	30 Days	**30 Days**	**30 Days**	**30 Days**
Roberts (2017)[35]				
N	795	NA	795	795

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Micra™	97.3%[d]	87.2% (≤1.0 V) 97.0% (≤2.0 V)	Death: 1 (0.13%) Hospitalization: 4 (0.50) Prolonged hospitalization (≥48 h): 9 (1.01) System revision[c]: 2 (0.25)	TMCs: 13 in 12 patients (1.51% [95% CI 0.78% to 2.62%]) • DVT: 1 (0.13) • Events at groin puncture site: 6 (0.75) • Cardiac effusion/perforation: 1 (0.13) • Device dislodgement: 1 (0.13) • Pacing issues: 1 (0.13) • Others: 3 (0.38)
OR (95% CI)	0.58 (0.27 to 1.25)[e]	NA	NA	NA
	1 Year	**1 Year**	**1 Year**	**1 Year**
El-Chami (2018)[36, 37]				
N	1,817	NA	NA	1,817
Micra™	97.3%[d]	NA	NA	TMCs: 46 in 41 patients (2.7% [95% CI 2.0% to 3.6%]) • Pericardial effusions: 8 (0.44) • Dislodgement: 1 (0.06) • Procedure-related infections: 3 (0.17) • Procedure-related deaths: 5 (0.28) As per FDA: Complications[f]: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication)
HR (95% CI)	0.71 (0.44 to 1.1)[e] 0.37 (0.27 to 0.52)[g]	NA	NA	NA
Micra CED				
	30 Days and 6 Months	**N/A**	**N/A**	**30 Days and 6 Months**

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Piccini (2021)[40]				
N	5,746	N/A	N/A	5,746
Micra™ complication rate, RR or HR (95% CI)	30-d unadjusted: NR 30-d adjusted: 0.3 (-0.6 to 1.3) 6-mo unadjusted: 0.84 (0.68 to 1.03) 6-mo adjusted: 0.77 (0.62-0.96)	NA	N/A	Acute (30 days), n (%) • Overall: 484 (8.4) • Embolism and thrombosis: 145 (2.5) • PE: 202 (3.5) • Events at puncture site: 78 (1.4) • Cardiac effusion/perforation: 47 (0.8) • Device-related: 81 (1.4) • Other: 136 (2.4) 6-months CIF estimates, % (95% CI) • Overall: 3.2 (2.9 to 3.6) • Embolism and thrombosis: <10 events • Device-related: 1.7 (1.5 to 1.9) • Other: 1.6 (1.3 to 1.8)
	24 months[h]	**N/A**	**N/A**	**24 months**[i]
El-Chami (2022)[41]				
N	6,219 (Micra™) 10,212 (transvenous)	N/A	N/A	6,219 (Micra™) 10,212 (transvenous)
Micra™	Adjusted: 3.1%	NA	N/A	Chronic complications CIF Estimates, % (95% CI) • Overall: 4.6 (4.2 to 4.9) • Embolism and thrombosis: ≤10 events • Device-related: 2.4 (2.2 to 2.5) • Other: 2.1 (2.0 to 2.3)

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Transvenous	Adjusted: 4.9%	NA	N/A	Chronic complications CIF Estimates, % (95% CI) • Overall: 6.5 (6.1 to 6.9) • Embolism and thrombosis: 0.2 (0.2 to 0.2) • Device-related: 4.8 (4.7 to 5.0) • Other: 1.4 (1.3 to 1.6)
RR or HR (95% CI)	Adjusted: 0.62 (0.45 to 0.85)	NA	N/A	Relative risk reduction (95% CI) • Overall: 31 (19 to 40) • Embolism and thrombosis: 46 (-17 to 75) • Device-related: 52 (42 to 60) • Other: -48 (-91 to -15)
Aveir IDE Trial				
	6 weeks **6 months**	**6 weeks** **6 months**	**N/A**	**6 weeks** **6 months**
FDA SSED (2022); PMA P15003[23]				
N	200	200		200
Aveir™	0.960 (0.922 to 0.982) 0.933 (0.898 to 0.956)	0.959 (0.921 to 0.982) 0.934 (0.899 to 0.960)	N/A	SADEs: 9 in 8 patients • Cardiac perforation/tamponade: 3 • Premature deployment with migration: 2 • Premature deployment without migration: 1 • Vascular access site bleeding: 1 • Embolism and thrombosis: 1

CED: coverage with evidence development; CI: confidence interval; CIF: cumulative incidence function; DVT: deep vein thrombosis; FDA: Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; NA; not available; NR: not reported; OR: odds ratio; PE: pulmonary embolism; PME: premarket approval; RR: relative risk; SADE: serious adverse device effects; TE: thromboembolism; TMC: Total major complication.

[a] Total number of patients who received the implant successfully.

[b] Number of patients for whom data were available for six-month evaluation.

[c] Device explant, reposition, or replacement.

[d] Calculations based on the major complication rate (2.7%, 95% CI 2.0 to 3.6%) reported by El-Chami (2018).

[e] Major complication vs IDE trial.

[f] Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.
[g] Major complication vs historical controls.
[h] Device reintervention rate
[i] Chronic complications

Aveir™ Postapproval Experience

Continued FDA approval of the Aveir™ pacing system is contingent on the results of the Aveir VR Real-World Evidence Study.[46] This post-approval study is designed to evaluate the long-term safety of the Aveir™ device in a real-world sample of 2,100 participants. Both acute and long-term safety will be evaluated as post implant complication-free rates at 30-days and 10-years. Ten-year reports are due in March 2032.

Reddy (2023) published the 1-year outcomes from the LEADLESS II IDE trial. [44] Safety and efficacy endpoints at one year were reported. Freedom from device-or-procedure-related complications was reported in 93.2% of patients (95% CI, 88.7% to 95.9%), compared with a performance goal of 83%, and a composite success rate of 95.1% (95% CI, 91.2% to 97.6%), compared with a performance goal of 80%. Most complications (11 of 15) were reported within the first three days post-implantation (four cardiac tamponade events, three premature deployments with or without device migration, two access site bleeding events, one pulmonary embolism, and one case of deep vein thrombosis. Four long-term complications were reported between 3.8 and 9.5 months post-implantation (two cases of heart failure and two cases of pacemaker-induced cardiomyopathy. The investigators estimated the mean device battery longevity is 17.6 ± 6.6 years (95% CI, 16.6 to 18.6).

Garg (2023) published evaluated the safety profile and assessed the complications of the Aveir™ leadless pacing system.[47] A MAUDE database search was conducted for reports received post-FDA approval to capture all adverse events. A total of 64 entries were included. The most commonly encountered problem was high threshold/noncapture (28.1%, 18 events), followed by stretched helix (17.2%, 11 events) and device dislodgement (15.6%, ten events-5 intraprocedural, while five in the postoperative Day 1). Other reported events included high impedance (14.1%, nine events), sensing issues (12.5%, eight events), bent/broken helix (7.8%, five events), premature separation (4.7%, three events), interrogation problem (3.1%, two events), low impedance (3.1%, two events), premature battery depletion (1.6%, one event) and inadvertent MRI mode switch (1.6%, one event) and miscellaneous (15.6%, n = 10). There were eight serious patient injury events-pericardial effusion requiring pericardiocentesis (7.8%, five events) due to cardiac perforation that resulted in two deaths (3.1%) followed by sustained ventricular arrhythmias (4.6%, n = 3).

Tokavanich (2023) published a retrospective case study review comparing the implant efficiency and clinical performance of the Aveir™ VR Leadless Pacemaker (LP) compared to the Micra™ VR LP.[48] A total of 67 patients were included in the study. The Micra™ VR group had shorter time in the electrophysiology lab (41 ± 12 vs. 55 ± 11.5 min, $p = 0.008$) and shorter fluoroscopic time (6.5 ± 2.2 vs. 11.5 ± 4.5 min, $p < 0.001$) compared to the Aveir™ VR group. The Aveir™ VR group had a significantly higher implant pacing threshold compared to the Micra™ VR group (0.74 ± 0.34 mA vs. 0.5 ± 0.18 mA at pulse width 0.4 ms, $p < 0.001$), but no difference was found at three and six months. There was no significant difference in the R-wave sensing and impedance and pacing percentage at implantation, three and six months. Complications of the procedure were rare. The mean projected longevity of the Aveir™ VR group was longer than the Micra™ VR group (18.8 ± 4.3 vs. 7.7 ± 0.75 years, $p < 0.001$). The authors conclude that Implantation of the Aveir™ VR required longer laboratory and

fluoroscopic time, but showed longer longevity at six months follow-up, compare to the Micra™ VR. Limitations include retrospective study design at a single site, small sample size and lack of long-term data.

Shantha (2023) published a retrospective case study review to compare effectiveness and safety between the Aveir-VR and Micra-VR.[49] The first patients (n= 25) to undergo Aveir-VR implant at our institution between June and November 2022, were compared to 25 age- and sex-matched patients who received MICRA-VR implants. In both groups, mean age was 73 years and 48% were women. Leadless pacemaker implant was successful in 100% of patients in both groups. Single attempt deployment was achieved in 80% of AVEIR-VR and 60% of Micra-VR recipients ($p = 0.07$). Fluoroscopy, implant, and procedure times were numerically longer in the Aveir-VR group ($p > 0.05$). No significant periprocedural complications were noted in both groups. Incidence of ventricular arrhythmias were higher in the Aveir-VR group (20%) compared to the Micra-VR group (0%) ($p = 0.043$). At two and eight weeks follow-up, device parameters remained stable in both groups with no device dislodgements. The estimated battery life at 8 weeks was significantly longer in the Aveir-VR group (15 years) compared to the Micra-VR group (8 years) ($p = 0.047$). The authors reported that it took three to four Aveir-VR implants for the learning curve for successful implantation to reach steady state.The authors conclude that the initial experience with Aveir-VR show that it has comparable effectiveness and safety to Micra-VR. Limitations include retrospective study design at a single site, small sample size and lack of long-term data.

The current evidence on the use of the Aveir™ device remains limited by a lack of adequate data on quality of life, long-term safety, effectiveness, reliability, and incidence of late device failures. The Aveir™ pivotal prospective cohort study primary safety and efficacy outcomes at six weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at six months were similar and at one year were 93.2% and 91.5%, respectively. Incidence of major complications at one year was 6.7% compared to 4.0% in the Micra pivotal trial. The two-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical experience with issues related to devices that have reached end-of-life. Two small retrospective case study reports comparing the Aveir device with the Micra device. Both reported fluoroscopy, implant, and procedure times were longer for the Aveir device. Other outcomes were similar. Through six months follow-up , device parameters remained stable in both groups with no device dislodgements. Long term survival data for the currently marketed version of the Aveir™ device has not been reported.

Section Summary: Ventricular Pacing for Individuals Who Are Medically Eligible for a Conventional Pacing System

The evidence for use of the Micra™ transcatheter pacing system consists of a pivotal prospective cohort study, a post-approval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Results at six months and one year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% patients). Most of the system- or procedural-related complications occurred within 30 days. At one year, the incidence of major complications did not increase substantially from six months (3.5% at six months vs 4% at one year). Results of the post-approval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days post-implantation and one year (1.5% and 2.7%, respectively). In both studies, the point

estimates of major complications were lower than the pooled estimates from six studies of conventional pacemakers used as a historical comparator. Results of the CMS study indicated that acute complication rates were similar for the Micra™ and transvenous pacemakers, after adjustment for baseline and encounter differences, and there was a slightly lower six-month complication rate for the leadless system. While the Micra™ transcatheter pacing system eliminates adverse events associated with lead and pocket issue, its use results in additional complications related to the femoral access site (groin hematomas, access site bleeding) and implantation and release of the device (traumatic cardiac injury). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra™ pacemaker compared to patients who received a transvenous device; overall six-month complications rates were significantly lower in the Micra™ group in the adjusted analysis (p=0.02). In a real-world study of Medicare patients, 41% lower rate of reinterventions and a 32% lower rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 3 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra device experienced significantly more other complications, driven by higher rates of pericarditis. No significant differences were noted in the composite endpoint of time to heart failure hospitalization or death for the full cohort (p=.28) or the subgroup without a history of heart failure (p=.98) It is also unclear whether all patients were considered medically eligible for a conventional pacing system. A 2021 analysis of the FDA Manufacturer's and User Facility Device Experience (MAUDE) database revealed significantly higher rates of death, cardiac tamponade, and rescue thoracotomy in Micra™ recipients compared to patients implanted with a transvenous pacemaker (p<0.001), although this study is limited by potential risk of ascertainment bias. A single-arm study of the Micra AV device reported that 85.2% of individuals with complete AV block and normal sinus rhythm successfully achieved a >70% resting AV synchrony (AVS) rate at 1 month postimplant and that AVS rates could be further enhanced with additional device programming. However, clinically meaningful rates of AVS are unknown. Longer-term device characterization is planned in the Micra AV Post-Approval Registry through 3 years.

The evidence for the use of the Aveir™ transcatheter leadless pacing system consists of a pivotal prospective cohort study. Primary safety and efficacy outcomes at six weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at six months were similar and at one year were 93.2% and 91.5%, respectively. Incidence of major complications was comparable to rates observed in the Micra™ pivotal trial (4.0%). The two-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device.

Considerable uncertainties and unknowns remain in terms of the durability of the devices and end-of-life device issues. Early and limited experience with the Micra™ device has suggested that retrieval of these devices is unlikely because in due course of time, the devices will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra™ device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. While the Aveir™ device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, clinical experience with device retrieval has not yet been reported.

OTHER INDICATIONS

Atrioventricular Synchronous pacing

Micra-AV

Wu (2023) published a systematic review and meta-analysis to examine the efficacy and safety of leadless pacemakers for atrioventricular synchronous pacing.[50] The primary efficacy outcome was atrioventricular synchrony after implantation, whereas the secondary efficacy outcome was the change in cardiac output represented by the left ventricular outflow tract velocity time integral (LVOT-VTI). The primary safety outcome was major complications related to the procedures and the algorithm. Eight published studies (464 participants) were included in the qualitative analysis. The pooled atrioventricular synchrony proportion was 78.9% (95% CI 71.9-86.0%), and a further meta-regression did not screen factors that contributed significantly to the heterogeneity. Additionally, a significant increase in atrioventricular synchrony of 11.3% (95% CI 7.0-15.7%, p < 0.01) was achieved in patients experiencing programming optimization. LVOT-VTI was significantly increased by 1.9 cm (95% CI 1.2-2.6, p < 0.01), compared with the VVI pacing mode. The overall incidence of complications was approximately 6.3%, with major complications related to the algorithm being extremely low. The authors conclude that the leadless pacemakers with atrioventricular synchronous pacing demonstrated favorable safety and efficacy. Future data on long-term performance are required.

Chinitz (2022) conducted a prospective, single-arm study (AccelAV) at 20 sites in the United States and Hong Kong to assess the efficacy of the Micra AV leadless pacemaker in promoting atrioventricular synchrony (AVS) in adults with a history of atrioventricular (AV) block (n=157).[51] This device uses an accelerometer and detection algorithm to mechanically sense atrial contractions to facilitate VDD pacing (ventricle pacing chamber, both atrium and ventricle are sensing chamber and mode of operation is dual (inhibited and triggered) and AVS in individuals with normal sinus function. Micra AV implantation and completion of the 1-month study visit was achieved by 139 individuals, of which 54 (mean age, 77 years; 55.6% female) comprised the intended use population with a predominant heart rhythm of complete AV block with normal sinus rhythm. The primary endpoint was the rate of AVS during a 20-minute resting period at 1 month postimplant in these patients. Atrioventricular synchronous pacing was defined as a ventricular marker preceding a P wave within 300 ms, regardless of the underlying cardiac rhythm. Secondary endpoints included stability of AVS during rest between one and three months, percent AVS during a 24-hr ambulatory period at one months, and change in stroke volume. Quality of life was also measured with the EQ-5D-3L health status assessment. At one month, AVS percentage at rest was 85.4% (95% CI, 81.1% to 88.9%; median, 90.0%) during VDD pacing, with 85.2% of patients achieving >70% resting AVS. At the 3-month visit, 37/54 remained in the same rhythm. Among these subjects, no significant change in AVS synchrony was detected (p=.43) between the 3-month (mean, 84.1%; 95% CI, 78.3% to 88.6%) and 1-month visits (mean, 84.1%; 95% CI, 81.2% to 89.9%). At the 1 month visit, average 24-hour ambulatory AVS was 74.5% (95% CI, 70.4% to 78.2%). EQ-5D-3L health status scores significantly improved by 0.07 points between baseline and 3 months (p = 0.031) among patients with complete AV block and normal sinus function. Ambulatory AVS percentage significantly increased from 71.9% to 82.6% (p < 0.001) in twenty patients who participated in a substudy at a mean follow-up of 9.5 months designed to characterize the impact of optimized device programming. Improvement in AVS was most evident during elevated sinus rates between 80 and 110 bpm. In the safety cohort (n=152), there were 14 major complications, including four pericardial effusions and two heart failure events. One pericardial effusion resulted in perforation and death in a 92-year-old woman with high

baseline risk. A second death was reported in an 83-year-old man at 127 days postimplant but was not considered system- or procedure-related. No device upgrades and one device explantation and replacement was reported during follow-up. Study interpretation is limited by lack of a comparator group and short duration of follow-up. The ongoing Micra AV Post-Approval Registry (NCT04253184) has follow-up planned through three years. The investigators also noted that the AVS percentage required to maintain a clinical benefit over time is unknown, but likely is not 100%.

VENTRICULAR PACING FOR INDIVIDUALS WHO ARE MEDICALLY INELIGIBLE FOR A CONVENTIONAL PACING SYSTEM.

Nonrandomized Controlled Trials

No studies that exclusively enrolled patients who were medically ineligible to receive a conventional pacing system were identified.

Micra™ Leadless Pacemaker

In the IDE trial, 6.2% or 45 patients received the Micra™ transcatheter pacing system because they were medically ineligible for a conventional pacing system due to compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. A stratified analysis of these 45 patients was not presented in the published paper[28] or the FDA documents.[1, 13, 22, 30]

In the postapproval registry as an abstract, the authors reported stratified results for 105 of 1,820 patients who had previous cardiac implantable electronic device (CIED) infection.[36, 52] Of these, 83 patients (79%) were classified as medically ineligible to receive a conventional pacemaker in the opinion of the physician. A stratified analysis of these 83 patients was not presented in the publication. Trial characteristics and results are summarized in Tables 4 and 5, respectively. In this cohort of patients with CIED infection, the Micra™ device was implanted successfully in 104 patients and the previous CIED was explanted the same day as the Micra™ device was implanted in 37% of patients. Major complications were reported in 3.8% of patients with an average follow-up of 8.5 months. Ten deaths were reported (14% at 12 months) but none were related to the Micra™ transcatheter pacing system or the implantation procedure.

Garg (2020) performed a post-hoc, stratified analysis of data from the Micra™ clinical trials (Micra Post-Approval Registry, Micra Continued Access [CA] Study, Micra Transcatheter Pacing Study, Medtronic Product Surveillance Registry) based on whether the patient was deemed to be ineligible to receive a conventional pacemaker by the implanter.[53] Of the 2,817 patients that underwent an attempted implantation of a Micra™ device, 546 (19%) were considered to be precluded from receiving a transvenous permanent pacemaker, for reasons that included venous access issues or previous device infections. Compared with individuals that were not precluded from a transvenous device, the precluded patients had significantly higher acute mortality and total mortality at 36 months (2.75% vs 1.32%, p=0.022; and 38.1% versus 20.6%, p<0.001, respectively). The major complication rate was not significantly different between the groups. The majority of medically ineligible patients were enrolled in the CA and Post-Approval Registry studies, which unlike the IDE study, did not exclude patients with a life expectancy <12 months.

Table 4. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for a Conventional Pacing System and/or Previous CIED Infection

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
El-Chami (2018)[36, 52]	Prospective single cohort (Micra Post-Approval Registry)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra™ with a CIED infection	Micra™ pacemaker (n=105)	8.5 (range 0 to 28.5)
Garg (2020)[53]	Post hoc analysis of prospectively collected data from Micra™ studies	Multinational	NR	Any patient in a Micra™ study considered ineligible for a conventional pacing system	Micra™ pacemaker (n=546)	Total major complications: 24 in 22 patients; (4 cases cardiac effusion/perforation, 4 events at groin puncture site, 1 case of thrombosis, 4 cases of pacing issues, 1 case of cardiac rhythm disorder, 3 cases of infection, and 7 other)

CIED: cardiac implantable electronic device

Table 5. Summary of Key Nonrandomized Trial Results in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection

Study	No. of Patients With System- or Procedure-Related Major Complications at One Year	Average Pacing Threshold at One Year	Major Complications at 1 Year
El-Chami (2018)[36, 52]			
N	105	82	105
Micra™	4 (4/105)	0.6 V	Total major complications: 6 in 4 patients (patient 1: effusion requiring pericardiocentesis; patient 2: elevated thresholds, complication of device removal [IVC filter entanglement], and subsequent abdominal wall infection, patients 3 and 4: pacemaker syndrome)
Garg (2020)[53]			
N	546	NR	546
Micra™	4 (22/546, reported at 36 months)	NR	Total major complications: 24 in 22 patients; (4 cases cardiac effusion/perforation, 4 events at groin puncture site, 1 case of thrombosis, 4

Study	No. of Patients With System- or Procedure-Related Major Complications at One Year	Average Pacing Threshold at One Year	Major Complications at 1 Year
			cases of pacing issues, 1 case of cardiac rhythm disorder, 3 cases of infection, and 7 other)

IVC: in cava filter; NR: not reported.

Section Summary: Ventricular Pacing for Individuals Who Are Medically Ineligible for a Conventional Pacing System

No studies that exclusively enrolled patients who were medically ineligible for a conventional pacing system were identified. However, a subgroup of patients in whom the use of conventional pacemakers was precluded was enrolled in the pivotal and the postapproval trials of the Micra™ device. Information on the outcomes in these subgroups of patients from the postapproval study showed that Micra™ was successfully implanted in 98% of cases and safety outcomes were similar to the original cohort. Even though the evidence is limited, and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks in the context of the life-saving potential of pacing systems in patients that are ineligible for conventional pacing systems.

USE OF LEADLESS PACEMAKERS EMERGENTLY

Systematic Reviews

Noor (2023) published a SR evaluating the feasibility and outcomes of emergency implantation of LPM in patients referred for urgent PM implantation.[54] In a total of four studies (1276 patients) of which 114 patients (8.9%) were implanted with leadless pacemakers (LPM) and the rest were implanted with either conventional PMs or some other alternatives. In the included studies, 468 (36.6%) patients were males. All four included studies were prospective cohort studies. The authors reported that LPM implantation demonstrated low procedural times, hospital stay, and fluoroscopy time but one study demonstrated more procedure time in an urgent setting, and pacing parameters were comparable in both comparison with other cardiac implantable electronic devices and elective LPM implantation. Quantative analysis was limited by the heterogeneity of studies and the small number of studies included. Other limitations included experience of the operators, possible selection bias. They conclude that randomized controlled trials are needed to evaluate safety and efficacy of LPMs in emergency settings.

DUAL CHAMBER LEADLESS PACEMAKERS

The Aveir DR i2i ™ is currently being evaluated in an open label prospective, multicenter, international, single-arm, pivotal investigational study designed to evaluate the clinical safety and efficacy of the Aveir DR leadless pacemaker in patients who were indicated for a dual-chamber bradycardia pacing pacemaker that stimulates the appropriate chamber of the heart when necessary or DDD(R).[55] The study was initiated February 2, 2022 and is estimated to be complete by November 2025. The primary completion date is September 2023. The study plan is to enroll up to 550 patients from up to 82 sites in the U.S., Canada, Europe and Asia-Pacific, and all patients will be followed for a minimum of 12 months post-implant. (ClinicalTrials.gov identifier NCT05252702).

Knop (2023) published a prospective, multicenter, single-group study to evaluate the safety and performance of a dual-chamber leadless pacemaker system.[56] Patients with a conventional indication for dual-chamber pacing were eligible for participation. The primary safety end point was freedom from complications (i.e., device- or procedure-related serious adverse events) at 90 days. The first primary performance end point was a combination of adequate atrial capture threshold and sensing amplitude at three months. The second primary performance end point was at least 70% atrioventricular synchrony at three months while the patient was sitting. Among the patients (n = 300) enrolled, 190 (63.3%) had sinus-node dysfunction and 100 (33.3%) had atrioventricular block as the primary pacing indication. The implantation procedure was successful (i.e., two functioning leadless pacemakers were implanted and had established implant-to-implant communication) in 295 patients (98.3%). A total of 35 device- or procedure-related serious adverse events occurred in 29 patients. The primary safety end point was met in 271 patients (90.3%; 95% confidence interval [CI], 87.0 to 93.7), which exceeded the performance goal of 78% ($p < 0.001$). The first primary performance end point was met in 90.2% of the patients (95% CI, 86.8 to 93.6), which exceeded the performance goal of 82.5% ($p < 0.001$). The mean (±SD) atrial capture threshold was 0.82 ± 0.70 V, and the mean P-wave amplitude was 3.58±1.88 mV. Of the 21 patients (7%) with a P-wave amplitude of less than 1.0 mV, none required device revision for inadequate sensing. At least 70% atrioventricular synchrony was achieved in 97.3% of the patients (95% CI, 95.4 to 99.3), which exceeded the performance goal of 83% ($p < 0.001$). This study was (Funded by Abbott Medical; Aveir DR i2i ClinicalTrials.gov number, NCT05252702.).

Section Summary

There is not enough evidence to support the use of dual chamber leadless pacemakers for any indication.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION, AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY

The American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society's (2012) focused update on device-based therapy of cardiac rhythm abnormalities incorporated into their joint 2008 guidelines for device-based therapy of cardiac rhythm abnormalities does not include recommendations on leadless cardiac pacemakers.[57]

In 2020, the Heart Rhythm Society (HRS), along with the International Society for Cardiovascular Infectious Diseases (ISCVID) and several other Asian, European and Latin American societies, endorsed the European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections.[58] The consensus states that for patients at high risk of device-related infections, avoiding a transvenous system, and implanting an epicardial system, may be preferential. It makes the following statements regarding leadless pacemakers:

- "There is hope that 'leadless' pacemakers will be less prone to infection and can be used in a similar manner [as epicardial systems] in high-risk patients."
- "In selected high-risk patients, the risk of infection with leadless pacemakers appears low. The device also seems safe and feasible in patients with pre-existing CIED infection and after extraction of infected leads."

The Heart Rhythm Society and American College of Cardiology Foundation (2012) expert consensus statement on pacemaker device and mode selection did not include recommendations on leadless cardiac pacemakers.[59]

SUMMARY

There is enough research to show that Micra™ single-chamber transcatheter pacing system may improve health outcomes for patients with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system. Although evidence is limited and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks, in the context of the life-saving potential of this pacing system for patients who are ineligible for conventional pacing systems. Therefore, this pacemaker system may be considered medically necessary for patients who meet the policy criteria.

There is not enough research to show that a leadless pacing system can improve health outcomes for patients who do not meet medical necessity criteria, including the use of the Aveir™ system or a non-FDA-approved system, or in patients who are eligible for a conventional pacing system. There is little evidence regarding the durability of devices, device end-of-life issues, and device-device interactions (both electrical and mechanical), which may occur when there is a deactivated leadless device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Therefore, a leadless pacemaker is considered investigational when criteria are not met.

There is not enough evidence to show that dual chamber leadless pacing systems can improve health outcomes for patients. There are currently no FDA approved dual chamber leadless pacemaker devices.

REFERENCES

1. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Micra Transcatheter Pacing System (PMS P150033). 2016. [cited 10/10/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150033B.pdf.
2. (FDA) UFDA. US Federal Drug Administration (FDA). Aveir™ DR Leadless System Summary of Safety and Effectiveness Data (SSED) 2023. [cited 10/10/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150035S003B.pdf.
3. Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker. *The New England journal of medicine.* 2015;373(12):1125-35. PMID: 26321198
4. Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart rhythm.* 2012;9:728-35. PMID: 22182495
5. Haight PJ, Stewart RE, Saarel EV, et al. Lateral thoracotomy for epicardial pacemaker placement in patients with congenital heart disease. *Interact Cardiovasc Thorac Surg.* 2018;26:845-51. PMID: 29300890

6. Cohen MI, Bush DM, Vetter VL, et al. Permanent epicardial pacing in pediatric patients: seventeen years of experience and 1200 outpatient visits. *Circulation.* 2001;103(21):2585-90. PMID: 11382728
7. Doll N, Piorkowski C, Czesla M, et al. Epicardial versus transvenous left ventricular lead placement in patients receiving cardiac resynchronization therapy: results from a randomized prospective study. *The Thoracic and cardiovascular surgeon.* 2008;56(5):256-61. PMID: 18615370
8. Harake DE, Shannon KM, Aboulhosn JA, et al. Transvenous pacemaker implantation after the bidirectional Glenn operation for patients with complex congenital disease. *Journal of cardiovascular electrophysiology.* 2018;29(3):497-503. PMID: 29240293
9. Tsutsumi, K. , Hashizume, K. , Kimura, N. , Taguchi, S. , Inoue, Y. , Kashima, I. and Takahashi, R. (2010), Permanent Pacemaker Implantation via the Iliac Vein: An Alternative in 4 Cases with Contraindications to the Pectoral Approach. Journal of Arrhythmia, 26: 55-61. doi:10.1016/S1880-4276(10)80037-7.
10. Healey JS, Toff WD, Lamas GA, et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. *Circulation.* 2006;114:11-7. PMID: 16801463
11. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Risk factors for lead complications in cardiac pacing: a population-based cohort study of 28,860 Danish patients. *Heart rhythm.* 2011;8:1622-8. PMID: 21699827
12. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J.* 2014;35:1186-94. PMID: 24347317
13. U.S. Food and Drug Administration (FDA). FDA Executive Summary Memorandum. General Issues: Leadless Pacemaker Devices Prepared for the February 18, 2016 meeting of the Circulatory System Devices Advisory Panel Gaithersburg Hilton; Gaithersburg, MD. 2016;. [cited 10/10/2023]. 'Available from:' https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM485093.pdf.
14. American Heart Association. Statement of the American Heart Association to the Food and Drug Administration Circulatory System Devices Panel February 18, 2016: Leadless Cardiac Pacemaker Devices. 2016. [cited 10/10/2023]. 'Available from:' https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM486235.pdf.
15. Reddy VY, Miller MA, Knops RE, et al. Retrieval of the Leadless Cardiac Pacemaker: A Multicenter Experience. *Circulation Arrhythmia and electrophysiology.* 2016;9(12). PMID: 27932427
16. Reddy VY, Knops RE, Sperzel J, et al. Permanent leadless cardiac pacing: results of the LEADLESS trial. *Circulation.* 2014;129:1466-71. PMID: 24664277
17. Knops RE, Tjong FV, Neuzil P, et al. Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial. *Journal of the American College of Cardiology.* 2015;65(15):1497-504. PMID: 25881930
18. Lakkireddy D, Knops R, Atwater B, et al. A worldwide experience of the management of battery failures and chronic device retrieval of the Nanostim leadless pacemaker. *Heart rhythm.* 2017;14(12):1756-63. PMID: 28705736
19. Tjong FVY, Knops RE, Neuzil P, et al. Midterm Safety and Performance of a Leadless Cardiac Pacemaker: 3-Year Follow-up to the LEADLESS Trial (Nanostim Safety and

Performance Trial for a Leadless Cardiac Pacemaker System). *Circulation.* 2018;137:633-35. PMID: 29431664
20. Reddy VY, Exner DV, Doshi R, et al. Primary Results on Safety and Efficacy From the LEADLESS II-Phase 2 Worldwide Clinical Trial. *JACC Clin Electrophysiol.* 2022;8(1):115-17. PMID: 34863657
21. Abbott. Press Releases: Abbott receives FDA approval for Aveir VR Leadless Pacemaker System to treat patients with slow heart rhythms. April 4, 2022. [cited 10/10/2023]. 'Available from:' https://abbott.mediaroom.com/2022-04-04-Abbott-Receives-FDA-Approval-for-Aveir-TM-VR-Leadless-Pacemaker-System-to-Treat-Patients-with-Slow-Heart-Rhythms.
22. Zuckerman B, Shein M, Paulsen J, et al. Circulatory System Devices Panel Meeting: Leadless Pacemakers. FDA Presentation. 2016. [cited 10/10/2023]. 'Available from:' https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM486733.pdf.
23. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data: Aveir Leadless Pacemaker (P150035). March 31, 2022. [cited 10/10/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150035B.pdf.
24. U.S. Food and Drug Administration (FDA). Letter to Health Care Providers. Leadless Pacing Systems: Risk of Major Complications Related to Cardiac Perforation During Implantation. November 17, 2021. [cited 10/10/2023]. 'Available from:' https://www.fda.gov/medical-devices/letters-health-care-providers/leadless-pacing-systems-risk-major-complications-related-cardiac-perforation-during-implantation.
25. Ritter P, Duray GZ, Zhang S, et al. The rationale and design of the Micra Transcatheter Pacing Study: safety and efficacy of a novel miniaturized pacemaker. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2015;17:807-13. PMID: 25855677
26. Ritter P, Duray GZ, Steinwender C, et al. Early performance of a miniaturized leadless cardiac pacemaker: the Micra Transcatheter Pacing Study. *Eur Heart J.* 2015;36:2510-9. PMID: 26045305
27. Tjong FVY, Beurskens NEG, de Groot JR, et al. Health-related quality of life impact of a transcatheter pacing system. *Journal of cardiovascular electrophysiology.* 2018;29(12):1697-704. PMID: 30168233
28. Reynolds D, Duray GZ, Omar R, et al. A Leadless Intracardiac Transcatheter Pacing System. *The New England journal of medicine.* 2016;374(6):533-41. PMID: 26551877
29. Lloyd M, Reynolds D, Sheldon T, et al. Rate adaptive pacing in an intracardiac pacemaker. *Heart rhythm.* 2017;14(2):200-05. PMID: 27871854
30. Transcript of the United States of America Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Medical Devices Advisory Committee: Circulatory System Devices Panel Meeting Meeting. February 18, 2016. [cited 10/10/2023]. 'Available from:' https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM489547.pdf.
31. Medtronic. Micra (brochure). n.d. [cited 10/10/2023]. 'Available from:' https://www.medtronic.com/content/dam/medtronic-com/01_crhf/brady/pdfs/micra-physician-portfolio-brochure.pdf.

32. Grubman E, Ritter P, Ellis CR, et al. To retrieve, or not to retrieve: System revisions with the Micra transcatheter pacemaker. *Heart rhythm.* 2017;14(12):1801-06. PMID: 28713024
33. Crossley GH, Piccini JP, Longacre C, et al. Leadless versus transvenous single-chamber ventricular pacemakers: 3 year follow-up of the Micra CED study. *Journal of cardiovascular electrophysiology.* 2023;34(4):1015-23. PMID: 36807378
34. Boveda S, Higuera L, Longacre C, et al. Two-year outcomes of leadless vs. transvenous single-chamber ventricular pacemaker in high-risk subgroups. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2023;25(3):1041-50. PMID: 36757859
35. Roberts PR, Clementy N, Al Samadi F, et al. A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry. *Heart rhythm.* 2017;14(9):1375-79. PMID: 28502871
36. El-Chami MF, Brock Johansen J, Zaidi A, et al. Leadless Pacemaker Implant in Patients with Pre-Existing Infections: Results from the Micra Post-Approval Registry. Paper presented at: Heart Rhythm Scientific Sessions. 2018 May 10; Boston, MA.
37. El-Chami MF, Al-Samadi F, Clementy N, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. *Heart rhythm.* 2018;15(12):1800-07. PMID: 30103071
38. El-Chami MF, Garweg C, Iacopino S, et al. Leadless pacemaker implant, anticoagulation status, and outcomes: Results from the Micra Transcatheter Pacing System Post-Approval Registry. *Heart rhythm.* 2022;19(2):228-34. PMID: 34757189
39. El-Chami MF, Shinn T, Bansal S, et al. Leadless pacemaker implant with concomitant atrioventricular node ablation: Experience with the Micra transcatheter pacemaker. *Journal of cardiovascular electrophysiology.* 2021;32(3):832-41. PMID: 33428248
40. Piccini JP, El-Chami M, Wherry K, et al. Contemporaneous Comparison of Outcomes Among Patients Implanted With a Leadless vs Transvenous Single-Chamber Ventricular Pacemaker. *JAMA Cardiol.* 2021;6(10):1187-95. PMID: 34319383
41. El-Chami MF, Bockstedt L, Longacre C, et al. Leadless vs. transvenous single-chamber ventricular pacing in the Micra CED study: 2-year follow-up. *Eur Heart J.* 2022;43(12):1207-15. PMID: 34788416
42. Hauser RG, Gornick CC, Abdelhadi RH, et al. Major adverse clinical events associated with implantation of a leadless intracardiac pacemaker. *Heart rhythm.* 2021;18(7):1132-39. PMID: 33713856
43. Hauser RG, Gornick CC, Abdelhadi RH, et al. Leadless pacemaker perforations: Clinical consequences and related device and user problems. *Journal of cardiovascular electrophysiology.* 2022;33(2):154-59. PMID: 34953099
44. Reddy VY, Exner DV, Doshi R, et al. 1-Year Outcomes of a Leadless Ventricular Pacemaker: The LEADLESS II (Phase 2) Trial. *JACC Clin Electrophysiol.* 2023. PMID: 36951813
45. Duray GZ, Ritter P, El-Chami M, et al. Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study. *Heart rhythm.* 2017;14(5):702-09. PMID: 28192207
46. U.S. Food and Drug Administration (FDA). Post-Approval Studies (PAS) Database: The Aveir VR RWE Study. April 2022. [cited 05/15/2023]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=6952&t_id=580926.

47. Garg J, Shah K, Bhardwaj R, et al. Adverse events associated with Aveir(TM) VR leadless pacemaker: A Food and Drug Administration MAUDE database study. *Journal of cardiovascular electrophysiology.* 2023;34(6):1469-71. PMID: 37209414
48. Tokavanich N, Machado C, Banga S, et al. Implant efficiency and clinical performance of Aveir™ VR and Micra™ VR leadless pacemaker: A multicenter comparative analysis of 67 patients. *Pacing Clin Electrophysiol.* 2023;46(8):827-32. PMID: 37382396
49. Shantha G, Brock J, Singleton MJ, et al. A comparative study of the two leadless pacemakers in clinical practice. *Journal of cardiovascular electrophysiology.* 2023;34(9):1896-903. PMID: 37522245
50. Wu S, Jin Y, Lu W, et al. Efficacy and Safety of Leadless Pacemakers for Atrioventricular Synchronous Pacing: A Systematic Review and Meta-Analysis. *J Clin Med.* 2023;12(7). PMID: 37048596
51. Chinitz LA, El-Chami MF, Sagi V, et al. Ambulatory atrioventricular synchronous pacing over time using a leadless ventricular pacemaker: Primary results from the AccelAV study. *Heart rhythm.* 2023;20(1):46-54. PMID: 36075532
52. El-Chami MF, Johansen JB, Zaidi A, et al. Leadless pacemaker implant in patients with pre-existing infections: Results from the Micra postapproval registry. *Journal of cardiovascular electrophysiology.* 2019;30(4):569-74. PMID: 30661279
53. Garg A, Koneru JN, Fagan DH, et al. Morbidity and mortality in patients precluded for transvenous pacemaker implantation: Experience with a leadless pacemaker. *Heart rhythm.* 2020. PMID: 32763431
54. Noor TA, Rana MOR, Kumari S, et al. Outcomes of primary leadless pacemaker implantation: A systematic review. *Ann Noninvasive Electrocardiol.* 2023:e13084. PMID: 37606307
55. Aveir DR i2i study. [cited 10/10/2023]. 'Available from:' https://clinicaltrials.gov/ct2/show/NCT05252702?term=Aveir+DR+i2i&draw=2&rank=1.
56. Knops RE, Reddy VY, Ip JE, et al. A Dual-Chamber Leadless Pacemaker. *The New England journal of medicine.* 2023;388(25):2360-70. PMID: 37212442
57. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology.* 2013;61(3):e6-75. PMID: 23265327
58. Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2020;22(4):515-49. PMID: 31702000
59. Gillis AM, Russo AM, Ellenbogen KA, et al. HRS/ACCF expert consensus statement on pacemaker device and mode selection. *Journal of the American College of Cardiology.* 2012;60:682-703. PMID: 22854177

CODES

Codes	Number	Description
CPT	0795T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; complete system (ie, right atrial and right ventricular pacemaker components)
	0796T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right atrial pacemaker component (when an existing right ventricular single leadless pacemaker exists to create a dual-chamber leadless pacemaker system)
	0797T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
	0798T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; complete system (ie, right atrial and right ventricular pacemaker components)
	0799T	Transcatheter removal of permanent dual-chamber leadless pacemaker including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right atrial pacemaker component
	0800T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
	0801T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; dual-chamber system (ie, right atrial and right ventricular pacemaker components)
	0802T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right atrial pacemaker component
	0803T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
	0804T	Programming device evaluation (in person) with iterative adjustment of implantable device to test the function of device and to select optimal

Codes	Number	Description
		permanent programmed values, with analysis, review, and report, by a physician or other qualified health care professional, leadless pacemaker system in dual cardiac chambers
	0823T	Transcatheter insertion of permanent single-chamber leadless pacemaker, right atrial, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography and/or right ventriculography, femoral venography, cavography) and device evaluation (eg, interrogation or programming), when performed
	0824T	Transcatheter removal of permanent single-chamber leadless pacemaker, right atrial, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography and/or right ventriculography, femoral venography, cavography), when performed
	0825T	Transcatheter removal and replacement of permanent single-chamber leadless pacemaker, right atrial, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography and/or right ventriculography, femoral venography, cavography) and device evaluation (eg, interrogation or programming), when performed
	0826T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional, leadless pacemaker system in single-cardiac chamber
	33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed (new eff 1/1/19)
	33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed
HCPCS	None	

Date of Origin: *December 2018*

Regence

Medical Policy Manual Surgery, Policy No. 220

Surgical Treatments for Lymphedema and Lipedema

Effective: May 1, 2024

Next Review: June 2024
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Lymphedema is an accumulation of fluid due to disruption of lymphatic drainage. Lymphedema can be caused by congenital or inherited abnormalities in the lymphatic system (primary lymphedema) but is most often caused by acquired damage to the lymphatic system (secondary lymphedema). Lipedema is a rare condition where increased fat tissue accumulates under the skin which causes non-pitting, bilateral swelling in the extremities.

MEDICAL POLICY CRITERIA

Note: Member contracts for covered services vary. Member contract language takes precedence over medical policy.

I. Liposuction or lipectomy to treat lipedema of the extremities may be considered **medically necessary** when all of the following are met (A.-G.):

   A. Surgical interventions are performed by hospital credentialed, board certified plastic surgeon; and

   B. The individual has a diagnosis of lipedema including all of the following clinical exam findings:

      1. Bilateral symmetric adiposity that is disproportionately affecting the

extremities with minimal involvement of the hands and feet; and

2. Non-pitting edema; and
3. Pain and tenderness on palpation of the affected areas; and
4. Negative Stemmer sign; and
5. Submission of photographs documenting the affected extremities requested for treatment and are consistent with the diagnosis of lipedema; and

C. There is documentation of significant physical functional impairment (e.g., difficulty ambulating or performing activities of daily living); and

D. The individual has not responded to at least three consecutive months of optimal medical management including complex decongestive therapy and compression therapy; and

E. For individuals with BMI greater than 35 kg/m^2, there has been a lack of effect on lipedema-affected areas of weight loss measures as documented in the medical records through nutrition and/or medical interventions with clinic visits over three consecutive months; and

F. The plan of care postoperatively is to continue to wear compression garments as instructed to maintain the benefits of treatment; and

G. The area requested to be treated has not previously been treated with liposuction or lipectomy.

II. Liposuction or lipectomy to treat lipedema for areas other than extremities (e.g., trunk or back) or when Criterion I. is not met is considered **investigational.**

III. Lymphatic physiologic surgery with or without a microscope performed during nodal dissection (e.g. axillary or groin) or breast reconstruction to prevent lymphedema (including, but not limited to, the Lymphatic Microsurgical Preventing Healing Approach) in individuals who are being treated for breast cancer is considered **investigational**.

IV. Liposuction or lipectomy to treat lymphedema (including, but not limited to, lipectomy, suction-assisted protein lipectomy, lipisuction, and lymph-sparing liposuction) is considered **investigational.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Documentation that surgery will be performed by hospital credentialed, board certified plastic surgeon

- Documentation supporting diagnosis of lipedema as defined by the policy criterion I.B.
- Documentation of specific significant physical functional impairment(s) including specific ADLs (e.g., walking, feeding, dressing/grooming, toileting, bathing, transferring).
- Documentation of no response to a minimum of three months of conservative therapy including compression therapy and complex decongestive therapy (CDT), which combines several approaches including manual lymph drainage (a massage technique), compression therapy, and physical mobilization.
- If the individual has a BMI greater than 35 kg/m^2, documentation of lack of effect of weight loss on lipedema-affected areas through nutrition and/or medical interventions with clinic visits over three consecutive months.
- Documentation of post-operative plan to include compression therapy.

CROSS REFERENCES

None

BACKGROUND

LYMPHEDEMA

A diagnosis of secondary lymphedema is based on history (e.g., cancer treatment, trauma) and physical examination (localized, progressive edema and asymmetric limb measurements) when other causes of edema can be excluded. Imaging, such as magnetic resonance imaging, computed tomography, ultrasound, or lymphoscintigraphy, may be used to differentiate lymphedema from others causes of edema in diagnostically challenging cases.

Breast Cancer-Related Lymphedema

Breast cancer treatment is one of the most common causes of secondary lymphedema. Both the surgical removal of lymph nodes and radiotherapy are associated with development lymphedema in patients with breast cancer.

In a systematic review of 72 studies (N=29,612 women), DiSipio (2013) reported that approximately 1 in 5 women who survive breast cancer will develop arm lymphedema.[1] Reviewers reported that risk factors for development of lymphedema that had a strong level of evidence were extensive surgery (i.e., axillary-lymph-node dissection, greater number of lymph nodes dissected, mastectomy) and being overweight or obese.

Management and Treatment

Early and ongoing treatment of lymphedema is necessary. Conservative therapy may consist of several features depending on the severity of the lymphedema. Patients are educated on the importance of self-care including hygiene practices to prevent infection, maintaining ideal body weight through diet and exercise, and limb elevation. Compression therapy consists of repeatedly applying padding and bandages or compression garments. Manual lymphatic drainage is a light pressure massage performed by trained physical therapists or by patients designed to move fluid from obstructed areas into functioning lymph vessels and lymph nodes. Complete decongestive therapy is a multiphase treatment program involving all of the previously mentioned conservative treatment components at different intensities. Pneumatic compression pumps may also be considered as an adjunct to conservative therapy or as an alternative to self-manual lymphatic drainage in patients who have difficulty performing self-

manual lymphatic drainage. In patients with more advanced lymphedema after fat deposition and tissue fibrosis has occurred, palliative surgery using reductive techniques such as liposuction may be performed.

LIPEDEMA

Lipedema is a rare condition primarily seen in women where increased fat tissue accumulates under the skin which causes non-pitting, bilateral swelling typically seen in the lower extremities. Lipedema can also be seen in the upper extremities. The condition usually worsens gradually, although in some cases minor lipedema may stabilize. Lipedema is often painful and may be accompanied by easy bruising and joint problems. There is no known cause for lipedema.

Management and Treatment

Management of lipedema is complex and distinct from lymphedema. The proposed main conservative treatment is complete or complex decongestive therapy (CDT). CDT combines several approaches including manual lymph drainage (a massage technique), compression therapy, and physical mobilization. Liposuction has been proposed as an alternative treatment option for lipedema.

EVIDENCE SUMMARY

SURGICAL TREATMENT FOR LYMPHEDEMA

The purpose of physiologic microsurgery treatments and liposuction for lymphedema is to provide a treatment option that is an improvement on existing therapies such as conservative therapy with compression garments or bandages, manual lymph drainage or pneumatic pumps, and decongestive therapy. Both surgical treatment and radiotherapy for breast cancer can lead to lymphedema and is one of the most common causes of secondary peripheral lymphedema.

Multiple Techniques

Systematic Reviews

Meuli (2023) published an updated systematic review which included 150 studies with 6496 patients who received LVA or LVNT.[2] A qualitative summary was conducted initially to determine the three most frequently reported outcomes for which a pooled analysis was then conducted. The authors reported an overall pooled change in excess limb circumference of -35.6%, change in excess volume of -32.7%, and a change in the number of cutaneous infection episodes per year of -1.9. Although the authors reported positive findings in reducing volume, circumference, and infection, the included studies suffer from significant quality and study design limitations. There exists significant heterogeneity in sampling, outcomes, and staging in the included studies which further limits possible conclusions.

Coriddi (2020) reported on a systematic review of PROs following surgical treatment of lymphedema, including lymphovenous bypass and vascularized lymph node transfer (VLNT).[3] Overall, 32 studies were identified (details regarding study design were not reported) with follow-up ranging from approximately 4 months to 43 months. The number of patients with breast cancer-related lymphedema was not described. The study reported findings for both validated and non-validated instruments assessing quality of life; however, only 18 studies

(n=717 patients) reported individual patient data to permit quantitative assessment of the proportion of patients experiencing quality of life improvements. All studies showed an improvement in QOL ranging from 50% to 100%. Only one study used a validated instrument which demonstrated a 50% improvement in QOL.

Markkula (2019) published a Cochrane systematic review to assess and compare the efficacy of surgical interventions for the prevention of the development of lymphedema (LE) in the arm after breast cancer treatment and to assess and compare the efficacy of surgical interventions for the treatment of established LE in the arm after breast cancer treatment.[4] Reductive and reconstructive techniques were considered including liposuction, lymphaticovenular anastomoses (LVA), lymphatico-lymphatic bypass (LLB), and vascularized lymph node transfer (VLNT). Three studies which included two studies assessing the effectiveness of LVA as part of preventive management protocols in the prevention of breast cancer-related lymphedema and one study addressing the effectiveness of VLNT in the treatment of established breast cancer-related lymphedema. The authors concluded that there is not enough evidence to support the widespread adoption of liposuction, LVA, or VLNT techniques and that high-quality RCTs are needed.

A 2019 systematic review by Tyker aimed to evaluate the efficacy of a variety of surgical treatments for patients with lymphedema following head and neck cancer therapy.[5] 26 studies met the inclusion criteria including 14 cohort studies, seven case reports, two RCTs, two systematic reviews, and one narrative review. Manual lymph drainage had the largest number of studies and participants and there was limited evidence evaluating the efficacy of liposuction and microsurgery techniques. The authors concluded that there is limited data from high-quality studies including RCTs and that more research is needed to understand the long-term efficacy of other treatment modalities.

A 2017 systematic review by Carl aimed to develop a treatment algorithm based on highest-quality lymphedema research.[6] The SR addressed lymphovenous anastomosis (LVA), vascularized lymph node transfer (VLNT), liposuction, excision, and combination surgical approaches for the treatment of lymphedema. Sixty-nine articles met inclusion criteria and were included in the review. In studies measuring excess volume reduction, the mean reduction was 96.6% for liposuction, 33.1% for LVA, and 26.4% for VLNT. Included excision articles did not report excess volume reduction. The authors stated that further studies with a focus on follow up after treatment will improve the validity of lymphedema surgery research. There was significant heterogeneity of the included studies in terms of lymphedema stage and etiology, method of assessing surgical outcomes, and inconsistent reporting of complications and quality of life outcomes. Additional trials are needed that compare surgical treatments to conservative therapies which may help define the most appropriate interventions for patients according to their clinical stage.

Additional single-arm studies have been published on liposuction for the treatment of lymphedema.[7, 8] However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Surgeries That Reconstruct or Bypass Using Donor Lymph Vessels

Leung (2015) reported on a systematic review of the surgical management of breast cancer-related lymphedema.[9] The search included studies reporting on the efficacy of surgical techniques used for the prevention or treatment of breast cancer-related lymphedema

published between 2000 and 2014. Only one study on lymphatico-lymphatic bypass was identified and published since 2000. The study included seven patients followed for 2.6 years. One patient had "complete recovery" as measured by the circumference of the affected limb and the remaining six patients had a "reasonable outcome". Postsurgery complications were cellulitis, donor-site lymphorrhea, and transient edema of donor leg.

Surgeries That Reconstruct or Bypass Using the Venous System

Systematic Reviews

Several systematic reviews specifically evaluating microsurgical procedures using the venous system (lymphaticovenular anastomosis [LVA], lymphovenous bypass) have been reported.[10, 11] Two broader systematic reviews of treatments for lymphedema including several microsurgical procedures have also been reported.[6, 9] Corneilissen (2018) and Leung (2015) were limited to studies of breast cancer-related lymphedema but the remaining reviews were not.

Chang (2021) reported on a systematic review and meta-analysis of LVA and vascularized lymph node transfer (VLNT) for treatment of lymphedema.[12] Overall, 66 total studies were included, with 16 studies included on LVA. Follow-up ranged from approximately 6 to 68 months. The number of patients with breast cancer-related lymphedema was not described. In addition, studies evaluating use of these procedures for both upper and lower extremity lymphedema were included. The results of the study showed both a reduction in limb circumference and a reduction in the number of cellulitis infections before and after surgery.

Cornelissen (2018) reported on a systematic review assessing the effect of LVA in breast cancer-related lymphedema.[10] Fifteen observational studies were identified (11 prospective, 4 retrospective) with follow-up times ranging from two months to eight years. Although LVA surgery was performed in the included studies, the technical procedure differed among studies: six studies used only end-to-end anastomoses; four studies used both end-to-end and end-to-side anastomoses; one study used the ‘‘Octopus technique''; and four studies did not report the LVA technique used. Only two studies included a control group (bandaging, decongestive therapy).

Scaglioni (2017) reported on a systematic review of LVA for the treatment of lymphedema.[11] Reviewers noted significant variations in surgical techniques, numbers of anastomoses, and supplementary interventions (i.e., compressive therapy, additional debulking surgery). Nine studies included secondary lymphedema alone, while eight studies included patients with both primary and secondary lymphedemas. The number of patients with breast cancer-related lymphedema was not described. As mentioned, the Carl (2017) and Leung (2015) reviews included multiple surgical techniques. Leung (2015) was limited to breast cancer-related lymphedema while Carl (2017) was not.

Basta (2014) published a systematic review which included 27 studies evaluating the efficacy and safety of microsurgical treatments for lymphedema.[13] Lymphovenous shunt procedures were used in 22 studies and lymph node transfer was used in the remaining five studies. The primary endpoint was reduction in excess volume or circumference. The authors reported an excess circumference reduction of 48.8% and an absolute circumference reduction of 3.3 cm. The studies that reported excess volume reduction show a reduction of 56.6%. The rate of no improvement in the included studies was 11.8% and complications included infection, lymphorrhea, reexploration for flag congestion, and reoperation.

Randomized Controlled Trials

No RCTs were identified.

Nonrandomized Studies

Maruccia (2019) published a retrospective study comparing vascularized lymph node transfer (VLNT) to combined VLNT and axillary scar release.[14] Thirty-nine patients were included and all had stage II or III breast cancer-related lymphedema. Primary outcomes were limb circumference and lymphedema-related quality of life. A significant difference between the circumference reduction rates at above elbow level was observed at three and six months of follow-up comparing the two groups, with higher values in the combined treatment group than VLNT alone. No significant difference was detected comparing reduction rate values at above and below elbow at 12 and 24 months postoperatively. Quality of life metrics showed significantly better scores in all domains at all follow-up appointments in the combined group.

Agko (2018) published a nonrandomized, noncomparative prospective study including 12 patients with lymphedema who received vascularized lymph node transfer followed by lipectomy.[15] The primary outcomes were limb size and number of infectious episodes in addition to an evaluation of compression garment utilization. The authors reported a limb circumference reduction rate of 37.9% after the VLNT procedure and this was increased to a reduction rate of 96.4% after the lipectomy procedure. Only one patient reported an infectious episode after either of the treatments. It was noted that all patients were able to eventually discontinue the use of compression garments. Limitations of this study include the lack of a comparator group, small sample size, and no long-term follow-up.

Additional single-arm studies have been published since the systematic reviews.[16] However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow-up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Subsection Summary: Surgeries That Reconstruct or Bypass Using the Venous System

No controlled trials were identified evaluating the physiologic microsurgeries using techniques such as lymphovenous bypass or LVA that reconstruct or bypass the obstructed lymphatic vessels using the venous system. Systematic reviews have indicated that most of the available evidence for these procedures comes from uncontrolled studies including fewer than 40 participants each, most of which lack adequate descriptions of how patients were selected for inclusion. Surgical technique, the severity of lymphedema, outcomes metrics, and follow-up times varied across studies making it difficult to synthesize the evidence. Surgical complications have been inconsistently reported but appear to be rare. RCTs of physiologic microsurgeries that bypass the obstructed lymphatic vessels using the venous system plus conservative therapy vs conservative therapy alone are needed.

SURGERIES THAT TRANSFER LYMPH TISSUE

Systematic Reviews

Systematic reviews evaluating microsurgical procedures that transfer lymph tissue (autologous lymph node transfer, vascularized lymph node transfer [VLNT]) have been reported. Ozturk (2016) reported on a systematic review of VLNT for treatment of lymphedema.[17] They included treatment for both primary and secondary lymphedema and as such comprised a

heterogeneous population. However, 191 of 305 of the surgeries were for breast cancer-related lymphedema. Eighteen studies were identified (3 prospective, 15 retrospective). For breast cancer-related lymphedema, VLNT with a skin island or VLNT with an autologous flap was used. There was inconsistent reporting of the staging of lymphedema. Reviewers did not state whether any of the studies included a control group. Two systematic reviews of various surgical methods previously described also included a review of lymph node transfer.[6, 9]

In addition to the systematic reviews of efficacy, Demiri (2018) reported on a systematic review of donor-site complications following autologous lymph node transfer for breast cancer-related lymphedema.[18]

Risk of bias was assessed in Ozturk (2016) using a checklist from the American Society of Plastic Surgeons guidelines for therapeutic studies. A summary of the assessment follows:

- 12 of 18 studies did not report whether patients were selected consecutively and one did not include consecutive patients;
- 13 of 18 studies had insufficient information on the surgical team;
- 3 of 18 studies had an insufficient follow-up to observe outcomes (ie, <1 year).

Randomized Controlled Trials

Dionyssiou (2016) reported on an RCT that evaluated VLNT plus physical therapy vs physical therapy alone for lymphedema in 36 women with stage II breast cancer-related lymphedema.[19] At 18 months, the reduction in the excess volume of the affected limb as a percentage of the intact limb was 57% in the VLNT group and 18% in the physical therapy group (treatment effect not reported, p<0.001). The mean number of lymphedema-related infections per patient per year was lower in the VLNT group (0.28 vs 1.16; treatment effect not reported, p=0.001). The trial had several limitations described in Tables 9 and 10. Notably, there was no description of allocation concealment and the trial was not blinded, possibly introducing both selection and ascertainment bias. The reporting did not describe the power calculations or justify a clinically important difference for the reported outcomes. The trial was not registered, so selective reporting cannot be ruled out.

Nonrandomized Studies

Additional single-arm studies have been published since the systematic reviews.[20-25] However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow-up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Subsection Summary: Surgeries That Transfer Lymph Tissue

One RCT with 36 participants was identified evaluating VLNT that uses lymph tissue transfer in patients with breast cancer-related lymphedema. The trial reported reductions in the excess volume of the affected limb and rates of lymphedema-related infections for VLNT plus physical therapy compared with physical therapy alone. Systematic reviews have indicated that most of the remaining available evidence for these procedures comes from uncontrolled studies including fewer than 50 participants each, most of which lacked adequate descriptions of how patients were selected for inclusion. Surgical techniques, the severity of lymphedema, outcomes metrics, and follow-up times varied across studies. Although surgical complications were inconsistently reported, a systematic review of complications estimated that donor-site lymphedema occurs in approximately 2% of surgeries and seroma occurs in approximately

4%. Additional RCTs of physiologic microsurgeries that use lymph tissue transfer with conservative therapy vs conservative therapy alone are needed.

PHYSIOLOGIC MICROSURGERY TO PREVENT LYMPHEDEMA

The purpose of lymphatic physiologic microsurgery simultaneous to lymphadenectomy for breast cancer (e.g., the Lymphatic Microsurgical Preventing Healing Approach [LYMPHA]) is to prevent lymphedema in individuals who are being treated for breast cancer. While recommendations on preventive measures for lymphedema exist, such as avoiding needle sticks, limb constriction, and air travel, most recommendations are based on clinical opinion. A systematic review of preventive measures for lymphedema by Cemal (2011) found strong scientific evidence only for the recommendations to maintain a normal body weight or avoid weight gain and to participate in a supervised exercise regimen.[26]

LYMPHA is a preventive LVA procedure performed during nodal dissection or reconstructive surgery that involves anastomosing arm lymphatics to a collateral branch of an axillary vein.

Systematic Reviews

Jorgensen (2017) reported on a systematic review of prophylactic LVA and shunts for preventing cancer-related lymphedema, not limited to breast cancer.[27] Twelve articles were included in the qualitative analysis (5 specific to breast cancer) and four of those studies (2 specific to breast cancer) were included in a meta-analysis. Jorgensen (2017) performed a meta-analysis of the incidence of lymphedema that included 4 studies (2 specific to breast cancer) with a control group consisting of patients without prophylactic LVA. The relative risk for incident lymphedema was 0.33 (95% CI, 0.19 to 0.56) favoring prophylactic LVA vs control; however, because the incidence of lymphedema varies over time and the follow-up times varied across studies, it is not clear whether it would be appropriate to pool the risk including all time points.

Jorgensen (2017) also performed a risk of bias assessment of the included studies. They noted the following:

- None of the studies had allocation concealment or blinding;
- Only 1 study was randomized;
- None of the studies were registered;
- Only 4 studies had a control group. Selection of the control groups was unclear or a potential source of bias in all 4 controlled studies.

Randomized Controlled Trials

Boccardo (2011) reported on results of an RCT including 46 women referred for axillary dissection for breast cancer treatment between 2008 and 2009 who were randomized to LYMPHA or no preventive surgery (control).[28] All LVA procedures were performed by the same surgeon, reported to be skilled in lymphatic microsurgery. The LVA surgeon was not the same surgeon who performed lymph node dissection. The same axillary dissection treatment was performed in the 2 treatment groups. Lymphedema was diagnosed as a difference in excess volume of at least 100 mL compared with preoperative volume measurements. Lymphedema was diagnosed in 1 (4%) woman in the LYMPHA group and 7 women (30 %) in the control group by 18 months of follow-up. The change in volume with respect to baseline was reportedly higher in the control group than in the LYMPHA group at 1, 3, 6, 12, and 18 months (all $p<0.01$). The trial had several limitations described in Tables 15 and 16. Notably,

the follow-up duration was only 18 months. Methods of randomization and allocation concealment were not described and there was no justification of the sample size. The patients and investigators were not blinded (ie, no sham procedure was performed) and there was no discussion of whether outcome assessors were blinded.

Nonrandomized Studies

Additional single-arm studies have been published since the systematic reviews.[29] However, these studies suffer from the same limitations as the studies included in the systematic reviews and do not capture longer periods of follow up and/or larger populations than the existing studies. Therefore, they are not discussed further.

Section Summary: Physiologic Microsurgery to Prevent Lymphedema

One RCT was identified evaluating LYMPHA to prevent lymphedema in 49 patients referred for axillary dissection for breast cancer. The trial reported that lymphedema developed in 4% of women in the LYMPHA group and 30% in the control group by 18 months of follow-up. Longer follow-up is needed to observe incident lymphedema occurring after 18 months and assess the durability of the procedure. The trial had limitations that could have introduced bias: methods of randomization and allocation concealment were not described, and there was no sham procedure or blinding. Systematic reviews have indicated that most of the remaining available evidence for LYMPHA comes from uncontrolled studies, although two controlled observational studies in women with breast cancer have been performed. Selection of the control group was identified as a potential source of bias in both controlled studies. Outcomes metrics and follow-up times varied across studies. Additional RCTs of LYMPHA are needed and 1 such trial is underway (see NCT03428581).

SURGICAL TREATMENT FOR LIPEDEMA

The purpose of liposuction treatments for lipedema is to provide a treatment option that is an improvement on existing therapies such as complete decongestive therapy.

Systematic Reviews

The Canadian Agency for Drugs and Technology in Health (CADTH) published a rapid response report summarizing the evidence on liposuction for the treatment of lipedema.[30]

The report consists of five nonrandomized, uncontrolled studies that suggest liposuction may be effective in reducing extremity size and complaints related to lipedema. Complaints related to lipedema included spontaneous pain, easy bruising, sensitivity to pressure, impairment in quality of life, restrictions to mobility, edema, feeling of tension, and general impairment. Outcome data was collected via patient self-assessment using tools that have not been validated for lipedema related complaints. Additionally, all studies included were noncomparative, nonrandomized studies and did not include long-term follow up.

Randomized Controlled Trials

No RCTs were identified.

Nonrandomized Studies

Baumgartner (2021) reported the results of a single center study of 60 patients to monitor the 12-year success of liposuction for treating lipedema from the patients' perspective using self-

reported outcomes.[31] Prior to liposuction, 18 patients had Stage I lipedema, and 42 had Stage II. Self-reported outcomes included responses from patients that were asked to indicate to what extent they are currently experiencing the following: spontaneous pain, sensitivity to pressure, edema, bruising, restriction of movement, cosmetic impairment, reduction in quality of life. The results showed significant improvement in scores across all indicators, as well as overall impairment score. There were 37 of the 60 patients that underwent combined decongestive therapy (CDT) with manual lymph drainage (MLD) plus compression garments before surgery. A subgroup analysis was conducted on these patients in order to assess treatment success, and the results showed seven patients required fewer conservative treatments and 10 no longer needed conservative treatment. The authors concluded that these results demonstrate a permanent improvement in lipedema symptoms for patients with Stage I and II lipedema. This study did not include Stage III lipedema patients and relies exclusively on self-reported outcomes.

Section Summary: Surgical Treatment for Lipedema

The existing literature addressing liposuction techniques for the treatment of lipedema only includes nonrandomized, uncontrolled studies with no comparator group. The evidence is lacking and further research with longer-term outcomes and patient selection criteria are needed. High quality randomized trials or comparative studies are needed.

PRACTICE GUIDELINE SUMMARY

NATIONAL LYMPHEDEMA NETWORK

The National Lymphedema Network published a position paper on the diagnosis and treatment of lymphedema in 2011.[32] The paper stated the following on microsurgical procedures:

"Microsurgical and supramicrosurgical (much smaller vessels) techniques have been developed to move lymph vessels to congested areas to try to improve lymphatic drainage. Surgeries involve connecting lymph vessels and veins, lymph nodes and veins, or lymph vessels to lymph vessels. Reductions in limb volume have been reported and a number of preliminary studies have been done, but there are no long-term studies of the effectiveness of these techniques."

INTERNATIONAL SOCIETY OF LYMPHOLOGY

International Society of Lymphology published a consensus document on the diagnosis and treatment of peripheral lymphedema in 2016.[33] The document stated the following on lymphaticovenous (or lymphovenous) anastomoses (LVA):

"LVA are currently in use at multiple centers around the world. These procedures have undergone confirmation of long-term patency (in some cases more than 20 years) and some demonstration of improved lymphatic transport (by objective physiologic measurements of long-term efficacy)."

NATIONAL CANCER INSTITUTE

The NCI Health Professional Version on lymphedema states:[34]

> “Surgery is rarely performed on patients who have cancer-related lymphedema. The primary surgical method for treating lymphedema consists of removing the

subcutaneous fat and fibrous tissue with or without creation of a dermal flap within the muscle to encourage superficial-to-deep lymphatic anastomoses. These methods have not been evaluated in prospective trials, with adequate results for only 30% of patients in one retrospective review. In addition, many patients face complications such as skin necrosis, infection, and sensory abnormalities. The oncology patient is usually not a candidate for these procedures. Other surgical options include the following: Microsurgical lymphaticovenous anastomoses in which the lymph is drained into the venous circulation or the lymphatic collectors above the area of lymphatic obstruction; liposuction; superficial lymphangiectomy; fasciotomy".

SUMMARY

There is enough research to show that liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) to treat lipedema may improve health outcomes in certain populations. Therefore, liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) may be considered medically necessary when policy criteria are met.

There is not enough research to show that liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) to treat lipedema improves health outcomes when policy criteria are not met. Therefore, liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) is considered investigational for patients with lipedema when policy criteria are not met.

There is not enough research to show that physiologic microsurgeries including, but not limited to, lymphatico-lymphatic bypass, lymphatic-venous-lymphatic plasty, lymphovenous bypass, lymphaticovenous anastomosis, autologous lymph node transplantation, and vascularized lymph node transfer improve health outcomes for people with lymphedema. Therefore, physiologic microsurgeries including, but not limited to, lymphatico-lymphatic bypass, lymphatic-venous-lymphatic plasty, lymphovenous bypass, lymphaticovenous anastomosis, autologous lymph node transplantation, and vascularized lymph node transfer is considered investigational for all indications, including but not limited to lymphedema.

There is not enough research to show that lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema (including, but not limited to, the Lymphatic Microsurgical Preventing Healing Approach) in individuals who are being treated for breast cancer improves health outcomes. Therefore, lymphatic physiologic microsurgery performed during nodal dissection or breast reconstruction to prevent lymphedema (including, but not limited to, the Lymphatic Microsurgical Preventing Healing Approach) in individuals who are being treated for breast cancer is considered investigational.

There is not enough research to show that liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) to treat lymphedema improves health outcomes. No clinical guidelines based on research recommend liposuction for the treatment of lymphedema. Therefore, liposuction (including, but not limited to, lipectomy, suction-assisted protein lipectomy, and lymph-sparing liposuction) is considered investigational for patients with lymphedema.

REFERENCES

1. DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *The Lancet Oncology.* 2013;14(6):500-15. PMID: 23540561
2. Meuli JN, Guiotto M, Elmers J, et al. Outcomes after microsurgical treatment of lymphedema: a systematic review and meta-analysis. *Int J Surg.* 2023;109(5):1360-72. PMID: 37057889
3. Coriddi M, Dayan J, Sobti N, et al. Systematic Review of Patient-Reported Outcomes following Surgical Treatment of Lymphedema. *Cancers (Basel).* 2020;12(3). PMID: 32121343
4. Markkula SP, Leung N, Allen VB, et al. Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. *The Cochrane database of systematic reviews.* 2019;2(2):CD011433. PMID: 30779124
5. Tyker A, Franco J, Massa ST, et al. Treatment for lymphedema following head and neck cancer therapy: A systematic review. *American journal of otolaryngology.* 2019;40(5):761-69. PMID: 31174933
6. Carl HM, Walia G, Bello R, et al. Systematic Review of the Surgical Treatment of Extremity Lymphedema. *Journal of reconstructive microsurgery.* 2017;33(6):412-25. PMID: 28235214
7. Lee M, Perry L, Granzow J. Suction Assisted Protein Lipectomy (SAPL) Even for the Treatment of Chronic Fibrotic and Scarified Lower Extremity Lymphedema. *Lymphology.* 2016;49(1):36-41. PMID: 29906063
8. Brorson H. Liposuction in Lymphedema Treatment. *Journal of reconstructive microsurgery.* 2016;32(1):56-65. PMID: 25893630
9. Leung N, Furniss D, Giele H. Modern surgical management of breast cancer therapy related upper limb and breast lymphoedema. *Maturitas.* 2015;80(4):384-90. PMID: 25747119
10. Cornelissen AJM, Beugels J, Ewalds L, et al. Effect of Lymphaticovenous Anastomosis in Breast Cancer-Related Lymphedema: A Review of the Literature. *Lymphatic research and biology.* 2018;16(5):426-34. PMID: 29356596
11. Scaglioni MF, Fontein DBY, Arvanitakis M, et al. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery.* 2017;37(8):947-53. PMID: 28972280
12. Chang DW, Dayan J, Greene AK, et al. Surgical Treatment of Lymphedema: A Systematic Review and Meta-Analysis of Controlled Trials. Results of a Consensus Conference. *Plastic and reconstructive surgery.* 2021;147(4):975-93. PMID: 33761519
13. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. *Plastic and reconstructive surgery.* 2014;133(4):905-13. PMID: 24352208
14. Maruccia M, Elia R, Ciudad P, et al. Postmastectomy upper limb lymphedema: Combined vascularized lymph node transfer and scar release with fat graft expedites surgical and patients' related outcomes. A retrospective comparative study. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2019;72(6):892-901. PMID: 30819649
15. Agko M, Ciudad P, Chen HC. Staged surgical treatment of extremity lymphedema with dual gastroepiploic vascularized lymph node transfers followed by suction-assisted

lipectomy-A prospective study. *Journal of surgical oncology.* 2018;117(6):1148-56. PMID: 29355987
16. Salgarello M, Mangialardi ML, Pino V, et al. A Prospective Evaluation of Health-Related Quality of Life following Lymphaticovenular Anastomosis for Upper and Lower Extremities Lymphedema. *Journal of reconstructive microsurgery.* 2018;34(9):701-07. PMID: 29689576
17. Ozturk CN, Ozturk C, Glasgow M, et al. Free vascularized lymph node transfer for treatment of lymphedema: A systematic evidence based review. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2016;69(9):1234-47. PMID: 27425000
18. Demiri E, Dionyssiou D, Tsimponis A, et al. Donor-Site Lymphedema Following Lymph Node Transfer for Breast Cancer-Related Lymphedema: A Systematic Review of the Literature. *Lymphatic research and biology.* 2018;16(1):2-8. PMID: 29087763
19. Dionyssiou D, Demiri E, Tsimponis A, et al. A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer. *Breast Cancer Res Treat.* 2016;156:73-9. PMID: 26895326
20. Nguyen AT, Suami H, Hanasono MM, et al. Long-term outcomes of the minimally invasive free vascularized omental lymphatic flap for the treatment of lymphedema. *Journal of surgical oncology.* 2017;115(1):84-89. PMID: 27439587
21. Ciudad P, Agko M, Perez Coca JJ, et al. Comparison of long-term clinical outcomes among different vascularized lymph node transfers: 6-year experience of a single center's approach to the treatment of lymphedema. *Journal of surgical oncology.* 2017;116(6):671-82. PMID: 28695707
22. Gennaro P, Gabriele G, Salini C, et al. Our supramicrosurgical experience of lymphaticovenular anastomosis in lymphoedema patients to prevent cellulitis. *European review for medical and pharmacological sciences.* 2017;21(4):674-79. PMID: 28272717
23. Granzow JW, Soderberg JM, Kaji AH, et al. An effective system of surgical treatment of lymphedema. *Annals of surgical oncology.* 2014;21(4):1189-94. PMID: 24522988
24. Granzow JW. Lymphedema surgery: the current state of the art. *Clinical & experimental metastasis.* 2018;35(5-6):553-58. PMID: 29980891
25. Granzow JW, Soderberg JM, Kaji AH, et al. Review of current surgical treatments for lymphedema. *Annals of surgical oncology.* 2014;21(4):1195-201. PMID: 24558061
26. Cemal Y, Pusic A, Mehrara BJ. Preventative measures for lymphedema: separating fact from fiction. *J Am Coll Surg.* 2011;213:543-51. PMID: 21802319
27. Jorgensen MG, Toyserkani NM, Sorensen JA. The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: a systematic review and meta-analysis. *Microsurgery.* 2018;38(5):576-85. PMID: 28370317
28. Boccardo FM, Casabona F, Friedman D, et al. Surgical prevention of arm lymphedema after breast cancer treatment. *Annals of surgical oncology.* 2011;18(9):2500-5. PMID: 21369739
29. Hahamoff M, Gupta N, Munoz D, et al. A Lymphedema Surveillance Program for Breast Cancer Patients Reveals the Promise of Surgical Prevention. *The Journal of surgical research.* 2019;244:604-11. PMID: 29397949
30. Peprah K, MacDougall D. *Liposuction for the Treatment of Lipedema: A Review of Clinical Effectiveness and Guidelines*. Ottawa ON: © 2019 Canadian Agency for Drugs and Technologies in Health., 2019, pp.
31. Baumgartner A, Hueppe M, Meier-Vollrath I, et al. Improvements in patients with lipedema 4, 8 and 12 years after liposuction. *Phlebology.* 2021;36(2):152-59. PMID: 32847472

32. National Lymphedema Network Medical Advisory Committee. The Diagnosis and Treatment of Lymphedema. Position Statement of the National Lymphedema Network 2011. [cited 3/19/2024]. 'Available from:' https://www.lymphnet.org/pdfDocs/nlntreatment.pdf.
33. International Society of Lymphology Executive Committee. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. 2016. [cited 3/19/2024]. 'Available from:' https://journals.uair.arizona.edu/index.php/lymph/article/view/20106.
34. Institute NC. Lymphedema- Health Professional Version. [cited 3/19/2024]. 'Available from:' https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq.

CODES

NOTE: Reporting 38999 for the treatment of lipedema is not appropriate as it is not a disease of the lymphatic system.

Codes	Number	Description
CPT	15832	Excision, excessive skin and subcutaneous tissue (includes lipectomy); thigh
	15833	;leg
	15834	;hip
	15835	;buttock
	15836	;arm
	15837	;forearm or hand
	15838	;submental fat pad
	15839	;other area
	15876	Suction assisted lipectomy; head and neck
	15877	;trunk
	15878	;upper extremity
	15879	;lower extremity
	38999	Unlisted procedure, hemic or lymphatic system
HCPCS	None	

Date of Origin: *June 2020*

Regence

Medical Policy Manual Surgery, Policy No. 224

Ablation for the Treatment of Chronic Rhinitis

Effective: January 1, 2024

Next Review: October 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ablation therapy is proposed as an alternative to medical management for patients with chronic rhinitis symptoms. Ablation therapy includes cryoablation (also known as cryosurgical ablation, cryosurgery, or cryotherapy), radiofrequency ablation, and laser ablation. Ablation therapy is thought to correct the imbalance of autonomic input to the nasal mucosa, thereby reducing nasal antigen responses and vascular hyperreactivity.

MEDICAL POLICY CRITERIA

Cryoablation, radiofrequency ablation, and/or laser ablation for chronic rhinitis (allergic or nonallergic) are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Rhinoplasty, Surgery, Policy No. 12.28
2. Balloon Ostial Dilation for Treatment of Sinusitis, Surgery, Policy No. 153
3. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166

4. Implantable Sinus Devices for Postoperative Use Following Endoscopic Sinus Surgery and for Recurrent Sinonasal Polyposis, Surgery, Policy No. 198
5. Absorbable Nasal Implant for Treatment of Nasal Valve Collapse, Surgery, Policy No. 209

BACKGROUND

Cryosurgical ablation (known as cryosurgery) is proposed as an alternative to medical management for patients with chronic rhinitis symptoms. The procedure involves ablation of tissue in the posterior nasal nerve region, using nitrous oxide to freeze the nasal tissue and cause nerve damage. The procedure is thought to correct the imbalance of autonomic input to the nasal mucosa thereby reducing nasal antigen responses and vascular hyperreactivity.

Medical management is the standard of care for chronic rhinitis. Surgical options such as vidian nerve resection have been investigated for patients with chronic rhinitis refractory to multiple medical therapies, and cryoablation is proposed as a less invasive alternative. Vidian neurectomy has not been widely adopted however, due to the need for general anesthesia, risk of serious adverse events (e.g., dry eyes in up to 25% of patients), and uncertainty about the procedure's long-term benefits.[1]

REGULATORY STATUS

In February 2019, the Clarifix® device was cleared for use in adults with chronic rhinitis through the 510(k) process (K190356).[2] Clearance was based on substantial equivalence to the predicate device, ClariFix (K162608). The only modification to the subject device was an update to the indications for use to include adults with chronic rhinitis.

EVIDENCE SUMMARY

CRYOABLATION

SYSTEMATIC REVIEWS

Desai (2023) published a systematic review of eight studies including 472 patients receiving cryoablation for the treatment of chronic rhinitis.[3] The results of the review indicated a significant reduction in post-treatment scores in all eight included studies. This review included a single RCT and seven additional non-randomized, non-comparative studies, several of which had small sample sizes of 30 or less.

Kompelli (2018) conducted a systematic review of cryoablation for chronic rhinitis, identifying 15 nonrandomized studies enrolling a total of 1266 patients.[4] Across all of the studies, 63% to 95.7% of patients noted improvement in overall symptoms, and no serious adverse events were reported. The authors concluded that although the procedure appeared to be safe and efficacious, methodological weaknesses and heterogeneity limited the strength of conclusions that could be drawn from this body of evidence. In addition to their uncontrolled design, most studies were outdated, published between 1977 and 1997. Only one study, reported by Hwang (2017) used an FDA-cleared device and a validated outcome measure.[5] This study is discussed in detail, along with other recent nonrandomized studies, in the following section.

RANDOMIZED CONTROLLED TRIALS

Stolovitsky (2021) conducted an RCT comparing radiofrequency ablation using the RhinAer device with sham treatment.[6] The trial enrolled 117 adults (age, 18 to 85 years; mean age, 57

years) with chronic rhinitis. Use of medication to treat chronic rhinitis was allowed in both groups. Based on an intention to treat analysis that accounted for all randomized participants, after 3-months follow-up, the proportion of participants with a ≥30% improvement in rTNSS score was higher in the active radiofrequency ablation group (66.7%; 95% CI, 55.1% to 76.9%) than in the sham group (41.0%; 95% CI, 25.6% to 57.9%; p=.01). A similar number of participants in the active (9.1% [7/77]) and sham (12.8% [5/39]) groups increased their medication use during the study (Table 12). The study was unblinded at 3 months, and individuals in the control group were allowed to crossover to the active intervention group.

Takashima (2022) reported 12-month follow-up for patients (n=77) initially randomized to the active intervention group. Study results for the active intervention group at 6- and 12-months are reported in Table 12. Treatment response and mean change from baseline remained stable through 12 months in the active intervention group, while concomitant medication use increased. The study is ongoing, with planned 3-year follow-up.

NONRANDOMIZED STUDIES

Three recent single arm, nonrandomized studies including 149 patients, reported in four publications, have evaluated cryoablation for patients with chronic rhinitis. The largest study (N = 98) was reported by Chang (2020)[7], with 2-year follow-up data on a subset of patients (n = 62) reported by Ow (2021)[8]. Scores on the rTNSS improved significantly over baseline at one month, three months, six months, and nine months, and improvements were sustained for up to two years among those patients who enrolled in the follow-up study. Smaller single-arm studies reported by Hwang (2017)[5] and Gerka Stuyt (2021)[9] also reported improvements in symptoms from baseline. Chang (2020) reported two serious procedure-related adverse events: severe epistaxis occurring on posttreatment day 19 due to a pledget inadvertently left in the nasal cavity from the day of treatment, and one case of mild epistaxis occurring on post-treatment day 36 which resolved with in-office cautery. Of 72 patients completing a telephone questionnaire about procedure-related discomfort, 56 (77.8%) experienced some degree of pain or discomfort. Seventeen patents reported severe headache, five reported severe nasal pain, and two reported severe sinus pain.[7] No serious adverse events were reported in the other studies.

Key limitations of these studies include no comparison groups, nonrandomization, and small sample size. A major limitation was their uncontrolled, open-label design. Additionally, loss to follow-up was high and MCID were not pre-specified for important outcome measures. Randomized controlled trials are needed to confirm improvements in symptom scores observed in nonrandomized studies.

SUMMARY OF EVIDENCE

For individuals with chronic rhinitis who receive cryoablation, the evidence includes nonrandomized studies and a systematic review of nonrandomized trials. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Three single-arm, open-label studies enrolling a total of 149 patients reported improvements from baseline in patient-reported symptom scores up to one year. Sustained improvement for up to two years was observed in one study, however only 62 of 98 patients enrolled in the longer-term follow-up phase. In the largest study, there were two serious procedure-related adverse events (2.0%), and 77.8% of patients who responded to a post-procedure questionnaire reported some degree of pain or discomfort. Study limitations, including lack of a control group

and high loss to follow-up, preclude drawing conclusions from this body of evidence. Randomized controlled trials are needed to confirm improvements reported in nonrandomized studies. A systematic review of 15 nonrandomized studies reported improvements with cryoablation; however, only one study used an approved device and validated outcome measuring, limiting conclusions from this systematic review. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

RADIOFREQUENCY ABLATION

RANDOMIZED CONTROLLED TRIALS

Stolovitsky (2021) conducted an RCT comparing radiofrequency ablation using the RhinAer device with sham treatment.[9,] The trial enrolled 117 adults (age, 18 to 85 years; mean age, 57 years) with chronic rhinitis. Use of medication to treat chronic rhinitis was allowed in both groups (Table 11). Based on an intention to treat analysis that accounted for all randomized participants, after 3-months follow-up, the proportion of participants with a ≥30% improvement in rTNSS score was higher in the active radiofrequency ablation group (66.7%; 95% CI, 55.1% to 76.9%) than in the sham group (41.0%; 95% CI, 25.6% to 57.9%; p=.01). A similar number of participants in the active (9.1% [7/77]) and sham (12.8% [5/39]) groups increased their medication use during the study (Table 12). The study was unblinded at 3 months, and individuals in the control group were allowed to crossover to the active intervention group.

Takashima (2022) reported 12-month follow-up for patients (n=77) initially randomized to the active intervention group.[10] Study results for the active intervention group at 6- and 12-months were shown to be different across treatment and sham groups. Treatment response and mean change from baseline remained stable through 12 months in the active intervention group, while concomitant medication use increased. Follow-up is only reported for the treatment group in this study and excludes the sham group. Additional long-term follow-up with appropriate comparators, such as carefully controlled medical management, are needed.

NONRANDOMIZED STUDIES

The effectiveness of radiofrequency ablation with the RhinAer device has been assessed in two industry-sponsored, nonrandomized, uncontrolled, open-label studies. Both studies included patients with chronic rhinitis. Lee (2022) enrolled 129 patients and reported outcomes of radiofrequency ablation up to 6 months.[11] Ehmer (2021) enrolled 50 patients, 47 of whom had 1-year follow-up; 2-year results were subsequently reported in an extension study of 34 patients.[12, 13] Both studies found symptom response rates and the proportion of responders durable at time points ranging from 3 months to 2 years. Lee et al reported quality of life outcomes using the miniRQLQ, a validated measure with an established MCID of 0.4 points. At 3 and 6 months post-treatment, the mean change in miniRQLQ scores from baseline was -1.6 and -1.8, respectively, indicating clinically important improvement in symptom-related quality of life. These studies are limited by nonrandomized, open-label designs and lack of control groups.

LASER ABLATION

NONRANDOMIZED STUDIES

Krespi (2020) conducted a nonrandomized study evaluating laser ablation for treatment of chronic rhinitis.[14] The study enrolled 32 adults treated with an endoscopic diode laser in an outpatient setting. Duration of follow-up was 3 months. Mean rTNSS was reduced from 6.0 (standard deviation [SD], 0.7) at baseline to 2.3 (SD, 0.4) at 3-month follow-up. Adverse events were not reported. The study had multiple limitations, including the small sample size, uncontrolled design, and duration of follow-up less than 6 months. Randomized studies comparing laser ablation with medical management and with longer follow-up are needed to determine efficacy and safety.

PRACTICE GUIDELINE SUMMARY

No practice guidelines were identified.

SUMMARY

There is not enough research to show that cryoablation, radiofrequency ablation, or laser ablation for chronic rhinitis improves health outcomes. In addition, no practice guidelines recommend cryoablation, radiofrequency ablation, or laser ablation for chronic rhinitis. Therefore, cryoablation, radiofrequency ablation, or laser ablation for chronic rhinitis is considered investigational.

REFERENCES

1. Lieberman P.L.. Chronic nonallergic rhinitis. In: UpToDate, Corren J (Ed), UpToDate, Waltham, MA. [cited 11/14/2023]. Available from: https://www.uptodate.com/contents/chronic-nonallergic-rhinitis.
2. Food & Drug Administration. Clarifix 510(k) Premarket Notification. 2019 (K190356). [cited 11/14/2023]. Available from: https://fda.report/PMN/K190356/19/K190356.pdf.
3. V Desai, G Sampieri, A Namavarian, JM Lee. Cryoablation for the treatment of chronic rhinitis: a systematic review. *J Otolaryngol Head Neck Surg.* 2023;52(1):37. PMID: 37120607
4. AR Kompelli, TA Janz, NR Rowan, SA Nguyen, ZM Soler. Cryotherapy for the Treatment of Chronic Rhinitis: A Qualitative Systematic Review. *Am J Rhinol Allergy.* 2018;32(6):491-501. PMID: 30229670
5. PH Hwang, B Lin, R Weiss, J Atkins, J Johnson. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol.* 2017;7(10):952-56. PMID: 28799727
6. JP Stolovitzky, RA Ow, SL Silvers, NB Bikhazi, CD Johnson, M Takashima. Effect of Radiofrequency Neurolysis on the Symptoms of Chronic Rhinitis: A Randomized Controlled Trial. *OTO Open.* 2021;5(3):2473974x211041124. PMID: 34527852
7. MT Chang, S Song, PH Hwang. Cryosurgical ablation for treatment of rhinitis: A prospective multicenter study. *Laryngoscope.* 2020;130(8):1877-84. PMID: 31566744
8. RA Ow, EM O'Malley, JK Han, KK Lam, DM Yen. Cryosurgical Ablation for Treatment of Rhinitis: Two-Year Results of a Prospective Multicenter Study. *Laryngoscope.* 2021;131(9):1952-57. PMID: 33616224
9. JA Gerka Stuyt, L Luk, D Keschner, R Garg. Evaluation of In-Office Cryoablation of Posterior Nasal Nerves for the Treatment of Rhinitis. *Allergy Rhinol (Providence).* 2021;12:2152656720988565. PMID: 33598336

10. M Takashima, JP Stolovitzky, RA Ow, SL Silvers, NB Bikhazi, CD Johnson. Temperature-controlled radiofrequency neurolysis for treatment of chronic rhinitis: 12-month outcomes after treatment in a randomized controlled trial. *Int Forum Allergy Rhinol.* 2023;13(2):107-15. PMID: 35714267
11. JT Lee, GM Abbas, DD Charous, et al. Clinical and Quality of Life Outcomes Following Temperature-Controlled Radiofrequency Neurolysis of the Posterior Nasal Nerve (RhinAer) for Treatment of Chronic Rhinitis. *Am J Rhinol Allergy.* 2022;36(6):747-54. PMID: 35818709
12. D Ehmer, CM McDuffie, JB McIntyre, et al. Long-term Outcomes Following Temperature-Controlled Radiofrequency Neurolysis for the Treatment of Chronic Rhinitis. *Allergy Rhinol (Providence).* 2022;13:21526575221096045. PMID: 35663498
13. D Ehmer, CM McDuffie, WC Scurry, Jr., et al. Temperature-Controlled Radiofrequency Neurolysis for the Treatment of Rhinitis. *Am J Rhinol Allergy.* 2022;36(1):149-56. PMID: 34382444
14. YP Krespi, KA Wilson, V Kizhner. Laser ablation of posterior nasal nerves for rhinitis. *Am J Otolaryngol.* 2020;41(3):102396. PMID: 31948695

CODES

Codes	Number	Description
CPT	30999	Unlisted procedure, nose
	31242	Nasal/sinus endoscopy, surgical; with destruction by radiofrequency ablation, posterior nasal nerve
	31243	Nasal/sinus endoscopy, surgical; with destruction by cryoablation, posterior nasal nerve
	31299	Unlisted procedure, accessory sinuses
HCPCS	~~C9771~~ None	~~Nasal/sinus endoscopy, cryoablation nasal tissue(s) and/or nerve(s), unilateral or bilateral~~ (Deleted 01/01/2024)

Date of Origin: *December 2021*

Regence

Medical Policy Manual Surgery, Policy No. 230

Devices for Treatment of Benign Prostatic Hyperplasia, Urethral Stricture, and Urethral Stenosis

Effective: January 1, 2024

Next Review: March 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Temporarily implanted nitinol devices (e.g., iTind) have been proposed as a minimally invasive alternative to transurethral resection of the prostate (TURP) to treat symptomatic benign prostatic hyperplasia. The device is temporarily implanted into the obstructed prostatic urethra to facilitate tissue reshaping and improve urine outflow. The implant is typically removed after five to seven days.

Drug-coated balloon catheter systems (e.g., Optilume®) have been proposed as minimally invasive alternatives to TURP, endoscopic management, and urethroplasty to treat obstructive urinary tract symptoms associated with benign prostatic hyperplasia or urethral stricture. The devices utilize balloon catheters to dilate the urethra or prostate lobes and deliver paclitaxel indicated to prevent future obstructive urinary symptoms.

MEDICAL POLICY CRITERIA

I. The use of a temporarily implanted nitinol device (e.g., iTind) is considered **investigational** for all indications, including treatment of lower urinary tract symptoms due to benign prostatic hyperplasia.

II. The use of a drug-coated balloon catheter system (e.g., Optilume® BPH Catheter System) is considered **investigational** for all indications, including treatment of obstructive urinary symptoms associated with benign prostatic hyperplasia.

III. The use of a drug-coated balloon catheter system (e.g., Optilume® Urethral Drug Coated Balloon) is considered **investigational** for all indications, including treatment of obstructive urinary symptoms associated with anterior urethral stricture.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Transurethral Water Vapor Thermal Therapy and Transurethral Water Jet Ablation (Aquablation) of the Prostate, Surgery Policy No. 210

BACKGROUND

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a common disorder among older individuals that results from hyperplastic nodules in the periurethral or transitional zone of the prostate. The clinical manifestations of BPH include increased urinary frequency, nocturia, urgency or hesitancy to urinate, and a weak stream when urinating. The urinary tract symptoms often progress with worsening hypertrophy and may lead to acute urinary retention, incontinence, renal insufficiency, and/or urinary tract infection. BPH prevalence increases with age and is present in more than 80% of individuals age 70 to 79 years.[1]

Two scores are widely used to evaluate BPH-related symptoms: the American Urological Association Symptom Index (AUASI) and the International Prostate Symptom Score (IPSS). The AUASI is a self-administered seven-item questionnaire assessing the severity of various urinary symptoms.[2] Total AUASI scores range from 0 to 35, with overall severity categorized as mild (≤7), moderate (8-19), or severe (20-35). The IPSS incorporates questions from the AUASI and a quality of life question or a "Bother score."[3]

Benign prostatic hyperplasia does not necessarily require treatment. The decision on whether to treat BPH is based on an assessment of the impact of symptoms on quality of life along with the potential side effects of treatment. For patients with moderate-to-severe symptoms (e.g., an AUASI score of ≥8), bothersome symptoms, or both, a discussion about medical therapy is reasonable. Benign prostatic hyperplasia should generally be treated medically first. Available medical therapies for BPH-related lower urinary tract dysfunction include α-adrenergic blockers (e.g., alfuzosin, doxazosin, tamsulosin, terazosin, silodosin), 5α-reductase inhibitors (e.g., finasteride, dutasteride), combination α-adrenergic blockers and 5α-reductase inhibitors, anti-muscarinic agents (e.g., darifenacin, solifenacin, oxybutynin), and phosphodiesterase-5 inhibitors (e.g., tadalafil).[1] In a meta-analysis of both indirect comparisons from placebo-controlled studies (n=6333) and direct comparative studies (n=507), Djavan (1999) found that the IPSS improved by 30% to 40% and the Qmax score (mean peak urinary flow rate) improved by 16% to 25% in individuals assigned to α-adrenergic blockers.[4] Combination therapy using an α-adrenergic blocker and 5α-reductase inhibitor has been shown to be more effective for improving IPSS than either treatment alone, with median scores improving by more than 40% over one year and by more than 45% over four years.

Patients who do not have sufficient response to medical therapy, or who are experiencing significant side effects with medical therapy, may be referred for surgical or ablative therapies. The American Urological Association (AUA) recommends surgical intervention for patients who have "renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with lower urinary tract symptoms (LUTS) attributed to BPH refractory to and/or unwilling to use other therapies."[5] Transurethral resection of the prostate (TURP) is generally considered the reference standard for comparisons of BPH procedures.[6] In the perioperative period, TURP is associated with risks of any operative procedure (e.g., anesthesia risks, blood loss). Although short-term mortality risks are generally low, a large prospective study with 10,654 patients by Reich (2008) reported the following short-term complications: "failure to void (5.8%), surgical revision (5.6%), significant urinary tract infection (3.6%), bleeding requiring transfusions (2.9%), and transurethral resection syndrome (1.4%)."[7] Incidental carcinoma of the prostate was diagnosed by histologic examination in 9.8% of patients. In the longer term, TURP is associated with an increased risk of sexual dysfunction and incontinence.

The use of the iTind temporarily implanted nitinol device has been investigated as a minimally invasive treatment for lower urinary tract symptoms associated with BPH. With the use of a rigid cystoscope, the device is temporarily implanted into the obstructed prostatic urethra where three double intertwined nitinol struts configured in a tulip shape gradually expand.[8] The resulting circumferential force facilitates tissue reshaping via ischemic necrosis of the mucosa, resulting in urethral expansion and prostatic incisions that function as longitudinal channels to improve urine outflow.[9] The implant is typically removed after five to seven days of treatment. A distal nylon wire facilitates device retrieval which may be approached using a snare to pull the device into either a cystoscope sheath or an open-ended silicone catheter (20-22 French units [Fr]).[10] The first-generation TIND device had one extra strut and a pointed tip covered by a soft plastic material.

The Optilume® BPH Catheter System is a drug and device combination that consists of two catheters: a non-drug coated catheter for pre-dilation (Optilume® BPH Prostatic Pre-dilation Catheter) and a paclitaxel coated catheter (Optilume® BPH Prostatic Dilation Drug Coated Balloon Catheter).[11] The Pre-dilation Catheter is used to initiate a commissurotomy between the lateral lobes of the prostate. The Drug Coated Balloon Catheter further dilates and completes the commissurotomy then transfers paclitaxel to the pre-dilated prostatic urethra and anterior commissure. The increase in cross-sectional area of the prostatic urethra from the anterior commissurotomy permits increased urine flow. Transfer of the paclitaxel from the balloon surface to the dilated area inhibits cell proliferation and maintains urethral patency.

URETHRAL STRICTURE AND STENOSIS

Urethral stricture is the chronic fibrosis and narrowing of the urethral lumen caused by acute injury, inflammatory conditions, and interventions including urethral instrumentation, surgery, and prostate cancer treatment.[12] Urethral stricture is the preferred term for abnormal narrowing of the anterior urethra, and narrowing of the posterior urethra is referred to as stenosis. Urethral stricture symptoms are often non-specific and overlap with other common conditions including LUTS and UTI. Patients with urethral stricture most often present with decreased urinary stream and incomplete bladder emptying but may also have UTI, epididymitis, rising post-void residual, decreased ejaculation force, urinary spraying, or dysuria. In high income countries, the most common cause of urethral stricture is idiopathic (41%)

followed by medical treatments (35%). In low- and middle-income countries, trauma is the most common cause of urethral stricture (36%).

Initial management of urethral stricture includes assessing patient medical history, physical examination, and urinalysis.[12] A combination of patient reported measures, uroflowmetry, and ultrasound post-void residual assessment are recommended for initial evaluation of suspected urethral stricture. Urethro-cystoscopy, retrograde urethrography, voiding cystourethrography, or ultrasound urethrography are recommended for diagnosis of urethral stricture. For urgent management of urethral stricture, urethral endoscopic management (e.g., urethral dilation, direct visual internal urethrotomy [DVIU]) or immediate suprapubic cystostomy are recommended. For non-urgent strictures, the length and location of the stricture should be determined to guide treatment. For initial treatment of short (less than two centimeters [cm]) bulbar urethral strictures, urethral dilation, DVIU, or urethroplasty are recommended.

Urethroplasty, instead of repeated endoscopic management, is recommended for management of recurrent anterior urethral strictures following failed dilation or DVIU. Urethral dilation and DVIU are also recommended for recurrent bulbar urethral strictures that are less than three cm in length. Urethral dilation and DVIU have similar long-term outcomes, with success ranging from 35-70% for short strictures. These endoscopic treatments have high success rates for strictures less than one cm but very low success rates for strictures over two cm. Urethroplasty has a higher long-term success rate than endoscopic treatment (80-95%), but American Urological Association (AUA) guidelines recommend weighing success against the increased anesthesia requirement and higher morbidity of urethroplasty.

The Optilume® Urethral Drug Coated Balloon is a 0.97 mm over-the-wire guidewire compatible catheter with a dual lumen design and a tapered, atraumatic tip.[13] The Optilume® Drug Coated Balloon is used to exert radial force to dilate narrow urethral strictures. Using a guidewire, the catheter is inserted into the area of the urethra that has a stricture, and the balloon is inflated to mechanically dilate the urethra and improve urine flow. During balloon inflation, paclitaxel is transferred from the balloon to the urethra to prevent stricture recurrence.

REGULATORY STATUS

In April 2019, the iTind System (Olympus; previously, Medi-Tate Ltd., Hadera, Israel) was granted a de novo 510(k) classification by the U.S. Food and Drug Administration (FDA) (DEN190020; product code: QKA).[14] The new classification applies to this device and substantially equivalent devices of this generic type (e.g., K210138). The iTind System is intended for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 years and older.

In September 2021, the Optilume® Urethral Drug Coated Balloon (Urotronic, Inc.) received premarket approval from the U.S. FDA (P210020, product code: QRH).[13] The Optilume® Urethral Drug Coated Balloon is indicated for the treatment of obstructive urinary symptoms associated with anterior urethral stricture in adult males with urethral stricture less than or equal to three cm in length.

In June 2023, the Optilume® BPH Catheter System (Urotronic, Inc.) received premarket approval by the U.S. FDA (P220029; product code: QXB).[11] The Optilume® BPH Catheter System is indicated for the treatment of obstructive urinary symptoms associated with BPH in males age 50 years and older.

EVIDENCE SUMMARY

TEMPORARILY IMPLANTED NITINOL DEVICE

Clinical Context and Therapy Purpose

The purpose of temporarily implanted nitinol devices in patients who have lower urinary tract symptoms due to BPH is to provide a treatment option that is an alternative to or an improvement on existing therapies such as medical management, transurethral resection of the prostate (TURP), or prostatic urethral lift (PUL).

Both short-term (up to 12 months) and long-term (12 months and longer) outcomes should be assessed. Treatment-related morbidity can also be assessed in the immediate post-procedure period.

Some validated patient-reported scales are summarized in Table 1.

Table 1. Patient-Reported Health Outcome Measures Relevant to Benign Prostatic Hyperplasia

Measure	Outcome Evaluated	Description	Clinically Meaningful Difference (If Known)
Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD)[15]	Ejaculatory function and quality of life	Patient-administered, 4-item scale. Symptoms rated as absent (15) to severe (0). QOL assessed as no problem (0) to extremely bothered (5).	NR
Sexual Health Inventory for Men (SHIM)[16]	Erectile function	Patient-administered, 5-item scale. Erectile dysfunction rated as severe (1-7), moderate (8-11), mild to moderate (12-16), or mild (17-21). Fewest symptoms present for patients with scores 22-25.	5-point change[17]
American Urological Association Symptom Index (AUASI); International Prostate Symptom Score (IPSS)[1, 3, 18]	Severity of lower urinary tract symptoms	Patient-administered, 7-item scale. Symptoms rated as mild (0-7), moderate (8-19), or severe (20-35). IPSS asks an additional question, rating QOL as delighted (0) to terrible (6).	• Minimum of 3-point change[1, 18] • Minimum of 30% change[19]
Benign Prostatic Hyperplasia Impact Index (BII)[2]	Effect of urinary symptoms on health domains	Patient-administered, 4-item scale. Symptoms rated as absent (0) to severe (13).	Minimum of 0.4-point change[18]

QOL: quality of life; NR: not reported.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies concerning older versions of the technology that are no longer commercially marketed were excluded, including Bertolo (2015)[20] and Porpiglia (2018).[21]

Review of Evidence

Systematic Reviews

In 2021, Franco published a Cochrane network meta-analysis assessing the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with BPH.[22] Twenty-seven trials representing 3017 men were included through February 2021. Compared to TURP at short-term follow-up, temporary implantable nitinol devices (TIND) may result in worse urologic symptoms scores (mean difference [MD] of IPSS score, 7.5; 95% CI, 0.68 to 15.69; low-certainty evidence) and little to no difference in quality-of-life scores (MD, 0.87; 95% CI, -1.04 to 2.79; low-certainty evidence).

Randomized Controlled Trials

Chughtai (2021) published the results of a multicenter, single-blinded RCT of the iTind implant compared to sham for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia.[23] . Fifty-seven participants received sham treatment, and out of 128 participants randomized to receive iTind, 10 did not undergo the procedure. The primary endpoint was the response rate, defined as the percentage of patients achieving a reduction of at least three points on the IPSS scale at three months. Patients were unblinded to their treatment after the 3-month follow-up visit. Mean patient age was 61.1 years and baseline characteristics were similar between groups, except for a higher Charlson Comorbidity Index score among iTind recipients (2.52 vs. 1.26; p<0.001). While a significantly higher proportion of patients treated with iTind achieved the primary endpoint compared to sham at three months (78.6% vs. 60%; p=.029), changes in overall IPSS, IPSS QoL, Qmax, SHIM, and International Index of Erectile Function (IIEF) scores were not statistically different between groups. Patients treated with iTind were followed through 12 months. Of 78 iTind subjects in the per-protocol population, a mean reduction of 9.25 points on the IPSS was found at 12 months, suggesting durability of treatment. A total of 16 serious adverse events among 10 subjects was reported within 0-30 days in the iTind group compared to two events in two subjects in the sham group. In the iTind group, a total of five serious adverse events were classified as device- or

procedure-related, including urinary retention (n=2), urinary tract infection (n=2) and sepsis (n=1). Six individuals (4.7%) had an alternative BPH surgery during 12-month follow-up due to deterioration of symptoms. An additional six participants (4.7%) resumed medication for symptomatic BPH. An RCT comparing the iTind device to the UroLift prostatic urethral lift (PUL) procedure is ongoing (NCT04757116).

Using questionnaire data from the Chughtai (2021)[23] study, Elterman (2023)[24] reported the effect of iTind on sexual function. Patient-reported sexual health data from subjects who completed study visits at 3 and 12 months, and who were not taking medication to treat BPH were included. Using primarily SHIM scores, the study found no evidence of decrease in sexual function due to iTind at 12 months. Limitations of the study include that the total number of study subjects that provided data and the n-values of the subgroups (stratified by age, prostate volume, and questionnaire scores) were not specified. Another major limitation was that the 12-month comparison was between baseline and 12-month scores within the iTind treatment arm, with no comparison between the iTind treatment and the sham treatment at 12-months.

Single-Arm Studies

MT-02 Cohort

81 subjects with lower urinary tract symptoms due to BPH were implanted with the second-generation iTind device and followed for up to three years.[25-27] Mean (SD) patient age was 65 (8.9) years with mean prostate volume 40.5 (12.25) milliliter (mL), Qmax 7.3 (2.6) mL/s, and IPSS score 22.5 (5.6). Devices were retrieved at a mean of 5.9 (1.1) days after implantation and no intraoperative complications were reported. At the 6-month and 12-month visits, 85.2% and 88.9% of treated patients reported a 3-point or greater improvement in IPSS, respectively. Compared to baseline, none of the 61 sexually active participants who completed a 12-month, two-item questionnaire reported sexual or ejaculatory dysfunction. Statistically significant improvements in total IPSS, Qmax, IPSS QoL, and post-void residual (PVR) volume were observed through 36 months. Clavien-Dindo grade I, II, and IIIa treatment-related adverse events were reported in 33 (41%), 5 (6.2%), and 8 (9.9%) patients within the first month post-treatment, respectively. Most common adverse events were hematuria (12.3%), urinary urgency (11.1%), acute urinary retention (9.9%), and pain (9.9%). No further adverse events were reported during long-term follow-up. From baseline through 36 months, 12 (14.8%) patients were considered treatment failures, of which seven were later found to have obstructive median lobes (p<.0001). Subsequent drug therapy was required in five (6.2%) patients and eight (8.6%) underwent surgical retreatment via TURP or laser. Sexually active patients who completed a two-item questionnaire reported no sexual or ejaculatory dysfunction through three years.

MT-06 Cohort

De Nunzio (2021) reported six-month interim outcomes for 70 subjects with lower urinary tract symptoms due to BPH seeking to preserve ejaculatory function who were implanted with the second-generation iTind device.[28] Mean patient age was 62.3 years with mean prostate volume 37.68 mL, Qmax 7.3, and IPSS urinary symptoms score 21.2. At six months, statistically significant improvements were seen in IPSS urinary symptoms, IPSS QoL, Qmax, and MSHQ-EjD. No significant changes in PVR volume, SHIM total score, or ISI total score were reported. Clavien-Dindo grade I, IIIa, and IIIb treatment-related adverse events were reported in 53 (75.7%), 3 (4.3%), and 1 (1.4%) patient(s), respectively. The most common

adverse events were transient hematuria (18.6%), dysuria (17%), urinary urgency (12.8%), and pain (11.4%). Follow-up is planned for three years.

Section Summary: Temporarily Implanted Nitinol Device

The prospective, international, multicenter, single-arm MT-02 prospective study of the iTind device has reported statistically significant improvements in total IPSS score, IPSS QoL score, Qmax, and PVR volume through three years. The subsequent single-arm MT-06 study enrolling men desiring to preserve ejaculatory function reported no significant change in the SHIM total score and a statistically significant improvement on the MSHQ-EjD questionnaire at six months. One RCT comparing the iTind device to sham treatment reported an improvement of at least three points on the IPSS scale at three months in 78.6% versus 60% of participants, respectively (p=.029). However, changes in overall IPSS, IPSS QoL, Qmax, SHIM, and IIEF scores were not significantly different between groups. Major limitations of the RCT include high loss to follow-up (~30% in each treatment arm) and short duration of follow-up. A follow-up study reported no evidence of decrease in sexual function at 12 months due to iTind, but evidence was limited by lack of comparison between the treatment arms. One network meta-analysis compared the safety and efficacy of various minimally-invasive treatments for lower urinary tract symptoms associated with BPH, finding that iTind may result in worse urologic symptoms scores compared to TURP at short-term follow-up. No studies have directly compared iTind to established alternatives. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

OPTILUME® BPH CATHETER SYSTEM

Clinical Context and Therapy Purpose

Use of a drug-coated balloon catheter system in patients who have obstructive urinary symptoms associated with BPH is to provide a treatment alternative to, or an improvement on, existing therapies such as pharmacological therapies, prostate ablation (e.g., laser, vapor), PUL, prostatectomy, or TURP.

Both short-term (up to 12 months) and long-term (12 months and longer) outcomes should be assessed. Treatment-related morbidity can also be assessed in the immediate post-procedure period. Some validated patient-reported scales are summarized in Table 1.

Randomized Controlled Trials

Kaplan (2023) published results of the PINNACLE double-blind, sham-controlled, multi-center RCT that assessed the Optilume® BPH Catheter System. 148 male participants 50 years or older, with symptomatic BPH and a prostate size between 20 and 80 grams, were randomized to receive the active treatment (n=100) or sham treatment (n=48). Sham treatment consisted of rigid cystoscopy followed by insertion of a sheathed (21F) Optilume® BPH Predilation Catheter that was not inflated. The timing, analgesia, and anesthesia protocols were the same in active and sham treatment groups. Participants and evaluators were blinded through one-year follow-up. Average improvement in IPSS from baseline to one year was significantly greater with active treatment (11.5±7.8) than sham treatment at three months (8.0±8.3), with an estimated difference of 3.4 between groups (95% CI, 0.6 to 6.2; p=0.008). However, this result was not significant when a 25% super-superiority margin was used (p=0.18). IPSS improved on average by 49% from baseline to one year in the active treatment group (95% CI, 42.7% to 55.4%), which met the prespecified performance goal of 30% (p<0.001). Significantly

more participants experienced at least a 30% improvement in IPSS at one year when compared to the sham group at three months (76.6% [66 of 96] versus 52.1% [25 of 48], p=0.003). The change in Qmax from baseline also significantly favored Optilume® BPH at 12 months over sham at three months (+9.7±10.1 versus +5.5±7.4 mL/s, p=0.009). Five serious treatment-related events occurred. Four post-procedural hematuria events that required cystoscopic management or extended observation, which resolved without sequelae, occurred. One event of urethral false passage required extended catheterization. Common nonserious adverse events that occurred in the Optilume® BPH arm, regardless of relatedness, included hematuria (40% [39 of 98]), urinary tract infection (14% [14 of 98], dysuria (9.2% [9 of 98]), urge/mixed incontinence (8.2% [8 of 98]), mild stress incontinence (7.1% [7 of 98]), bladder spasms (6.1% [6 of 98]), elevated PSA (6.1% [6 of 98]), and urinary urgency (6.1% [6 of 98]). This study is limited by different follow-up times for the Optilume BPH and sham treatment groups and eligibility criteria were limited to men with prostates below 80 grams.

Single-Arm Studies

Kaplan (2021) published one-year outcomes of the EVEREST-I single-arm study that evaluated the safety and efficacy of the Optilume® BPH Catheter System. Participants were greater than 50 years old with moderate to severe LUTS secondary to BPH, peak urinary flow rate of 5 to 15 mL/s, prostatic urethra length 30 to 55 millimeters, and prostate volume 20 to 80 grams (n=80). After treatment, participants were followed up at time of Foley catheter removal, two weeks, 30 days, and 3, 6, and 12 months after treatment. The primary endpoint was the proportion of subjects with greater than or equal to 40% improvement in IPSS. 75 participants completed the one-year follow-up. At three months and one year, 81% of participants experienced greater than or equal to 40% improvement in IPSS from baseline (90% CI, 72.6 to 88.1). Mean IPSS was 22.3 at baseline and 7.9 at one year. Qmax improved from 10.9 to 18.4 mL/s, and IPSS-measured quality of life improved from 4.6 to 1.3 at one-year follow-up. 113 adverse events were reported. The most frequent treatment-related adverse events were post-procedural hematuria (15.0%), postoperative urinary retention (13.8%), urinary incontinence (13.8%), urinary tract infection (8.8%), ejaculation disorder (8.8%), and dysuria (7.5%). Most postoperative urinary retention events were caused by clots blocking the Foley catheter outlet, and greater than 90% (11 of 12) events resolved within one week. Interim data analysis revealed a worse safety profile with use of the large diameter balloon catheter, including higher rates of bleeding and incontinence. As a result, this device size option was removed for the last 31 participants treated in the study. This study is limited by lack of a control group, and longer-term follow-up is necessary to determine treatment durability.

Section Summary: Optilume® BPH Catheter System

Data from one RCT and one single-arm study suggest that the Optilume® BPH Catheter System may improve peak urinary flow rate and symptoms associated with benign prostatic hyperplasia, but symptom scores did not reach statistical significance in the RCT. There are multiple limitations of the data including lack of control group in one study, concerns about serious adverse events (hematuria was most common), and the treatment may not be generalizable for prostates above 80g. Long-term follow-up is also needed to determine durability of this treatment. No studies have directly compared the Optilume® BPH Catheter System to established treatments. There is also a lack of data on paclitaxel in tissues at long-term follow-up. There is not yet enough evidence that the technology results in an improvement in the net health outcome.

OPTILUME® DRUG COATED URETHRAL DILATION CATHETER

Clinical Context and Therapy Purpose

Use of a drug-coated urethral dilation catheter in male patients who have obstructive urinary symptoms associated with anterior urethral stricture is to provide a treatment alternative to, or an improvement on, existing therapies such as urethral dilation with an uncoated balloon catheter, endoscopic management or urethroplasty. Relevant outcomes include patient-reported measures such as the AUASI and IPSS to assess symptoms, uroflowmetry to determine severity of obstruction, and evaluation of stricture diameter with urethroscopy, retrograde urethrography, or ultrasound urethrography.

Randomized Controlled Trials

Elliot (2022) published one-year outcomes from the ROBUST III multi-center, single-blind trial that evaluated the safety and efficacy of the Optilume® DCB for treatment of recurrent anterior urethral strictures.[29] Participants were adult males with anterior urethral strictures less than or equal to 12Fr in diameter and less than or equal to three cm long, who had at least two prior endoscopic treatments, IPSS score greater than or equal to 11, and maximum urine flow rate less than 15 mL per second. The primary efficacy endpoint was anatomical success, defined as diameter greater than or equal to 14Fr determined by urethral cystoscopy or calibration at six months. 127 participants were randomized 2:1 to treatment and control groups and were blinded to treatment through six months. Endoscopic control treatments were the standard of care at each site and included treatment with an uncoated balloon catheter, direct visual internal urethrotomy (DVIU), serial diltion with urethral sounds, or a combination of these treatments. Post-procedure follow-up occurred at Foley catheter removal (two to five days in both groups), 30 days, three months, six months, and one year. At six months, anatomical success was 75.6% in the DCB group and 26.8% in the control group, with an estimated difference of 44.4% ($p<0.0001$). Freedom from repeat intervention through one year was significantly higher for the DCB group than the control group (83.2% versus 21.7%, $p<0.0001$). From baseline to 30 days, both groups experienced a significant increase in Qmax, IPSS, and IPSS quality of life scores. However, the control group experienced deterioration in all of these categories by one year while the significant improvements remained at one year in the DCB group. Adverse event types and rates were similar between groups, except that the DCB group had higher rates of post-procedure mild hematuria and dysuria (11.4% versus 2.1% for both event types). A limitation of this study is that Optilume DCB was compared to dilation and DVIU, so it is unknown how this treatment compares to urethroplasty, which is considered standard of care for urethral stricture. The authors also acknowledged that these early positive results could be impacted by surgeons dilating the urethra with Optilume, but in this study the immediate post-treatment diameter was similar between treatment groups.

Single-Arm Studies

DeLong (2022) published interim, one-year results from the ROBUST II study that investigated the safety and efficacy of a paclitaxel-coated balloon for treatment of recurrent urethral strictures. The study included 16 adult males with a single anterior urethral stricture less than or equal to three cm in length, and who had at least two prior stricture treatments.[30] The primary safety endpoint was the rate of treatment-related serious complications 90 days after treatment. Efficacy outcomes were symptomatic assessments (IPSS), erectile function (IIEF), Qmax, and anatomic success defined by the ability to pass a 16F flexible cystoscope through the treatment site. Anatomic success was achieved for 73% of participants at six months.

Average IPSS improved from 18.4 to 6.0 at one year (p<0.001). Qmax improved from 6.9 mL/s to 20.8 mL/s (p<0.001). There was no change in IIEF. Four participants received additional treatment for urethral stricture within one year. No treatment-related serious complications occurred. This study is limited by small sample size and lack of a comparison group.

Virasoro (2020) published interim, one-year results from the ROBUST I study that enrolled 53 males with bulbar urethral strictures less than or equal to two cm with one to four prior endoscopic treatments.[31] All participants were treated with mechanical balloon dilation or DVIU prior to drug-coated balloon treatment. 46 participants completed the 12 month follow up. The preliminary efficacy endpoint was anatomic success, defined by urethral lumen greater than or equal to 14Fr at 12 months. The primary safety endpoint was serious complications through 90 days. Anatomic success was achieved in 32 of 46 participants (70%; 95% CI 54 to 82%) at 12 months. The 14 failures included seven cystoscopic recurrences, five retreatments, and two patients who exited the study early due to symptom recurrence. There were no serious adverse events related to the treatment within 90 days and no serious adverse events related to the procedure at 12 months. Follow-up is planned through five years post-treatment for the ROBUST I study, and published two- and three-year outcomes are discussed below.

Mann (2021) published two-year outcomes of the ROBUST I study in which 46 participants completed the 24-month follow-up.[32] The primary efficacy endpoint was greater than or equal to 50% improvement in IPSS at 24 months, and the primary safety endpoint was serious urinary adverse events. 43% of participants had undergone at least one or more previous urethral dilation procedure. The primary endpoint was achieved in 32 of 46 participants (70%), and baseline IPSS improved from a mean of 25.2 to 6.9 at 24 months (p<0.0001). There were no treatment-related serious adverse events at 24 months. There were 71 mild-to-moderate adverse events, most frequently: urinary tract infection (17%), fever (8%), dysuria (7%), acute urinary retention (6%), and headache (6%).

Virasoro (2022) published three-year outcomes of ROBUST I which included results for 33 participants who completed the three-year follow-up visit and 10 patients who experienced clinical failures at previous visits (n=43).[33] The primary efficacy endpoint, greater than or equal to 50% reduction in IPSS, occurred in 29 of 43 participants (67%). Average IPSS improved from 25.2 at baseline to 5.5 at three years (p<0.0001). 33 of 43 participants (77%) did not require retreatment. Significant improvements were also observed in quality of life, urinary flow rate, and post-void residual urine volume. Similar to previous results at earlier follow-ups, device-related adverse events were mild or moderate and resolved quickly after onset. There were no serious treatment-related adverse events. The ROBUST I study is limited by lack of a comparator group and small sample size.

Section Summary: Optilume® Drug Coated Urethral Dilation Catheter

Data from one RCT and two single-arm studies reported that the Optilume® Urethral Drug Coated Balloon significantly reduced stricture recurrence, increased urinary flow rate, and improved urinary symptom scores. The RCT reported significantly greater improvement with the drug-coated balloon than with endoscopic management. Drug-coated balloon treatment was more durable than endoscopic treatment at one year follow-up. Limitations of the RCT are that most participants had bulbar urethral strictures, so it is unknown whether the treatment is generalizable to all types of urethral strictures; hematuria was more common with the drug-coated balloon; and this treatment has not been compared to urethroplasty which is most successful for treating recurrent strictures. In these studies, long-term follow-up beyond one-

year occurred only in small single-arm studies. Further, additional long-term data on paclitaxel in tissues is needed to assess device safety. There is not yet enough evidence that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN UROLOGICAL ASSOCIATION

In 2021, the American Urological Association (AUA) published guidelines on the surgical evaluation and treatment of lower urinary tract symptoms attributed to benign prostatic hyperplasia.[5] These guidelines do not address the use of temporarily implanted nitinol devices or drug-coated balloon catheters.

In 2023, the AUA published an amendment to the 2016 guidelines for the treatment of urethral stricture disease.[12] These guidelines state, “Surgeons may offer urethral dilation or direct visual internal urethrotomy, combined with drug-coated balloons, for recurrent bulbar urethral strictures less than three cm in length (Conditional Recommendation; Evidence Level: Grade B).”

SUMMARY

TEMPORARY IMPLANTED NITINOL DEVICES

There is not enough research to show that temporarily implanted nitinol devices (e.g., iTind) work better than established treatments to improve health outcomes for people with benign prostatic hyperplasia. No clinical guidelines based on research recommend temporarily implanted nitinol devices to treat benign prostatic hyperplasia. Therefore, temporarily placed nitinol devices (e.g., iTind) are considered investigational for all indications, including but not limited to treatment of symptoms due to benign prostatic hyperplasia.

OPTILUME® BENIGN PROSTATIC HYPERPLASIA CATHETER SYSTEM

There is not enough research to show that drug-coated balloon catheters (e.g., Optilume® BPH) work better than established treatments to improve health outcomes for people with benign prostatic hyperplasia. No clinical guidelines based on research recommend drug-coated balloon catheter systems to treat benign prostatic hyperplasia. Therefore, drug-coated balloon catheter systems (e.g., Optilume® BPH) are considered investigational for all indications, including but not limited to treatment of symptoms due to benign prostatic hyperplasia.

OPTILUME® URETHRAL DRUG COATED BALLOON

There is not enough research to show that drug-coated balloon catheters (e.g., Optilume® Urethral Drug Coated Balloon) work better than established treatments to improve health outcomes for people with urethral stricture or stenosis. The AUA recommends drug-coated balloons conditionally and only in combination with established endoscopic management of urethral strictures. Therefore, drug-coated balloon catheter systems (e.g., Optilume® Urethral Drug Coated Balloon) are considered investigational for all indications, including but not limited to treatment of symptoms due to urethral stricture or stenosis.

REFERENCES

1. AV Sarma, JT Wei. Clinical practice. Benign prostatic hyperplasia and lower urinary tract symptoms. *N Engl J Med.* 2012;367(3):248-57. PMID: 22808960
2. MJ Barry, FJ Fowler, Jr., MP O'Leary, RC Bruskewitz, HL Holtgrewe, WK Mebust. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. *Med Care.* 1995;33(4 Suppl):AS145-55. PMID: 7536866
3. P O'Leary M. Validity of the "bother score" in the evaluation and treatment of symptomatic benign prostatic hyperplasia. *Rev Urol.* 2005;7(1):1-10. PMID: 16985801
4. B Djavan, M Marberger. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol.* 1999;36(1):1-13. PMID: 10364649
5. LB Lerner, KT McVary, MJ Barry, et al. Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART II-Surgical Evaluation and Treatment. *J Urol.* 2021;206(4):818-26. PMID: 34384236
6. HE Foster, MJ Barry, P Dahm, et al. Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline. *J Urol.* 2018;200(3):612-19. PMID: 29775639
7. O Reich, C Gratzke, A Bachmann, et al. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol.* 2008;180(1):246-9. PMID: 18499179
8. D Amparore, S De Cillis, G Volpi, et al. First- and Second-Generation Temporary Implantable Nitinol Devices As Minimally Invasive Treatments for BPH-Related LUTS: Systematic Review of the Literature. *Curr Urol Rep.* 2019;20(8):47. PMID: 31278441
9. C Fiori, S De Cillis, G Volpi, et al. iTIND for BPH: Technique and procedural outcomes: A narrative review of current literature. *Turk J Urol.* 2021;47(6):470-81. PMID: 35118965
10. D Balakrishnan, P Jones, BK Somani. iTIND: the second-generation temporary implantable nitinol device for minimally invasive treatment of benign prostatic hyperplasia. *Ther Adv Urol.* 2020;12:1756287220934355. PMID: 32655690
11. U.S. Food and Drug Administration (FDA) Summary of Safety and Effectiveness Data. Drug Coated Prostatic Dilation Catheter for Benign Prostatic Hyperplasia. June 30, 2023. [cited 11/13/2023]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf22/P220029B.pdf.
12. H Wessells, A Morey, L Souter, L Rahimi, A Vanni. Urethral Stricture Disease Guideline Amendment (2023). *J Urol.* 2023;210(1):64-71. PMID: 37096574
13. U.S. Food and Drug Administration (FDA) Summary of Safety and Effectiveness Data. Optilume Urethral Drug Coated Balloon. June 30, 2023. [cited 11/10/2023]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf21/P210020B.pdf.
14. U.S. Food and Drug Administration (FDA) De Novo Classification. iTind System Temporarily-placed Urethral Opening System for Benign Prostatic Hyperplasia. April 20, 2019. [cited 11/16/2023]. Available from: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN190020.pdf.
15. RC Rosen, JA Catania, SE Althof, et al. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. *Urology.* 2007;69(5):805-9. PMID: 17482908

16. JC Cappelleri, RC Rosen. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. *Int J Impot Res.* 2005;17(4):307-19. PMID: 15875061
17. J Sonksen, NJ Barber, MJ Speakman, et al. Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. *Eur Urol.* 2015;68(4):643-52. PMID: 25937539
18. MJ Barry, WO Williford, Y Chang, et al. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol.* 1995;154(5):1770-4. PMID: 7563343
19. CG Roehrborn, TH Wilson, LK Black. Quantifying the contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia: 4-year data from the CombAT trial. *J Urol.* 2012;187(5):1732-8. PMID: 22425127
20. F Porpiglia, C Fiori, R Bertolo, D Garrou, G Cattaneo, D Amparore. Temporary implantable nitinol device (TIND): a novel, minimally invasive treatment for relief of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH): feasibility, safety and functional results at 1 year of follow-up. *BJU Int.* 2015;116(2):278-87. PMID: 25382816
21. F Porpiglia, C Fiori, R Bertolo, et al. 3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction. *BJU Int.* 2018;122(1):106-12. PMID: 29359881
22. JV Franco, JH Jung, M Imamura, et al. Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis. *Cochrane Database Syst Rev.* 2021;7(7):CD013656. PMID: 34693990
23. B Chughtai, D Elterman, N Shore, et al. The iTind Temporarily Implanted Nitinol Device for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Multicenter, Randomized, Controlled Trial. *Urology.* 2021;153:270-76. PMID: 33373708
24. D Elterman, MN Alshak, S Martinez Diaz, et al. An Evaluation of Sexual Function in the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia in Men Treated with the Temporarily Implanted Nitinol Device. *J Endourol.* 2023;37(1):74-79. PMID: 36070450
25. F Porpiglia, C Fiori, D Amparore, et al. Second-generation of temporary implantable nitinol device for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia: results of a prospective, multicentre study at 1 year of follow-up. *BJU Int.* 2019;123(6):1061-69. PMID: 30382600
26. G Kadner, M Valerio, I Giannakis, et al. Second generation of temporary implantable nitinol device (iTind) in men with LUTS: 2 year results of the MT-02-study. *World J Urol.* 2020;38(12):3235-44. PMID: 32124019
27. D Amparore, C Fiori, M Valerio, et al. 3-Year results following treatment with the second generation of the temporary implantable nitinol device in men with LUTS secondary to benign prostatic obstruction. *Prostate Cancer Prostatic Dis.* 2021;24(2):349-57. PMID: 33005003
28. C De Nunzio, F Cantiello, C Fiori, et al. Urinary and sexual function after treatment with temporary implantable nitinol device (iTind) in men with LUTS: 6-month interim results of the MT-06-study. *World J Urol.* 2021;39(6):2037-42. PMID: 32851439

29. SP Elliott, K Coutinho, KJ Robertson, et al. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume(®) Drug-Coated Balloon for Anterior Urethral Strictures. *J Urol.* 2022;207(4):866-75. PMID: 34854748
30. JM DeLong, MJ Ehlert, BA Erickson, KJ Robertson, R Virasoro, SP Elliott. One-Year Outcomes of the ROBUST II Study Evaluating the Use of a Drug-Coated Balloon for Treatment of Urethral Stricture. *Société Internationale d'Urologie Journal.* 2022;3(1):21-27. PMID:
31. R Virasoro, JM DeLong, RA Mann, et al. A drug-coated balloon treatment for urethral stricture disease: Interim results from the ROBUST I study. *Can Urol Assoc J.* 2020;14(6):187-91. PMID: 31977303
32. RA Mann, R Virasoro, JM DeLong, et al. A drug-coated balloon treatment for urethral stricture disease: Two-year results from the ROBUST I study. *Can Urol Assoc J.* 2021;15(2):20-25. PMID: 32744999
33. R Virasoro, JM DeLong, RE Estrella, et al. A Drug-Coated Balloon Treatment for Urethral Stricture Disease: Three-Year Results from the ROBUST I Study. *Res Rep Urol.* 2022;14:177-83. PMID: 35572815

CODES

Codes	Number	Description
CPT	0619T	Cystourethroscopy with transurethral anterior prostate commissurotomy and drug delivery, including transrectal ultrasound and fluoroscopy, when performed
	52284	Cystourethroscopy, with mechanical urethral dilation and urethral therapeutic drug delivery by drug-coated balloon catheter for urethral stricture or stenosis, male, including fluoroscopy, when performed
	53855	Insertion of a temporary urethral stent, including urethral measurement
HCPCS	C9769	Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts (Nitinol, iTind device)

Date of Origin: *2023*

Regence

Medical Policy Manual Surgery, Policy No. 231

Radiofrequency Ablation and Injection of Sacroiliac Joint Nerves

Effective: January 1, 2024

Next Review: August 2024
Last Review: August 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Radiofrequency ablation (RFA), also known as radiofrequency neurotomy, involves heating a portion of a pain-transmitting nerve to functionally denervate a designated joint (e.g., sacroiliac) and prevent the transmission of pain signals to the brain. A nerve block is injected prior to the RFA procedure for diagnostic purposes.

MEDICAL POLICY CRITERIA

Radiofrequency ablation (neurotomy) or injection (e.g., anesthetic agent, steroid) of the nerves innervating the sacroiliac joint is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Decompression of Intervertebral Discs Using Laser Energy (Laser Discectomy) or Radiofrequency Energy (Nucleoplasty), Surgery, Policy No. 131
2. Pulsed Radiofrequency for Chronic Spinal Pain, Surgery, Policy No. 156
3. Sacroiliac Joint Fusion, Surgery, Policy No. 193

BACKGROUND

The sacroiliac joint (SIJ) is a joint between the sacrum and ilium of the pelvis. The SIJ is a strong weight bearing joint with a self-locking mechanism that provides stability with movement on the left and right side of the sacrum. Similar to other structures in the spine, it is assumed that the SIJ may be a source of low back pain.

Treatments being investigated for SIJ pain include prolotherapy, corticosteroid injection, radiofrequency ablation, stabilization, and arthrodesis. Radiofrequency ablation (denervation, neurotomy) involves destruction of the nerves using heat generated by a radiofrequency current. A catheter or electrode is placed near or in the target nerve. The position of the electrode is confirmed by fluoroscopy. Once the electrode is in place, a radiofrequency current is applied to heat and destroy the surrounding tissues, including the target nerve. Before the RFA procedure, a nerve block is injected into one or two of the nerves innervating the SIJ to locate the target nerve for ablation.

REGULATORY STATUS

A number of radiofrequency generators and probes have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. In 2005, the Sinergy® (Halyard; formerly Kimberly-Clark), a water-cooled single-use probe, was cleared by the FDA, listing the Baylis Pain Management Probe as a predicate device. The intended use is in conjunction with a radiofrequency generator to create radiofrequency lesions in nervous tissue.

FDA product codes: GXD, GXI.

EVIDENCE SUMMARY

The principal outcome for treatment of pain is symptom relief and improved functional level. Relief of pain can be subjective depending on the validity of the measurement tool used. Randomized controlled trials (RCTs) are desirable to control for the placebo effect and determine whether any treatment effect provides a significant advantage over the placebo. In addition, well-designed studies comparing radiofrequency ablation (RFA) treatment with conventional treatment are important to determine the overall effectiveness of this therapy for the treatment of sacroiliac joint (SIJ) pain. This evidence review includes both SIJ RFA and injections (e.g., anesthetic, steroid).

Systematic Reviews

Maccagnano (2022) published a systematic review (SR) comparing clinical outcomes of thermal (RFT) versus cooled radiofrequency ablation (RFC) in patients (n=276) with SIJ pain.[1] The analysis revealed a small and non-significant difference in pain reduction and an improvement in quality of life in RFT subgroup (pain measured in Visual Analogic Scale: RFT subgroups standardized mean difference (SMD) =-3.643 (95% confidence interval [CI] -4.478 to 2.807), RFC subgroup SMD = -3.285 (95% confidence interval [CI] -4.428 to -2.141), p=0.587; Quality of Life measured in Oswestry Disability Index: RFT subgroup SMD=-35.969 (95% CI -53.993 to -17.945), RFC subgroup SMD=-20.589% (95% CI -33.424 to -7.754), p=0.123). Publication bias was found in quality-of-life assessment due to the low number and high heterogeneity of studies. Two techniques showed no major complications.

Chou (2021) conducted a SR and meta-analysis on interventional treatments for acute and chronic pain for the Agency for Healthcare Research and Quality for use by the Centers for Medicare and Medicaid Services.[2] The systematic review identified two trials (n=79) on cooled RFA versus sham for SIJ pain with results at three months, and one trial (n=28) on cooled RFA versus sham with results at one month. Meta-analysis indicated that cooled RFA is probably more effective for pain and function compared to sham at one and three months with moderate to large benefits. The strength of evidence was rated moderate for pain and function at three months and low for function at one month. When comparing cooled RFA to conventional RFA, one trial (n=43) showed no differences at one or three-month follow-up and a small, nonstatistically significant reduction in pain at six months. The strength of evidence was rated as low.

Chappel (2020) performed a meta-analysis of RFA for chronic back pain.[3] The review included five RCTs comparing RFA to sham or medical treatment in patients with chronic SIJ pain with follow-up from one to three months, and one study that had a follow-up to 12 months. This meta-analysis did not include pulsed RFA. Low-quality evidence indicated that RFA led to a modest reduction in pain at one to three-month follow-up, but there was no significant reduction in pain in the single RCT (n=228) that had six- and 12-month follow-up. The RCT by Juch (2017) with 12-month follow-up is described in greater detail below. [4]

Chen (2019) published a meta-analysis of five RCTs comparing RFA to sham or medical treatment in patients with chronic SIJ pain.[5] Various RFA procedures were represented, including percutaneous, cooled, and palisade SIJ radiofrequency neurotomy. Pain outcomes from all RCTs were pooled for the meta-analysis. Disability outcomes were only available for two studies utilizing cooled RFA. While studies showed no significant heterogeneity for disability outcomes, heterogeneity was high for pain outcomes.

Randomized Controlled Trials

Cohen (2023) published the results from a multicenter, randomized comparative effectiveness study to assess cooled RFA with standard medical management for chronic SIJ pain.[6] Patients (n=210) with clinically suspected sacroiliac joint pain who obtained short-term benefit from diagnostic sacroiliac joint injections and prognostic lateral branch blocks were randomly assigned to receive cooled radiofrequency ablation (cRFA) of the L5 dorsal ramus and S1-S3 lateral branches or standard medical management (SMM) consisting of pharmacotherapy, injections and integrative therapies. The primary outcome measure was mean reduction in low back pain score on a 0-10 Numeric Rating Scale (NRS) at three months. Secondary outcomes included measures of quality of life (QOL) and function. The mean NRS pain score for the cRFA group was 3.8 ± 2.4 (mean reduction 2.5±2.5) compared with 5.9 ±1.7 (mean reduction 0.4±1.7) in the SMM group ($p<0.0001$). More than half (52.3%) of subjects in the cooled radiofrequency ablation group experienced > 2.0 points (30%) pain relief and were deemed responders versus 4.3% of standard medical management patients ($p<0.0001$). Comparable improvements favoring cooled radiofrequency ablation were noted in Oswestry Disability Index score (mean 29.7 ± 15.2 vs 41.5 ± 13.6; $p<0.0001$) and QOL (mean EuroQoL-5 score 0.68 ± 0.22 vs 0.47 ± 0.29; $p<0.0001$). Long term outcomes are lacking and there is potential bias as each of the authors are consultants for the RFA device company.

Mehta (2018) published results from a double-blind, randomized, sham-controlled trial assessing the efficacy of radiofrequency neurotomy with a strip-lesioning device in patients with chronic SIJ pain.[7] Seventeen of 30 enrolled patients were randomized to active (n=11) or

sham (n=6) treatment. Recruitment was terminated after an interim analysis indicated a statistically significant difference in the pain outcome between groups. After the three-month study endpoint, patients receiving sham treatment were allowed to crossover. While a statistically significant reduction in pain scores was reported at three months, there was no significant difference in functional outcome as measured by the Physical Component Score at three months. Due to the crossover design, it is difficult to gauge long-term outcomes and durability of the treatment.

Dutta (2018) published a randomized prospective study comparing RFA with depo-methylprednisolone (DMP) injection for SIJ pain.[8] Patients (n=30) were randomly assigned to RFA or DMP injection of the L4 medial branch and L5 dorsal rami and the lateral sacral branches. Both groups reported a reduction in pain as measured by the Numeric Rating Scale (NRS) at one month. At six months the NRS score began to rise for the DMP group while the RFA group remained the same (since the last visit). Both groups had improvement in the Oswestery Disability Index (ODI) score at three and six months with the RFA group having a lower score at both time points. This study is limited by a small sample size.

Juch (2017) reported a nonblinded multicenter RCT of radiofrequency denervation in 228 of 2498 patients with suspected sacroiliac pain who were asked to participate in the trial.[4] Patient selection criteria included body mass index (<35 kg/m^2), age (<70 years old), and pain reduction of at least 50% within 30 to 90 minutes of receiving a diagnostic sacroiliac block (n=228). An additional 202 patients had a negative diagnostic sacroiliac block; 1666 patients declined to participate in the trial. Patients meeting criteria were randomized to exercise plus radiofrequency denervation (n=116) or an exercise program alone (n=112) and were followed for a year. The RFA group had a modest improvement for the primary outcome at 3 months (-0.71; 95% CI: -1.35 to -0.06), but the control group improved over time and there were no statistically significant differences between the groups for pain intensity score (p=.09) or in the number of patients who had more than a 30% reduction in pain intensity (p=0.48) at 12 months. Limitations included the use of several techniques to achieve radiofrequency denervation, self-selection, lack of blinding, and a high dropout rate (31%) in the control group.

Van Tilburg (2016) reported a sham-controlled randomized trial of percutaneous RFA in 60 patients with SIJ pain.[9] Patients selected had clinically suspected SIJ pain and a decrease of two or more points on a 10-point pain scale with a diagnostic sacroiliac block. At three-month follow-up, there was no statistically significant difference in pain level over time between groups (group by period interaction, p=0.56). Both groups improved over time (≥ 2.0 points out of 10; p-value for time, p<.001). In their discussion, trialists mentioned the criteria and method used for diagnosing SIJ pain might have resulted in the selection of some patients without SIJ pain.

Canovas (2016) published a randomized, prospective study comparing blockade injection, bipolar thermal RFA (needle distance 1 cm) and a modified bipolar RFA (needle distance > 1.0 cm) in 60 patients.[10] One month after the treatment, pain reduction was >50% in the three groups p<0.001. Three and 12 months after the technique, the patients of the group A did not have a significant reduction in pain. At three months, almost 50% patients of the group B referred to improvement of the pain (p=0.03), and <25% at 12 months, and those results were statistically significant (p=0.01) compared to the baseline. Group C showed an improvement of 50% at three and 12 months (p<.001). All patients completed the study.

Zheng (2014) reported on an RCT of palisade sacroiliac RFA in 155 patients with ankylosing spondylitis.[11] Palisade RFA uses a row of radiofrequency cannulae perpendicular to the dorsal sacrum. Inclusion criteria were ages 18 to 75 years; diagnosis of ankylosing spondylitis; chronic low back pain for at least three months; axial pain below L5; no peripheral involvement; pain aggravation on manual pressing of the SIJ area; and at least 50% pain relief following fluoroscopically guided anesthetic injection into the joint. Patients who met the inclusion criteria were randomized to palisade RFA or celecoxib. Blinded evaluation to 24 weeks found that RFA (2.8) resulted in lower global VAS scores than celecoxib (5.0; p<.001) as well as improved scores for secondary outcome measures. This study lacked a sham control.

Patel (2012) reported a randomized, double-blind, placebo-controlled trial of lateral branch neurotomy with a cooled radiofrequency probe.[12] Twelve-month follow-up was reported in 2016.[13] Fifty-one patients who had a positive response to two lateral branch blocks were randomized 2:1 to lateral branch radiofrequency or to sham. At a three-month follow-up, significant improvements were observed in pain levels (-2.4 vs -0.8), physical function (14.0 vs 3.0), disability (-11.0 vs 2.0), and QOL (0.09 vs 0.02) for radiofrequency treatment compared with controls (all respectively). With treatment success defined as a 50% or greater reduction in numeric rating scale score, 47% of radiofrequency-treated patients and 12% of sham-treated patients achieved treatment success. The treatment response was durable to 12 months in the 25 of 34 patients who completed all follow-up visits.[13] Of the nine patients who terminated study participation, four of 34 (12%) were considered treatment failures.

Section Summary

There are no sham controlled RCTs that support injections of the nerves that innervate the sacroiliac joint to treat pain. Meta-analysis of available sham controlled RCTs suggests that there may be a small effect of RFA on SIJ pain at short-term (one- to three-months) follow-up. However, the randomized trials of RFA have methodologic limitations, and there is limited data on the duration of the treatment effect. The single RCT with six and 12-month follow-up showed no significant benefit of RFA compared to an exercise control group at these time points. In addition, heterogeneity of RFA treatment techniques precludes generalizing results across different studies.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF PAIN AND NEUROSCIENCE

In 2021, the American Society of Pain and Neuroscience published practice a guideline on radiofrequency ablation (neurotomy).[14] All of the workgroup members utilized radiofrequency neurotomy in clinical practice. A consensus statement, based on Grade II-1 evidence (well-designed, controlled, nonrandomized clinical trial), was that "lateral branch radiofrequency ablation (neurotomy) may be used for the treatment of posterior sacral ligament and joint pain following positive response to appropriately placed diagnostic blocks."

AMERICAN SOCIETY OF ANESTHESIOLOGISTS & AMERICAN SOCIETY OF REGIONAL ANESTHESIA AND PAIN MEDICINE

The American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine have a 2010 guideline for chronic pain management.[15] The guideline recommends that “Diagnostic sacroiliac joint injections or lateral branch blocks may be considered for the evaluation of patients with suspected sacroiliac joint pain.” Based on the

opinions of consultants and society members, the guideline recommends that “Water-cooled radiofrequency ablation may be used for chronic sacroiliac joint pain.”

SUMMARY

There is not enough research to show that radiofrequency ablation (RFA) or injection (e.g., anesthetic agent, steroid) of the nerves innervating the sacroiliac joint (SIJ) improves net health outcomes in patients with sacroiliac joint pain. High quality data from randomized controlled trials are needed to compare RFA and injections to the nerves innervating the SIJ with the currently accepted treatments for SIJ pain. Therefore, the use of radiofrequency ablation (RFA) or injection (e.g., anesthetic agent, steroid) of the nerves innervating the sacroiliac joint for the treatment of sacroiliac joint pain is considered investigational.

REFERENCES

1. Maccagnano G, Noia G, Cassano GD, et al. Thermal versus cooled radiofrequency in patients with sacroiliac joint pain: a systematic review of the literature and pooled analysis of clinical outcomes. *J Neurosurg Sci.* 2022;66(6):485-93. PMID: 35301836
2. ©2021. Technology Assessment: Interventional Treatments for Acute and Chronic Pain: Systematic Review. Comparative Effectiveness Review No. 247. Issue date: Available at: https://www.ncbi.nlm.nih.gov/pubmed/34524764. Accessed on
3. Chappell ME, Lakshman R, Trotter P, et al. Radiofrequency denervation for chronic back pain: a systematic review and meta-analysis. *BMJ Open.* 2020;10(7):e035540. PMID: 32699129
4. Juch JNS, Maas ET, Ostelo R, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. *JAMA.* 2017;318(1):68-81. PMID: 28672319
5. Chen CH, Weng PW, Wu LC, et al. Radiofrequency neurotomy in chronic lumbar and sacroiliac joint pain: A meta-analysis. *Medicine (Baltimore).* 2019;98(26):e16230. PMID: 31261580
6. Cohen SP, Kapural L, Kohan L, et al. Cooled radiofrequency ablation versus standard medical management for chronic sacroiliac joint pain: a multicenter, randomized comparative effectiveness study. *Reg Anesth Pain Med.* 2023. PMID: 37407279
7. Mehta V, Poply K, Husband M, et al. The Effects of Radiofrequency Neurotomy Using a Strip-Lesioning Device on Patients with Sacroiliac Joint Pain: Results from a Single-Center, Randomized, Sham-Controlled Trial. *Pain Physician.* 2018;21(6):607-18. PMID: 30508988
8. Dutta K, Dey S, Bhattacharyya P, et al. Comparison of Efficacy of Lateral Branch Pulsed Radiofrequency Denervation and Intraarticular Depot Methylprednisolone Injection for Sacroiliac Joint Pain. *Pain Physician.* 2018;21(5):489-96. PMID: 30282393
9. van Tilburg CW, Schuurmans FA, Stronks DL, et al. Randomized Sham-controlled Double-Blind Multicenter Clinical Trial to Ascertain the Effect of Percutaneous Radiofrequency Treatment for Sacroiliac Joint Pain: Three-month Results. *Clin J Pain.* 2016;32(11):921-26. PMID: 26889616
10. Cánovas Martínez L, Orduña Valls J, Paramés Mosquera E, et al. Sacroiliac joint pain: Prospective, randomised, experimental and comparative study of thermal

radiofrequency with sacroiliac joint block. *Rev Esp Anestesiol Reanim.* 2016;63(5):267-72. PMID: 26642949
11. Zheng Y, Gu M, Shi D, et al. Tomography-guided palisade sacroiliac joint radiofrequency neurotomy versus celecoxib for ankylosing spondylitis: a open-label, randomized, and controlled trial. *Rheumatol Int.* 2014;34(9):1195-202. PMID: 24518967
12. Patel N, Gross A, Brown L, et al. A randomized, placebo-controlled study to assess the efficacy of lateral branch neurotomy for chronic sacroiliac joint pain. *Pain Med.* 2012;13(3):383-98. PMID: 22299761
13. Patel N. Twelve-Month Follow-Up of a Randomized Trial Assessing Cooled Radiofrequency Denervation as a Treatment for Sacroiliac Region Pain. *Pain Pract.* 2016;16(2):154-67. PMID: 25565322
14. Lee DW, Pritzlaff S, Jung MJ, et al. Latest Evidence-Based Application for Radiofrequency Neurotomy (LEARN): Best Practice Guidelines from the American Society of Pain and Neuroscience (ASPN). *J Pain Res.* 2021;14:2807-31. PMID: 34526815
15. American Society of Anesthesiologists Task Force on Chronic Pain M, American Society of Regional A, Pain M. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology.* 2010;112(4):810-33. PMID: 20124882

CODES

Codes	Number	Description
CPT	64451	Injection(s), anesthetic agent(s) and/or steroid; nerves innervating the sacroiliac joint, with image guidance (ie, fluoroscopy or computed tomography)
	64625	Radiofrequency ablation, nerves innervating the sacroiliac joint, with image guidance (ie, fluoroscopy or computed tomography)
HCPCS	None	

Date of Origin: *August 2023*

Regence

Medical Policy Manual Surgery, Policy No. 232

Vertebral Body Tethering and Stapling

Effective: January 1, 2024

Next Review: November 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vertebral body stapling and vertebral body tethering, both fusionless surgical procedures, have been evaluated to determine whether the procedures could be used as alternatives to traditional orthotic bracing.

MEDICAL POLICY CRITERIA

Vertebral body stapling and vertebral body tethering for the treatment of scoliosis are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

SCOLIOSIS

Scoliosis is an abnormal lateral and rotational curvature of the vertebral column. Adolescent idiopathic scoliosis is the most common form of idiopathic scoliosis, defined by the U.S. Preventive Services Task Force as “a lateral curvature of the spine with onset at ≥10 years of age, no underlying etiology, and risk for progression during puberty.”[1] Progression of the curvature during periods of rapid growth can result in deformity, accompanied by cardiopulmonary complications. Diagnosis is made clinically and radiographically. The curve is measured by the Cobb angle, which is the angle formed between intersecting lines drawn perpendicular to the top of the vertebrae of the curve and the bottom vertebrae of the curve. Patients with adolescent idiopathic scoliosis are also assessed for skeletal maturity, using the Risser sign, which describes the level of ossification of the iliac apophysis.

The Risser sign measures remaining spinal growth by progressive anterolateral to posteromedial ossification. Risser sign ranges from 0 (no ossification) to 5 (full bony fusion of the apophysis). Immature patients will have 0% to 25% ossification (Risser grade 0 or 1), while 100% ossification (Risser grade 5) indicates maturity with no spinal growth remaining. Children may progress from a Risser grade 1 to grade 5 over a brief (eg, 2-year), period.

Males and females are equally affected by scoliosis, but curve progression is up to 10 times more common in females than males.[2] Patients who are overweight or obese have a greater risk of presenting with larger Cobb angles and more advanced skeletal maturity, possibly due to delayed detection.[3] A retrospective review of 341 patients with adolescent idiopathic scoliosis who underwent surgery at a single tertiary pediatric hospital between 2013 and 2018 found that the major curve magnitude at presentation was significantly higher in patients with public compared to private insurance (50.0° versus 45.1°; p=.0040 and in Black compared to White patients (51.8° versus 47.0°; p=.042). Additionally, the odds of having an initial major curve magnitude <40° within the range of nonoperative treatment were 67% lower among Black patients with public insurance compared to Black patients with private insurance (odds ratio [OR], 0.33; 95% CI, 0.13 to 0.83; p=.019).[4]

Treatment

Treatment of scoliosis currently depends on 3 factors: the cause of the condition (idiopathic, congenital, secondary), the severity of the condition (degrees of the curve), and the growth of the patient remaining at the time of presentation. Children who have vertebral curves measuring between 25° and 40° with at least 2 years of growth remaining are considered to be at high risk of curve progression. Genetic markers to evaluate the risk of progression are also being evaluated. Because severe deformity may lead to compromised respiratory function and is associated with back pain in adulthood, surgical intervention with spinal fusion is typically recommended for curves that progress to 45° or more.

Bracing

Bracing is used to reduce the need for spinal fusion by slowing or preventing further progression of the curve during rapid growth. Commonly used brace designs include the Milwaukee, Wilmington, Boston, Charleston, and Providence orthoses. The longest clinical experience is with the Milwaukee cervical-thoracic-lumbar-sacral orthosis. Thoracic-lumbar-sacral orthoses, such as the Wilmington and Boston braces, are intended to improve tolerability and compliance for extended (>18-hour) wear and are composed of lighter weight plastics with a low profile (underarm) design. The design of the nighttime Charleston and Providence braces is based on the theory that increased corrective forces will reduce the needed wear time (ie, daytime), thereby lessening social anxiety and improving compliance.

The smart brace consists of a standard rigid brace with a microcomputer system, a force transducer, and an air-bladder control system to control the interface pressure. Braces that are more flexible than thoracic-lumbar-sacral orthoses or nighttime braces, such as the SpineCor® Scoliosis System, are also being evaluated. The SpineCor is composed of a thermoplastic pelvic base with stabilizing and corrective bands across the upper body.

Surgery

Fusionless surgical procedures, such as vertebral body stapling and vertebral body tethering, are being evaluated as alternatives to bracing. Both procedures use orthopedic devices off-label. The goal of these procedures is to reduce the rate of spine growth unilaterally, thus allowing the other side of the spine to “catch up.” The mechanism of action is believed to be down-regulation of the growth plate on the convex (outer) side by compression and stimulation of growth on the endplate of the concave side by distraction. In the current stapling procedure, nickel-titanium alloy staples with shape memory are applied to the convex side of the curve. The shape memory allows the prongs to be straight when cooled and clamp down into the bone when the staple returns to body temperature. Anterolateral tethering uses polyethylene ligaments that are attached to the convex side of the vertebral bodies by pedicle screws or staples. The ligament can be tightened to provide greater tension than the staple. The optimum degree of tension is not known. The polyethylene ligaments are more flexible than staples and are predicted to allow more spinal mobility. The goal of a fusionless growth modulating procedure is to reduce the curve and prevent progression, maintain spine mobility following correction, and provide an effective treatment option for patients who are noncompliant or who have a large curve but substantial growth is remaining. Observational data suggest that overweight patients may be at higher risk for scoliosis progression after surgery.[5]

Regulatory Status

Staples, using a shape memory nickel-titanium alloy, have been cleared for marketing by the FDA through the 510(k) process for various bone fixation indications. For example, nitinol staples (Sofamor Danek) are indicated for fixation with spinal systems. Other memory shape staples cleared for marketing by the FDA through the 510(k) process for bone fixation include the OSStaple™ (BioMedical Enterprises) and the reVERTO™ Dynamic Compression Device. FDA product code: JDR. Vertebral body stapling in scoliosis is considered off-label use.

A vertebral body tethering device (The Tether™; Zimmer Biomet Spine) received an FDA Humanitarian Device Exemption (HDE) (H190005, product code QHP) in June 2019. The FDA HDE states that this device is indicated for "skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis, with a major Cobb angle of 30 to 65 degrees whose osseous structure is dimensionally adequate to accommodate screw fixation, as determined by radiographic imaging. Patients should have failed bracing and/or be intolerant to brace wear."

EVIDENCE SUMMARY

VERTEBRAL BODY STAPLING

Review of Evidence

Nonrandomized Comparative Study

In a multicenter study, Cuddihy (2015) reported on a matched comparison of VBS and bracing for immature patients with moderate (25° to 44°) idiopathic scoliosis.[6] Forty-two consecutive patients in the VBS group (57 curves) met inclusion criteria, and 52 patients in the bracing group (66 curves) were matched by initial Cobb angle, age at the start of treatment, follow-up of at least 2 years, and sex. The average curve size was 31°, and the average follow-up was 40.8 months in the VBS group and 105 months in the bracing group (maturity). For smaller thoracic curves (25° to34°), there was a nonstatistically significant trend for stapling to be more effective (progression <10°, 81%) compared with bracing (61%; p=.16). For larger thoracic curves (>35°), VBS did not halt curve progression, with a success rate of 18% compared with 50% for bracing. For lumbar curves (25° to 34°), results were comparable for VBS and bracing. There were insufficient numbers of patients with lumbar curves of 35° or greater to compare results.

Observational Studies

Several case series and one case-control study evaluating VBS are described below and in Tables 1 and 2.

Cuddihy (2015) compared VBS to bracing in a matched cohort of skeletally immature patients with moderate idiopathic scoliosis.[6] A total of 52 patients (66 curves) were matched according to age at the start of treatment (10.6 years vs. 11.1 years, respectively) and gender. In smaller thoracic curves (25° to 34°) there was a nonsignificant trend toward better results with VBS versus bracing. For those with thoracic curves ≥35°, VBS was not found to be effective, and for lumbar curves 25° to 35°, results appear to be similar for both VBS and bracing.

Murray (2020) described VBS in 7 patients with a mean age of 9.3 years (range, 7.8 to11.1 years) and an average preoperative Cobb angle of 30° (standard deviation [SD], 6°); the mean follow-up was 83 months (range, 72 to 95 months).[7] At the first postoperative visit and most recent follow-up visit, the average Cobb angle was 20° (SD, 7°) and 37° (SD, 22°), respectively. One patient showed improvement of greater than 10° from preoperative to final postoperative Cobb angle, 4 patients showed no change in their curve, and 2 showed progression of their curves by greater than 10° compared with preoperative imaging.

Bumpass (2015) described VBS in 31 consecutive patients with a mean age of 10.5 years (range, 7.0 to 14.6 years) and scoliotic curves of 25° to 40°.[8] Not all patients could (or would) wear a brace. At a mean follow-up to maturity of 48 months (range, 25 to 79 months), curves less than 35° had a control rate (<10° progression) of 75% while curves with a Cobb angle of at least 35° had a control rate of 22% (p=.01). The overall control rate was 61%, with 11 (31%) patients requiring subsequent fusion and 2 (6%) overcorrections.

Theologis (2013) described VBS in 12 children younger than 10 years old (range, 6.3 to 9.7 years) who were considered extremely likely to require fusion (ie, curves of 30° to 39° in a young child).[9] At an average 3.4-year follow-up (range, 2.2 to 5.4 years), curves had decreased by a mean of 10° (range, -3° to 20°). All curves in this high-risk population were successfully treated, with either no change (within 10°) or improvement in the curve (>10°).

Laituri (2012) retrospectively reviewed 7 children ages 8 to 11 years old who had undergone VBS and had at least 2 years of follow-up.[10] All children either had curve progression, despite bracing, or were unable to wear a brace. Before stapling, the mean angle was 34.1°. The mean percentage correction was 36% (range, 16.2% to 56%). None of the children had curve progression or required postoperative bracing or spinal fusion.

O’Leary (2011) reported that VBS in young children with large Cobb angles was ineffective.[11] Patients with adolescent idiopathic scoliosis were not included in this report. Diagnoses included myelodysplasia, congenital scoliosis, juvenile and infantile idiopathic scoliosis, Marfan syndrome, paralytic scoliosis, and neuromuscular scoliosis. At an average 22-month follow-up, curves averaged 69°, and 8 of 11 patients had undergone or were scheduled to undergo further spinal surgery for curve progression. It is unknown whether the young age at surgery, the severe preoperative curve, or the nature of underlying scoliosis contributed to the high failure rate.

Betz (2010) reported on 29 patients with juvenile or adolescent idiopathic scoliosis (from a database of 93 patients) who met the study inclusion criteria.[12] Selected were patients with idiopathic scoliosis, a coronal curve magnitude of 20° to 45°, Risser grade 0 or 1, and staples with tines proportional to staple size (beginning in 2002). The average age at the time of stapling was 9.4 years (range, 4 to 13 years), with an average follow-up of 3.2 years (range, 2 to 5.3 years). For thoracic curves greater than 35° at baseline, 75% progressed to greater than 50° (the threshold for recommending spinal fusion). For thoracic curves less than 35° at baseline, 6% of patients progressed to greater than 50° (the threshold for surgery).

Table 1. Summary of Key Observational Study Characteristics for Vertebral Body Stapling

Study	Country	Study Design	N[a]	Participants			Minimum FU, y
				Mean Age, y	***Curve***	***Risser Grade***	
Murray (2020)[7]	U.S.	Case series	7	9.3	27.3° to 37.9°	NR	6
Cuddihy (2015)[6]	U.S.	Case control	123	11	25° to 44°	0	2
Bumpass (2015)[8]	U.S.	Case series	33	11	25° to 40°	0	2
Theologis (2013)[9]	U.S.	Case series	12	8	30° to 39°	NR	2
Laituri (2012)[10]	U.S.	Case series	7	9	25° to 41°	NR	2
O'Leary (2011)[11]	U.S.	Case series	11	7	68° to 105°	0	1
Betz (2010)[12]	U.S.	Case series	29	9	20° to 45°	0	2

FU: follow-up; NR: not reported; U.S.: United States

[a] Number of patients in all studies, except for Bumpass et al (2015) and Cuddihy et al (2015), where N is the number of curves.

Table 2. Summary of Key Observational Study Outcomes for Vertebral Body Stapling

Study	Tx	Change In Curve				
		>10° Progressed	***Stable***	***>10° Improved***		
Murray (2020)[7]	VBS	2	4			
		>10° Progressed	***Stable/Improved***	***p***	**Progressed ≥50°**	**Subsequent Fusion**
Cuddihy (2015)[6]	VBS	Thoracic curves 25° to 34°: (19) Thoracic curves 35° to 44°: (82) Lumbar curves 25° to 34°: (20) Lumbar curves 35° to 44°: (40)	Thoracic curves 25° to 34°: (81) Thoracic curves 35° to 44°: (18) Lumbar curves 25° to 34°: (80) Lumbar curves 35° to 44°: (60)	>.05 for all comparisons of VBS vs. brace	NR	NR
	Brace	Thoracic curves 25° to 34°: (39) Thoracic curves 35° to 44°: (50) Lumbar curves 25° to 34°: (19) Lumbar curves 35° to 44°: (100)	Thoracic curves 25° to 34°: (61) Thoracic curves 35° to 44°: (50) Lumbar curves 25° to 34°: (81) Lumbar curves 35° to 44°: (0)			
		>10° Progressed	**Stable**	**>10° Corrected**		

Study	Tx	Change In Curve				
Bumpass (2015)[8]	VBS	13 (39)	14 (42)	6 (18)	9 (27)	11 (31)
Theologis (2013)[9]	VBS	0 (0)	5 (42)	7 (58)	0 (0)	0 (0)
Laituri (2012)[10]	VBS	0 (0)	2 (29)	5 (71)	0 (0)	0 (0)
O'Leary (2011)[11]	VBS	3 (27)	6 (55)	2 (18)	0 (0)	8 (73)
		Baseline Curve	**>10° Progressed**	**Stable/Improved**		
Betz (2010)[12]	VBS	<35° ≥35°	4 (22) 6 (75)	14 (78) 2 (25)	1 (6) 6 (75)	NR NR

Values are n (%) unless otherwise indicated.
NR: not reported; Tx: treatment; VBS: vertebral body stapling.

Section Summary: Vertebral Body Stapling

Evidence on the use of VBS for patients with idiopathic scoliosis consists of a nonrandomized comparative study, a case-control study, and several small case series. Results from the nonrandomized comparative study and case-control study have indicated that VBS might slow curve progression in children with thoracic curves less than 35° and is at least as effective as bracing, but VBS appears to be less effective than bracing in patients with Cobb angles of 35° or more. Results from these studies are considered preliminary because few patients have been followed to skeletal maturity. Studies from other centers are consistent with results from those of the inventor of the procedure. Complications can include broken staples, staple dislodgement, curve overcorrection, congenital diaphragmatic hernia rupture, contralateral pleural effusion, pneumothoraces, and superior mesenteric artery syndrome. Investigators have commented that their approach is almost always to recommend bracing first and offer stapling only if the child or adolescent has difficulty wearing the brace. Notably, for patients with thoracic curves of 35° or greater, Cuddihy (2015) now perform vertebral body tethering (see next section) instead of VBS.

VERTEBRAL BODY TETHERING

Review of Evidence

Systematic Reviews

Mariscal (2023) published a meta-analysis of 12 studies on the efficacy and safety of anterior vertebral body tethering (AVBT) in adolescent idiopathic scoliosis[13]. Significant corrections of the main thoracic, proximal thoracic, and thoracolumbar/lumbar curves were seen at 1-2 years post procedure, but no significant corrections were seen in the sagittal plane. Follow-up time was 24-60 months. The most common complications were overcorrection (8%) and tether breakage (5.9%) The reoperation rate was 10%. The studies included case series and cohort studies with no control groups, and there were no clinical trials. The authors note that while AVBT corrects curve deformities in the coronal plane, full assessment of AVBT is not possible with the available evidence.

Zhu (2022) published a systematic review and meta-analysis of 26 studies representing 1045 subjects (mean age range, 11.1 to 14.9 years) treated with vertebral body tethering (VBT) for scoliosis, finding that the Cobb angle of the major curve was significantly corrected from 40.0° to 59.0° at baseline to 15.9° to 38.0° immediately post-surgery and 10° to 38° at final follow-up.[14] The overall clinical success rate was 73.02% (95% CI, 68.31% to 78.05%). The pooled overall unplanned reoperation rate after VBT was 8.66% (95% CI, 5.53% to 13.31%; 23 studies). The top 3 reinterventions were conversion to posterior spinal fusion (3.51%; 95% CI, 2.45% to 5.01%), tether removal (2.3%; 95% CI, 1.47% to 3.58%), and tether replacement (1.09%; 95% CI, 0.57% to 2.08%). The overall complication incidence rate was 36.8% (95% CI, 23.9% to 49.7%; 24 studies). Most common complications included curve progression with tether breakage (16.79%; 95% CI, 7.43% to 26.15%), pulmonary complications (6%; 95% CI, 4.66% to 7.68%), and overcorrections (4.55%; 95% CI, 3.4% to 6.06%). A subgroup analysis of patients with more than 36 months follow-up time indicated that these patients had increased clinical success (73.88% vs. 65.93%), unplanned reoperation (15.8% vs. 4.55%), and complication rates (52.17% vs. 23.79%) compared to those with less than 36 months follow-up, respectively. Thus, based on the increased reoperation and complication rates observed with longer follow-up, the authors concluded that further improvements to the implant and refinement of patient selection criteria are warranted and should be assessed in the

context of high-quality randomized controlled trials. Study demographics and outcomes based on race, ethnicity, and sex were not reported, potentially limiting the generalizability of these findings.

Observational Studies

As noted in the Regulatory section above, in June 2019, the U.S. Food and Drug Administration (FDA) granted a Humanitarian Device Exemption to a new vertebral body tethering device called The Tether (Zimmer Biomet Spine, HDE #H190005, product code QHP). Available evidence for The Tether includes only one small retrospective cohort study of 57 pediatric patients that is yet unpublished and is only summarized in the FDA's Humanitarian Device Exemption Summary of Safety and Probable Benefit report.[15] In this study, pediatric patients who failed brace treatment (e.g., greater than 5° of progression and/or intolerance to brace wear) received vertebral body tethering with Dynesys vertebral body screws, which are similar to those of the marketed version of The Tether , but that have a slightly higher screw profile. Study participants were 86.4% female, with a mean age of 12.4 years. At baseline, mean Cobb angles were 30° to 44° in 75.4% of participants and 45° to 65° in 24.6% of participants. After 2 years, among the 44 subjects with 24-month data (out of the original 57), 43 met the probable benefit success criteria of achievement of a Cobb angle of 40°or less. Overall, the mean Cobb angles improved from 40.4° to 14.3° (+65%). Although assessment of quality of life at the last follow-up visits were described as "positive" based on the Pediatric Quality of Life Inventory, the clinical importance of this data is unclear as no baseline assessments were completed for comparison. A total of 8 participants had serious adverse events (14%), including overcorrection of the instrumented curve (8.8%), definite cord break (1.8%), development of a new curve (1.8%), and spondylolisthesis (1.8%). Other common adverse events were back pain (24.6%), overcorrection of the instrumented curve (21.1%), nausea/vomiting (21.1%), and extremity pain (21.1%). A total of 8 patients (6%) required surgical revision due to adverse events.

As noted in a 2015 review article, other devices used for vertebral body tethering are under development, and the optimum tension for vertebral body tethering is currently unknown.[16]

Other studies not included in the Zhu (2022) systematic review[14] are discussed below.

Samdani (2014, 2015) published 2 retrospective reviews on the off-label use of the Dynesys system for anterior vertebral body tethering for idiopathic scoliosis.[17, 18] They reported pursuing vertebral body tethering at their children’s hospital due to lack of success with VBS for thoracic curves greater than 35°. At the time of these reports, 32 patients had a minimum of 1-year follow-up,[18] and 11 consecutive patients had a 2-year follow-up.[17] The mean age at surgery was 12 years, and all patients were skeletally immature. Three patients also had VBS for their lumbar curves. For the 11 patients with 2-year follow-up, on average, 7.8 levels (range, 7 to 9 levels) were tethered. Thoracic Cobb angle averaged 44.3° preoperatively, was corrected to 20.3° after surgery, and improved to 13.5° at 2 years. The lumbar curve improved from 25.1° preoperatively to 7.2° at 2 years. Two patients required that tension be reduced after 2 years due to overcorrection.

Pehlivanoglu (2021) conducted a prospective cohort study of 13 skeletally immature patients (mean age, 11.8 years) who underwent vertebral body tethering with the Dynesys system for adolescent idiopathic scoliosis with double curves.[19] At baseline, the mean thoracic/thoracolumbar and lumbar curve magnitudes were 48.2° and 45.3°, respectively. An average of 11.8 levels of tethering were undertaken. Postoperatively, mean

thoracic/thoracolumbar curve magnitudes were 14.3° to 17.3°. At the last follow-up (mean, 36.4 months), the mean thoracic/thoracolumbar curve magnitudes were 8.2° to 9.7°. No major complications were reported.

Meyers (2022) performed a retrospective review of adolescent scoliosis patients (N=49; 74% female) treated with VBT via the Dynesys system after reaching peak height velocity (Risser stage 3-5).[20] Mean patient age was 15 ±- 1.9 years with mean follow-up duration 32.5 ± 9.1 months. In patients with thoracic major curvatures (n=24), the Cobb angle improved from 51.1 ± 6.9° to 27.2 ± 8.1° (47.7% correction; p<.01). In those with thoracolumbar major curves, curvature improved from 37.2 ± 10.7° to 18.8 ± 9.4° (49.5% correction; p<.01). Improvements in major curve inclinometer measurements and SRS-22 domains improved significantly (p≤.05), except for the SRS-22 activity domain. Overall, 37/49 (76%) of patients were deemed clinically successful with residual major curves ≤30°. At final follow-up, 2 major complications were reported. At 3.1 years after VBT, 1 patient required posterior fusion of the thoracic curve due to curve progression and revision of the thoracolumbar tether due to tether breakage. A second patient developed late onset superior mesenteric artery syndrome (SMAS) 1 year postoperatively which required Ladd's derotation surgery. Overall, 20 (41%) patients experienced tether breakage. However, only 4 of 19 (21%) patients with broken tethers failed to meet criteria for clinical success which was comparable to the 7 of 29 (24%) patients with intact tethers. Thus, treatment success in subjects with limited remaining skeletal growth was feasible. While treatment success was not impacted by age or Risser stage, patients with treatment failures reported slightly larger major Cobb angles at baseline.

Section Summary: Vertebral Body Tethering

There is limited published evidence on vertebral body tethering. The Tether is the only vertebral body tethering device that the FDA has approved for marketing based on a June 2019 Humanitarian Device Exemption. Available evidence for The Tether is limited to a small, single-center, uncontrolled, unpublished retrospective cohort study of 57 pediatric patients. Although reported Cobb angle corrections are promising, serious adverse events occurred, data are lacking on other important health outcomes, and there are important study design limitations, including lack of a control group. Additional early reports of a correction in Cobb angle from published reports on the Dynesys system are also promising, but little is known about longer-term outcomes with this procedure. A meta-analysis of vertebral body tethering studies with more than 36 months follow-up reported a 74% clinical success rate, a 52% complication rate, and a 16% unplanned reoperation rate. Most commonly reported complications were tether breakages, pulmonary complications, and overcorrections. Larger, controlled studies are needed to verify these preliminary findings.

PRACTICE GUIDELINE SUMMARY

SOCIETY ON SCOLIOSIS ORTHOPAEDIC AND REHABILITATION TREATMENT

The guidelines from the Society on Scoliosis Orthopaedic and Rehabilitation Treatment (2016) included recommendations on the following conservative treatments for idiopathic scoliosis[21]: assessment, bracing, physiotherapy, physiotherapeutic scoliosis-specific exercises and other conservative treatments for idiopathic scoliosis, exercises, special inpatient rehabilitation, and bracing (nighttime rigid bracing, soft bracing, part-time rigid bracing, full-time bracing). The guidelines did not address vertebral body stapling or vertebral body tethering.

SCOLIOSIS RESEARCH SOCIETY

The Scoliosis Research Society has indicated that the treatment of adolescent idiopathic scoliosis falls into 3 main categories (observation, bracing, surgery) and is based on the risk of curve progression.[22] Vertebral body stapling and tethering are not addressed by the Society.

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

Information updated on the American Academy of Orthopaedic Surgeons' OrthoInfo website indicates that the type of treatment required for idiopathic scoliosis in children and adolescents depends on the kind and degree of the curve, child's age, and the number of remaining growth years until the child reaches skeletal maturity.[2] Vertebral body tethering and VBS are not addressed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

In 2022, the National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance on vertebral body tethering for idiopathic scoliosis in children and young people.[23] Recommendations stated that "evidence on the safety of vertebral body tethering for idiopathic scoliosis in children and young people is limited but raises concerns of serious complications. Evidence on its efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research."

SUMMARY

There is not enough evidence to show that vertebral body tethering or stapling improves net health outcomes in patients with scoliosis. No clinical practice guidelines based on research recommend the use of vertebral body tethering or stapling for the treatment of scoliosis. Therefore, vertebral body tethering and/or stapling for the treatment of scoliosis is considered investigational.

REFERENCES

1. U.S. Preventive Services Task Force (USPSTF). Final Recommendation Statement: Adolescent Idiopathic Scoliosis: Screening. 2018. [cited 11/14/2023]. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/adolescent-idiopathic-scoliosis-screening.
2. American Academy of Orthopaedic Surgeons (AAOS). Idiopathic Scoliosis in Children and Adolescents. April 2021. [cited 11/14/2023]. Available from: https://orthoinfo.aaos.org/en/diseases--conditions/idiopathic-scoliosis-in-children-and-adolescents.
3. A Margalit, G McKean, A Constantine, CB Thompson, RJ Lee, PD Sponseller. Body Mass Hides the Curve: Thoracic Scoliometer Readings Vary by Body Mass Index Value. *J Pediatr Orthop.* 2017;37(4):e255-e60. PMID: 27861214
4. MJ Heffernan, M Younis, B Song, et al. Disparities in Pediatric Scoliosis: The Impact of Race and Insurance Type on Access to Nonoperative Treatment for Adolescent Idiopathic Scoliosis. *J Pediatr Orthop.* 2022;42(8):427-31. PMID: 35856501
5. A Mishreky, S Parent, F Miyanji, et al. Body mass index affects outcomes after vertebral body tethering surgery. *Spine Deform.* 2022;10(3):563-71. PMID: 35013996

6. L Cuddihy, AJ Danielsson, PJ Cahill, et al. Vertebral Body Stapling versus Bracing for Patients with High-Risk Moderate Idiopathic Scoliosis. *Biomed Res Int.* 2015;2015:438452. PMID: 26618169
7. E Murray, R Tung, A Sherman, RM Schwend. Continued vertebral body growth in patients with juvenile idiopathic scoliosis following vertebral body stapling. *Spine Deform.* 2020;8(2):221-26. PMID: 32026438
8. DB Bumpass, SK Fuhrhop, M Schootman, JC Smith, SJ Luhmann. Vertebral Body Stapling for Moderate Juvenile and Early Adolescent Idiopathic Scoliosis: Cautions and Patient Selection Criteria. *Spine (Phila Pa 1976).* 2015;40(24):E1305-14. PMID: 26655807
9. AA Theologis, P Cahill, M Auriemma, R Betz, M Diab. Vertebral body stapling in children younger than 10 years with idiopathic scoliosis with curve magnitude of 30 degrees to 39 degrees. *Spine (Phila Pa 1976).* 2013;38(25):E1583-8. PMID: 23963018
10. CA Laituri, RM Schwend, GW Holcomb, 3rd. Thoracoscopic vertebral body stapling for treatment of scoliosis in young children. *J Laparoendosc Adv Surg Tech A.* 2012;22(8):830-3. PMID: 23039706
11. T O'Leary P, PF Sturm, KW Hammerberg, JP Lubicky, SM Mardjetko. Convex hemiepiphysiodesis: the limits of vertebral stapling. *Spine (Phila Pa 1976).* 2011;36(19):1579-83. PMID: 21681138
12. RR Betz, A Ranade, AF Samdani, et al. Vertebral body stapling: a fusionless treatment option for a growing child with moderate idiopathic scoliosis. *Spine (Phila Pa 1976).* 2010;35(2):169-76. PMID: 20081512
13. G Mariscal, J Morales, S Pérez, et al. Meta-analysis on the efficacy and safety of anterior vertebral body tethering in adolescent idiopathic scoliosis. *Eur Spine J.* 2023;32(1):140-48. PMID: 36443510
14. F Zhu, X Qiu, S Liu, K Man-Chee Cheung. Minimum 3-year experience with vertebral body tethering for treating scoliosis: A systematic review and single-arm meta-analysis. *J Orthop Surg (Hong Kong).* 2022;30(3):10225536221137753. PMID: 36420934
15. U.S. Food and Drug Administration (FDA). SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB): The Tether Vertebral Body Tethering System. 2019. [cited 11/14/2023]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf19/H190005b.pdf.
16. A Courvoisier, A Eid, E Bourgeois, J Griffet. Growth tethering devices for idiopathic scoliosis. *Expert Rev Med Devices.* 2015;12(4):449-56. PMID: 26027921
17. AF Samdani, RJ Ames, JS Kimball, et al. Anterior vertebral body tethering for idiopathic scoliosis: two-year results. *Spine (Phila Pa 1976).* 2014;39(20):1688-93. PMID: 24921854
18. AF Samdani, RJ Ames, JS Kimball, et al. Anterior vertebral body tethering for immature adolescent idiopathic scoliosis: one-year results on the first 32 patients. *Eur Spine J.* 2015;24(7):1533-9. PMID: 25510515
19. T Pehlivanoglu, I Oltulu, Y Erdag, et al. Double-sided vertebral body tethering of double adolescent idiopathic scoliosis curves: radiographic outcomes of the first 13 patients with 2 years of follow-up. *Eur Spine J.* 2021;30(7):1896-904. PMID: 33611658
20. J Meyers, L Eaker, J Zhang, T di Pauli von Treuheim, B Lonner. Vertebral Body Tethering in 49 Adolescent Patients after Peak Height Velocity for the Treatment of Idiopathic Scoliosis: 2-5 Year Follow-Up. *J Clin Med.* 2022;11(11). PMID: 35683548
21. S Negrini, S Donzelli, AG Aulisa, et al. 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. *Scoliosis Spinal Disord.* 2018;13:3. PMID: 29435499

22. Scoliosis Research Society (SRS). Adolescent Idiopathic Scoliosis. n.d. [cited 11/14/2023]. Available from: http://www.srs.org/professionals/online-education-and-resources/conditions-and-treatments/adolescent-idiopathic-scoliosis.
23. National Institute for Health and Care Excellence (NICE). Interventional procedures guidance: Vertebral body tethering for idiopathic scoliosis in children and young people [IPG728]. June 29, 2022. [cited 11/14/2023]. Available from: https://www.nice.org.uk/guidance/ipg728.

CODES

Codes	Number	Description
CPT	0656T	Vertebral body tethering, anterior; up to 7 vertebral segments
	0657T	Vertebral body tethering, anterior; 8 or more vertebral segments
	0790T	Revision (eg, augmentation, division of tether), replacement, or removal of thoracolumbar or lumbar vertebral body tethering, including thoracoscopy, when performed
	22836	Anterior thoracic vertebral body tethering, including thoracoscopy, when performed; up to 7 vertebral segments
	22837	Anterior thoracic vertebral body tethering, including thoracoscopy, when performed; 8 or more vertebral segments
	22838	Revision (eg, augmentation, division of tether), replacement, or removal of thoracic vertebral body tethering, including thoracoscopy, when performed
	22899	Unlisted procedure, spine
HCPCS	None	

Date of Origin: *November 2023*

Regence

Medical Policy Manual Surgery, Policy No. 233

Coronary Intravascular Lithotripsy

Effective: January 1, 2024

Next Review: December 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Coronary intravascular lithotripsy is used to prepare stenotic, calcified de novo coronary vessels for stent placement. Ultrasound waves are applied intravascularly to selectively break-up calcium deposits to aid with stent placement.

MEDICAL POLICY CRITERIA

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. New and Emerging Medical Technologies and Procedures, Medicine, Policy No. 149

BACKGROUND

Coronary artery calcification (CAC) can interfere with percutaneous coronary intervention (PCI)

due to inadequate stent expansion, difficulty transiting the catheter through a calcified lesion, coated drug separation from a stent, proclivity for in-stent restenosis and stent thrombosis, and a change to the underlying pharmacokinetics.

Shockwave intravascular lithotripsy (IVL) utilizes a percutaneous catheter device to produce acoustic pressure waves to break superficial and deep calcium deposits and aid with the subsequent deployment of a vascular stent. Guidance with an intravascular imaging device either with intravascular ultrasound or optical coherence tomography (OCT) is used to define calcium density and to aid in choosing the lesion modification strategy. There are several adjunctive therapies to aid in the modification of calcified plaques in order to facilitate stent delivery. These include rotational atherectomy (RA), scoring, cutting and super high-pressure balloons, orbital atherectomy (OR), laser atherectomy (LA) and IVL.[1]

REGULATORY STATUS

In 2021, The US Food and Drug administration (FDA) granted Premarket Approval (PMA) for the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C2 Coronary Intravascular Lithotripsy (IVL) Catheter (Product code QMG, PMA number P200039).[2]

The Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C2 Coronary IVL Catheter is indicated for lithotripsy-enabled, low-pressure balloon dilatation of severely calcified, stenotic *de novo* coronary arteries prior to stenting.[3]

EVIDENCE SUMMARY

CORONARY INTRAVASCULAR LITHOTRIPSY (IVL)

The evidence summary includes systematic reviews and randomized clinical trials not included in the systematic reviews.

Systematic Reviews

Caminiti (2023) published a systematic review with meta-analysis to investigate the success rate of IVL for the treatment of stent underexpression (SU) because of coronary calcified plaque.[4] The meta-analysis included 13 studies with 354 patients, majority male (77%). The mean follow-up time was 2.6 months (95% CI 1 to 15.3). Strategy success was seen in 88.7% (95% CI 82.3 to 95.1) of patients. The mean minimal stent area was reported in 6 studies, the pre-IVL value was 3.4 mm2 (95% CI 3 to 3.8), and the post-IVL value was 6.9 mm2 (95% CI 6.5 to 7.4). The mean diameter stenosis (percentage) was reported in seven studies, the pre-IVL value was 69.4% (95% CI 60.7 to 78.2), and the post-IVL value was 14.6% (95% CI 11.1 to 18). The rate of intraprocedural complications was 1.6% (95% CI 0.3 to 2.9). The authors concluded that the “stent through” technique was safe to treat SU.

Mhanna (2022) published a systematic review evaluating the utility of adjunctive IVL.[5]The study included a total of eight single-arm observational studies, including 980 patients (1011 lesions), were included. 48.8% of the patients presented with acute coronary syndrome. Severe calcifications were present in 97% of lesions. Clinical success was achieved in 95.4% of patients (95%CI:92.9%-97.9%). Angiographic success was achieved in 97% of patients (95%CI:95%-99%). There was an overall increase in postprocedural lumen area as well as significant reduction of calcium angle and maximum calcium thickness.

Most of the evidence of safety and effectiveness of Coronary IVL extends from the four prospective, nonrandomized, single arm, manufacturer sponsored, multisite DISRUPT CAD studies: Disrupt CAD I (NCT02650128); Disrupt CAD II (NCT03328949); Disrupt CAD III; and Disrupt CAD IV (NCT04151628). The following publications (systematic review with meta-analysis, meta-analysis, and a pooled analysis) discuss the results of these, as well as retrospective registry studies.[6-8]

Satter (2022) published a meta-analysis for IVL outcomes in severely calcified coronary lesions.[6] The primary outcomes included clinical and angiographic success event ratios. The secondary outcomes included minimal lumen diameter (MLD), diameter stenosis (DS), lumen area, maximum calcium thickness, and calcium angle at minimal lumen area (MLA) and final minimal stent area (MSA). A total of seven studies (n = 760) were included. The DISRUPT CAD I – IV, a subgroup analysis of the DISRUPT CAD I study, and two registry (retrospective cohort analysis) studies. The primary outcomes: pooled clinical and angiographic success event ratio parentage of IVL was 94.4 % and 94.8 %, respectively. On a random effect model for standard inverse variance for secondary outcomes showed: minimal lumen diameter increase with IVL was 4.68 mm (p < 0.0001, 95 % CI: 1.69 to 5.32); diameter decrease in the stenotic area after IVL session was -5.23 mm (95 % CI: -22.6 to 12.8). At the MLA and final MSA sites, MLA gain was 1.42 mm2 (95 % CI: 1.06 to 1.63; p < 0.00001) and 1.34 mm2 (95 % CI: 0.71 to 1.43; p < 0.00001), respectively. IVL reduced calcium thickness at the MLA site (SMD -0.22; 95 % CI: -0.40 to 0.04; p = 0.02); calcium angle was not affected at the MLA site. The tertiary outcomes: most common complication was MACEs (n = 48/669), and least common complication was abrupt closure of the vessel (n = 1/669). The analysis was limited by inclusion of only single-arm observational studies. The definition of sever calcification was not uniform likely due to a lack of consistency of imaging type (ultrasound or optical coherence tomography). Only two studies reported diameter stenosis data. The post procedural outcomes did not include any form of adjunctive treatment (atherectomy or specialty cutting balloons). The authors suggest that more studies, including randomized, double-blind trials, are needed to study safety and efficacy in a head-to-head comparison with other debulking procedures.

Kereiakes (2021) published a pooled safety and effectiveness results from the four DISRUPT CAD I-IV studies.[7] Data was included from patients (n = 628) enrolled in 72 sites from 12 countries. The primary safety endpoint was a composite score of cardiac death, all myocardial infarction, or target vessel revascularization at 30 days. Procedural success was defined as stent delivery with a residual stenosis of >= 30% assessed by quantitative coronary angiography and without in-hospital major adverse CV events. The primary safety and effectiveness endpoints were achieved in 92.7% and 92.4% of patients, respectively. The rate of in-hospital major adverse cardiovascular events was 6.5% (4.7% to 8.8%), driven by non-Q-wave myocardial infarction (5.7%, 4.1% to 7.9%). The rate of 30-day major adverse cardiovascular events was 7.3% (5.4% to 9.7%), also driven by non-Q-wave myocardial infarction (5.9%, 4.2% to 8.1%). At 30 days, the rates of target lesion failure, cardiac death, and stent thrombosis were 7.2%, 0.5%, and 0.8%, and rates of postprocedure and final serious angiographic complications were 2.1% and 0.3%, respectively, with no procedure associated perforations, abrupt closure, or episodes of no reflow, suggesting procedural success in treating both eccentric and concentric calcified lesions. Results of multivariate logistic regression show that treatment of bifurcation lesion (p = 0.006), prior myocardial infarction (p = 0.04), and lesion length ≥ 25 mm (p = 0.049) were independent predictors of 30-day major adverse cardiovascular events. Prior myocardial infarction (p = .016) and treatment of

bifurcation lesion (P = .015) were predictors of lack of procedural success. Several of the authors of this analysis have professional affiliations with the device manufacture.

Sattar (2021) published a SR with meta-analysis examining the safety and efficacy of coronary IVL for left coronary calcified disease (LCAD).[8]They included four studies in their analysis (n = 282 patients) including results from the Disrupt CAD I and CAD II trials. In LCAD, ICL can yield lumen gain of up to 4.16 mm. The overall post-procedure lumen diameter was significantly higher than the pre-procedure diameter. The authors concluded that IVL offer a significant improvement in the vessel lumen to facilitate coronary stent delivery and deployments in severely calcified coronary arteries. They also indicated recommended that there is a need for randomized controlled trials and longer-term follow-up before recommending the routine use of Coronary Intravascular Lithotripsy.

Sheikh (2021) published a systematic review assessing the efficacy and feasibility of IVL in treating severe coronary calcification.[9] The review included a total of 62 studies with 1389 patients (1414 lesions; 74.7% male patients with a mean age of 72.03 years) with significant coronary calcification or under-expanded stents underwent IVL. Significant improvement was demonstrated in acute and sustained vessel patency with a procedural success rate of 78.2 – 100% in hospital. The authors conclude that recent studies have highlighted that the use of IVL with adjuvant intracoronary imaging has revolutionized the way of treating heavily calcified, non-dilatable coronary lesions and is likely to succeed the conventional ways of treating these complex lesions. And that further studies are needed to gauge the long-term efficacy and safety of IVL against techniques currently available for calcium modification including conventional balloons, cutting or scoring balloons, rotational atherectomy and laser atherectomy.

Randomized Controlled Trials

Two studies published in 2023 reported the results of the ROTA shock trial.[10, 11] The ROTA shock study is a randomized, prospective, non-blinded, double-arm, multicenter non-inferiority trial. Patients (n=70) were randomly (1:1) assigned to undergo either IVL or rotational atherectomy (RA) before percutaneous coronary intervention of severely calcified coronary lesions. The mean patient age was 73.3 ± 7.2 years, and the majority were male (75.4%). The primary endpoint minimal stent area (MSA) was lower but non-inferior after IVL (mean: 6.10 mm^2 , 95% confidence interval [95% CI]: 5.32-6.87 mm^2) versus RA (6.60 mm^2 , 95% CI: 5.66-7.54 mm^2 ; difference in MSA: -0.50 mm^2 , 95% CI: -1.52-0.52 mm^2 ; non-inferiority margin: -1.60 mm^2). Stent expansion was similar (RA: 0.83 ± 0.10 vs. IVL: 0.82 ± 0.11; p = 0.79). There were no significant differences regarding contrast media consumption (RA: 183.1 ± 68.8 vs. IVL: 163.3 ± 55.0 mL; p = 0.47), radiation dose (RA: 7269 ± 11288 vs. IVL: 5010 ± 4140 cGy cm^2; p = 0.68), and procedure time (RA: 79.5 ± 34.5 vs. IVL: 66.0 ± 19.4 min; p = 0.18). Two patients randomized to IVL were required to crossover to the RA group. In addition to small sample size and gender bias, limitations included a lower threshold for non-inferiority than originally predicted and the baseline vessel dimensions and reference vessel area in final OCT scans were larger in the RA than in the IVL group, leading to a bias for the comparison of MSA between these two groups.[10] An additional evaluation of the ROTA shock trial compared plaque modification of severely calcified lesions by coronary intravascular lithotripsy (IVL) with that of rotational atherectomy (RA) using optical coherence tomography (OCT). They concluded that RA leads to a greater acute lumen gain, IVL induces more and longer fractures of the calcified plaque.[11]

A 2023 prospective single center randomized study to investigate if pre-treatment with IVL in severely calcified lesions increases stent expansion, assessed by optical coherence tomography (OCT), when compared to predilatation with conventional and/or specialty balloon strategy.[12] A total of 40 patients were included. The minimal stent expansion in the IVL-group (n = 19) was 83.9 ± 10.3% and 82.2 ± 11.5% in the conventional group (n = 21) (p = 0.630). Minimal stent area was 6.6 ± 1.5 mm^2 and 6.2 ± 1.8 mm^2, respectively (p = 0.406). No peri-procedural, in-hospital and 30-day follow-up major adverse cardiac event (MACE) were reported. The authors concluded that in severely calcified coronary lesions there were no significant difference in stent expansion measured by OCT when comparing IVL, as plaque modification, with conventional and/or specialty angioplasty balloons.

Section Summary

Coronary intravascular lithotripsy (IVL) is a relatively new technology. The evidence reviewed includes six systematic reviews (SR) and two recent randomized clinical trials. All SRs are based on single armed studies and in mostly male subjects. Most of the evidence of safety and effectiveness of Coronary IVL extends from the four prospective, nonrandomized, single arm, manufacturer sponsored, multisite DISRUPT CAD studies: Disrupt CAD I (NCT02650128); Disrupt CAD II (NCT03328949); Disrupt CAD III; and Disrupt CAD IV (NCT04151628), which predisposes to publication bias. Two randomized trials were recently published including a prospective non-inferiority trial (n = 70) comparing outcomes of IVL or rotational atherectomy (RA) and a prospective study (n = 40) comparing pretreatment with IVL to predilatation with conventional and/or speciality balloon strategy. Both studies suggested IVL is not inferior to the comparator procedures. The RCTs have limitations such as small sample size, mostly male participants, heterogeneity of baseline lumen diameters. Adequately powered randomized controlled trails comparing IVL to currently used procedures are needed to assess the safety and efficacy of IVL.

PRACTICE GUIDELINE SUMMARY

None

SUMMARY

There is not enough research to support the use of coronary intravascular lithotripsy in any indication. No clinical guidelines based on research recommend coronary intravascular lithotripsy. Therefore, coronary intravascular lithotripsy is considered investigational for all indications.

REFERENCES

1. Hennessey B, Pareek N, Macaya F, et al. Contemporary percutaneous management of coronary calcification: current status and future directions. *Open Heart.* 2023;10(1). PMID: 36796870
2. FDA. Food and Drug Administration; Premarket Approval - Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C2 Coronary Intravascular Lithotripsy (IVL) Catheter (P200039). [cited 11/29/2023]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200039S001.

3. FDA. Food and Drug Administration; Summary of Safety and Effectiveness Data - Intravascular Lithotripsy System [cited 11/29/2023]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200039B.pdf.
4. Caminiti R, Vetta G, Parlavecchio A, et al. A Systematic Review and Meta-Analysis Including 354 Patients from 13 Studies of Intravascular Lithotripsy for the Treatment of Underexpanded Coronary Stents. *Am J Cardiol.* 2023;205:223-30. PMID: 37611414
5. Mhanna M, Beran A, Nazir S, et al. Efficacy and Safety of Intravascular Lithotripsy in Calcified Coronary Lesions: A Systematic Review and Meta-Analysis. *Cardiovasc Revasc Med.* 2022;36:73-82. PMID: 34024748
6. Sattar Y, Almas T, Arshad J, et al. Clinical and angiographic success and safety comparison of coronary intravascular lithotripsy: An updated meta-analysis. *Int J Cardiol Heart Vasc.* 2022;39:100975. PMID: 35242998
7. Kereiakes DJ, Di Mario C, Riley RF, et al. Intravascular Lithotripsy for Treatment of Calcified Coronary Lesions: Patient-Level Pooled Analysis of the Disrupt CAD Studies. *JACC Cardiovasc Interv.* 2021;14(12):1337-48. PMID: 33939604
8. Sattar Y, Ullah W, Virk HUH, et al. Coronary intravascular lithotripsy for coronary artery calcifications- systematic review of cases. *J Community Hosp Intern Med Perspect.* 2021;11(2):200-05. PMID: 33889320
9. Sheikh AS, Connolly DL, Abdul F, et al. Intravascular lithotripsy for severe coronary calcification: a systematic review. *Minerva Cardiol Angiol.* 2023;71(6):643-52. PMID: 34713678
10. Blachutzik F, Meier S, Weissner M, et al. Coronary intravascular lithotripsy and rotational atherectomy for severely calcified stenosis: Results from the ROTA.shock trial. *Catheter Cardiovasc Interv.* 2023;102(5):823-33. PMID: 37668088
11. Blachutzik F, Meier S, Weissner M, et al. Comparison of Coronary Intravascular Lithotripsy and Rotational Atherectomy in the Modification of Severely Calcified Stenoses. *Am J Cardiol.* 2023;197:93-100. PMID: 37012181
12. Oomens T, Vos NS, van der Schaaf RJ, et al. EXpansion of stents after intravascular lithoTripsy versus conventional predilatation in CALCified coronary arteries. *Int J Cardiol.* 2023;386:24-29. PMID: 37178801

CODES

Codes	Number	Description
CPT	92972	Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)
HCPCS	C1761	Catheter, transluminal intravascular lithotripsy, coronary

Date of Origin: *December 2023*

Uniform Medical Plan

Gender Affirming Interventions for Gender Dysphoria: Clinical Criteria and Policy

Document Number: 54-0006
Issued: January 1, 2017
Effective: January 1, 2017
Revised: September 16, 2019

UMP members should refer to Regence medical policy 153 for information about UMP's coverage of transgender services, with the exception of information in the "Medical Policy Criteria" box in policy 153. Instead of the criteria listed in that box, the UMP-specific clinical criteria outlined below must be met to receive transgender surgical services.

I. Medical Treatments for Gender Dysphoria

A. Psychotherapy may be considered medically necessary as a treatment of gender dysphoria.
B. Continuous hormone therapy may be considered medically necessary as a treatment of gender dysphoria when all of the following criteria are met:
    1. Clinical records document that the patient has the capacity to make fully informed decisions and consent for treatment; and hormone therapy is part of a comprehensive, patient-centered treatment plan; and
    2. A licensed behavioral health practitioner or a licensed physician, advanced registered nurse practitioner (ARNP), physician's assistant (PA) or psychologist is treating the patient for primary care or transgender services and:
        a) Assesses the patient and makes or confirms the diagnosis of gender dysphoria as defined by the DSM-V criteria, and
        b) Determines or confirms that the gender dysphoria is not due to another mental or physical health condition.

II. Surgical Treatments of Gender Dysphoria

A. Gender reassignment surgery (see UMP clinical criteria policy and Regence medical policy 153 guidelines) may be considered medically necessary in the treatment of gender dysphoria when all of the following criteria are met:
    1. Age at least 18 years. For patients younger than 18 years of age, mastectomy may be considered a medically necessary surgical procedures. Other requirements outlined in this section must be met to proceed with mastectomy in those younger than 18 years of age.
    2. Clinical records document that the patient has the capacity to make fully informed decisions and consent for treatment as part of a comprehensive, patient-centered treatment plan; and that any other mental health condition, if present, is adequately controlled; and
    3. At least 2 licensed mental health professionals have diagnosed gender dysphoria, and recommend surgical treatment (*Only one mental health professional referral is required for mastectomy); and
        a) Assesses the patient and makes or confirms the diagnosis of gender dysphoria as defined by the DSM-V criteria, and
        b) Determines or confirms that the gender dysphoria is not due to another mental or physical health condition; and

4. Documentation of continuous hormonal therapy for at least 12 months, unless there is a documented medical contraindication to hormonal therapy. Hormonal therapy is not required prior to mastectomy; and
5. Twelve months of living in a gender role that is congruent with the patient's gender identity.

B. Prior authorization is required for all proposed surgical interventions. Section II.A of this policy lists the requirements and documentation that must be submitted for prior authorization review. Surgeries are not required to be completed at the same time and, instead, may be performed and receive prior authorization in progressive stages. UMP covers the following procedures with prior authorization that meet medical necessity criteria:
   1. Blepharoplasty, covered only if restorative function medical criteria are met (not specific to transgender surgery);
   2. Breast augmentation will require preauthorization with following criteria:
      a) Documentation of continuous hormonal therapy for at least 12 months, unless there is documented medical contraindication to hormonal therapy; and
      b) Have not reached a Tanner Stage 5.
   3. Bilateral mastectomy with or without chest reconstruction;
   4. Clitoroplasty;
   5. Colovaginoplasty;
   6. Colpectomy;
   7. Genital surgery;
   8. Genital electrolysis and laser hair removal as required as part of the genital surgery is covered with prior authorization and is limited to the genitals and, if applicable, the graft site, as required for genital surgery. Electrolysis and laser hair removal not meeting these guidelines and the guidelines for Surgical Treatments of Gender Dysphoria outlined in the Gender Affirming Interventions for Gender Dysphoria Criteria and Policy is not covered.
   9. Hysterectomy;
   10. Labiaplasty;
   11. Metoidioplasty;
   12. Orchiectomy;
   13. Penectomy;
   14. Phalloplasty;
   15. Placement of testicular prosthesis;
   16. Rhinoplasty, covered only if restorative function medical criteria are met (not specific to transgender surgery);
   17. Salpingo-oophorectomy;
   18. Scrotoplasty;
   19. Urethroplasty;
   20. Vaginectomy; and
   21. Vaginoplasty.

C. Other than gender reassignment surgeries listed in this policy, surgery and/or additional treatments to change specific appearance characteristics are considered not medically necessary as treatments of gender dysphoria, including, but not limited to the following:
   1. Brow lifts;
   2. Calf implants;
   3. Cheek/malar implants;
   4. Chin/nose implants;
   5. Chondrolaryngoplasty;
   6. Collagen injections;

7. Drugs for hair loss or growth;
8. Facial or trunk hair removal via laser or electrolysis;
9. Facial feminization;
10. Face lift;
11. Forehead lift;
12. Hair transplantation;
13. Jaw shortening;
14. Lip reduction;
15. Liposuction;
16. Mastopexy;
17. Neck tightening;
18. Pectoral implants;
19. Reduction thyroid chondroplasty;
20. Removal of redundant skin;
21. Suction-assisted lipoplasty of the waist;
22. Trachea shave;
23. Voice modification surgery; and
24. Voice therapy/lessons.

Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Surgery, Policy No. 52

Ventricular Assist Devices and Total Artificial Hearts

Effective: January 1, 2022

Next Review: December 2021
Last Review: December 2021

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ventricular assist devices and total artificial hearts provide mechanical circulation for patients with end-stage heart disease who are waiting for, or cannot survive, a heart transplant.

MEDICAL POLICY CRITERIA

Note: This policy does not address the use of percutaneous ventricular assist devices (pVADs) which may be considered medically necessary.

I. Implantable ventricular assist devices (i.e., LVADs, RVADs and BiVADs)

A. Implantable ventricular assist devices with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** for any of the following indications (1-3):

1. As a bridge to transplantation for patients who meet all of the following criteria:

a. Currently listed as a heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation

b. Not expected to survive until a donor heart can be obtained

2. For use in the post-cardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass.
3. As destination therapy in patients meeting all of the following criteria:
    a. End-stage heart failure
    b. Documented ineligibility for human heart transplantation
    c. One of the following criteria is met:
        i. New York Heart Association (NYHA) class III or IV* for at least 28 days who have received at least 14 days support with an intraaortic balloon pump or are dependent on intravenous inotropic agents, with two failed weaning attempts. (NYHA Class III = marked limitation of physical activity; less than ordinary activity leads to symptoms. NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest.)
        ii. NYHA class IV* heart failure for at least 60 days. (NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest)

B. Ventricular assist devices and aortic counterpulsation devices are considered **investigational** in all other circumstances, including but not limited to the use of a non-FDA approved device.

II. Total Artificial Hearts

A. Total artificial hearts with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** as a bridge to heart transplantation in patients meeting all of the following criteria:
1. Have biventricular failure
2. Currently listed as heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation
3. Not considered a candidate for a univentricular or biventricular support device
4. Have no other reasonable medical or surgical treatment options
5. Not expected to survive until a donor heart can be obtained

B. Total artificial hearts are considered **investigational** in all other circumstances, including but not limited to the following:
1. Use as destination therapy
2. Use of a total artificial heart that does not have FDA PMA, 510(k), or HDE clearance

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision

outcome.

- History and Physical/Chart Notes
- For Implantable Ventricular Assist Devices:
    - Documentation as to whether this is a bridge to heart transplant, being used post-cardiotomy for patient who is unable to be weaned of cardiopulmonary bypass, or as destination therapy
    - For destination therapy:
        - Documentation of end-stage heart failure, ineligibility for human heart transplant, and current NYHA classification, including duration of NYHA classification, symptoms, and treatments tried.
- For Total Artificial Heart:
    - Documentation that this is a bridge to heart transplant and patient has biventricular failure; is listed as heart transplant candidate or undergoing evaluation to determine candidacy for heart transplant; is not considered a candidate for univentricular or biventricular support device; has no other reasonable medical or surgical treatment options; and is not expected to survive until a donor heart can be obtained

CROSS REFERENCES

1. Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults, Medicine, Policy No. 152
2. Surgical Ventricular Restoration, Surgery, Policy No. 149
3. Heart Transplant, Transplant, Policy No. 02
4. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

VENTRICULAR ASSIST DEVICES (VADS)

Biventricular, Right Ventricular, and Left Ventricular Devices

There are three kinds of ventricular assist devices: biventricular (BiVADs), right ventricular (RVADs), and left ventricular (LVADs). Surgically implanted ventricular assist devices (VADs) are attached to the native heart and vessels to provide temporary mechanical circulatory support by augmenting cardiac output. LVADs to support the left ventricle are the most commonly used VADs, but right ventricular and biventricular devices may also be used. LVADs are most commonly used as a bridge to transplantation for those patients who are not expected to survive without mechanical support until a heart becomes available. LVADs may also be used as a bridge to recovery in patients with reversible conditions affecting cardiac output (e.g., post-cardiotomy cardiogenic shock). More recently, given the success of LVADs for prolonged periods of time, there has been interest in using LVADs as permanent "destination" therapy for patients with end-stage heart disease who are not candidates for human heart transplantation due to age or other comorbidities.

Aortic Counterpulsation Devices

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-

controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved.

TOTAL ARTIFICIAL HEARTS

The total artificial heart (TAHs) replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. TAHs may be implanted temporarily as a bridge to heart transplantation or permanently as destination therapy in those who are not candidates for transplantation.

The CardioWest™ Total Artificial Heart is a temporary TAH, which is used in the inpatient hospital setting as a bridge to heart transplantation. The CardioWest TAH is implanted after the native ventricles have been excised. The AbioCor® Implantable Replacement Heart is a permanent TAH currently available as destination therapy for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. The device has an internal battery that allows the recipient to be free from all external connections for up to one hour. The system also includes two external batteries that allow free movement for up to two hours. During sleep and while batteries are being recharged, the system can be plugged into an electrical outlet. In order to receive the AbioCor® artificial heart, in addition to meeting other criteria, patients must undergo a screening process to determine if their chest volume is large enough to hold the two-pound device which is too large for about 90% of women and many men.

REGULATORY STATUS

Device Name	Device Type	Manufacturer	FDA Approval	Indication
HeartMate II®	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
HeartMate 3™	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
Thoratec® IVAD	BiVAD	Thoratec Corp.	PMA + Supplement	Bridge to transplant and post-cardiotomy
Levitronix Centrimag®	RVAD	Levitronix, LLC	HDE	Postcardiotomy (temporary circulatory support for up to 14 days)
Novacor®	LVAD	World Heart, Inc.	PMA	Bridge to transplant
DeBakey VAD® Child	LVAD	MicroMed Technology, Inc.	HDE	Bridge to transplant in children 5-16 years of age
EXCOR® Pediatric System	BiVAD	Berlin Heart, Inc.	HDE	Bridge to transplant, pediatric (newborns to teens)
Jarvik 2000	LVAD	Jarvik Heart, Inc.	*IDE-Investigational*†	
HeartWare® Ventricular Assist System (HVAD®)	VAD	Heartware Intl., Inc.	PMA	Bridge to transplant – for use in-hospital or out-of-hospital

Device Name	Device Type	Manufacturer	FDA Approval	Indication
AutoCat 2 WAVE® IABP System	IABP	Arrow Intl., Inc.	none	
Maquet CS300™ IABP	IABP	Maquet Cardiovascular, LLC	none	
SynCardia Temporary TAH (formerly called CardioWest™)	Temporary total artificial heart	SynCardia Systems, Inc.	510(k)	Bridge to transplant – for use inside the hospital
AbioCor® TAH	Implantable Replacement Heart System	AbioMed, Inc.	HDE	Destination therapy

†FDA Investigational Device Exemption (IDE) is not considered a full FDA approval. Devices with an IDE designation are considered investigational.

In August 2015, the U.S. Food and Drug Administration (FDA) published a safety communication about serious adverse events with implantable left ventricular assist devices.[1]

In August 2016, HeartWare® recalled its VAD Pumps due to a design flaw that was deemed by FDA as potentially causing serious injuries or death (class I recall). The devices affected were manufactured and distributed from March 2006 and May 2018. FDA product codes: 204 and 017.

A class I recall was issued for the HeartMate 3™ in April 2018 affecting all manufacturing dates. FDA product code: DSQ.

Although adverse events have been reported, the FDA recognizes “that LVADs are life-sustaining, life-saving devices for patients with advanced left ventricular heart failure. When used for the currently approved indications in appropriately selected patients, we believe the benefits of these LVADs continue to outweigh the risks”

EVIDENCE SUMMARY

The principal outcome associated with treatment of refractory heart failure (HF) is to prolong survival, either temporarily as a bridge to decision, recovery, or heart transplantation, or permanently as a replacement for the damaged heart in patients who are not candidates for heart transplantation.

VENTRICULAR ASSIST DEVICES

BRIDGE TO TRANSPLANTATION, LEFT VENTRICULAR ASSIST DEVICES

Systematic Reviews

A systematic review published in 2011 supported the conclusions reached in the 1996 BCBSA TEC assessment.[2, 3] The 2011 review included 31 observational studies that compared outcomes of transplant in patients who did and did not have pre-transplant left ventricular assist devices (LVADs). Survival at one year was more likely in patients who had

LVAD treatment, but this benefit was confined to patients who received an intra-corporeal device (relative risk [RR]: 1.8, 95% confidence interval [CI] 1.53 to 2.13). For patients treated with an extracorporeal device, the likelihood of survival was not different from patients who were not treated with an LVAD (RR: 1.08, 95% CI 0.95 to 1.22). There was no difference in the risk of rejection between patients who did and did not receive LVAD treatment.

Nonrandomized Studies

Adult patients

Additional reports not included in the 1996 TEC assessment or the 2011 systematic review are consistent with the above analysis.[4-6] It should be recognized that left ventricular assist devices cannot change the number of patients undergoing heart transplantation due to the fixed number of donor hearts. However, the LVAD will categorize its recipient as a high priority heart transplant candidate. Currently available LVADs consist of pulsatile devices that require both stiff power vent lines that perforate the skin and bulky implantable pump chambers. There is considerable research interest in developing non-pulsatile axial flow systems that have the potential for small size and low-noise levels.[7-12]

Aissaoui (2018) published an observational study comparing 224 patients in Germany and France with end-stage heart failure who received VAD as first option (group I, n=83) or either heart transplantation or medical therapy as first option (group II, n=141).[13] The estimated two-year survival was 44% for group I and 70% for group II (p<0.001). The study was limited by the lack of randomization and possible patient selection bias.

Grimm (2016) compared outcomes for patients based on the duration of LVAD use, using data from the United Network for Organ Sharing database.[14] Of the 1,332 included patients, 130 (9.8%) were classified as short duration (< 90 days), 729 (54.7%) were classified as intermediate duration (90 to 365 days), and 473 (35.5%) were classified as long duration (>365 days). A greater proportion of patients in the intermediate and long duration groups were considered functionally independent prior to transplantation compared with the short duration patients. There was no difference in 30-day survival, six-month survival, or one-year survival between the groups. Also, despite worse renal function in the intermediate and long-term groups, there was no difference between groups in new-onset post-transplant renal failure.

Another report by Grimm (2016),which used the United Network for Organ Sharing database, suggested that patients bridged to transplant with an LVAD have better outcomes than those bridged with TAH or biventricular assist devices.[15] Cheng (2016) compared BiVAD to TAH outcomes in this database, and found similar wait-list survival between the groups.[16]

Deo (2014) reported no significant differences in outcomes for 37 patients bridged to transplant with a ventricular assisted device (VAD) and 70 patients who underwent a heart transplant directly.[17] In 2013, Slaughter reported combined outcomes for patients included in the HeartWare® bridge-to-transplant study.[18] The study included 322 patients with heart failure, eligible for heart transplant, who received the HeartWare® (140 patients from the original study; 190 patients in the continue-access protocol) who were monitored to outcome or had completed 180 days of follow-up at the time of this analysis. Survival at 60, 180, and 360 days was 97%, 91%, and 84%, respectively. The most common adverse events were respiratory dysfunction, arrhythmias, sepsis, and driveline exit-site infections. Patients generally had improvements in quality of life measures.

Aaronson (2012) reported results of a multicenter, prospective study of a newer generation LVAD, the HeartWare®, which is a smaller, continuous flow centrifugal device that is implanted in the pericardial space.[19] The study enrolled 140 patients who were awaiting heart transplantation who underwent HeartWare® implantation. A control group of 499 subjects was comprised of patients drawn from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, which collects data on patients who receive FDA-approved durable mechanical circulatory support devices. The study's primary outcome was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes were comparisons of survival between groups and functional, quality of life, and adverse event outcomes in the HeartWare® group. Success occurred in 90.7% of the HeartWare® group and 90.1% of controls ($p<0.001$, noninferiority with a 15% margin). Serious adverse events in the HeartWare® group included, most commonly, bleeding, infections, and perioperative right heart failure.

Evidence suggests that the HeartMate II® axial achieves similar or better results than the earlier pulsatile HeartMate I model. In six reports with samples ranging from 32 to 279 patients, most participants received the new device as a bridge to transplantation.[20-25] Survival rates at six months and one year were 67% to 87%, and 50% to 80%, respectively. These rates are similar to those reported from INTERMACS.[26] An additional report from INTERMACS comparing the HeartMate II® to other LVAD devices for patients who received them with a bridge to transplantation indication reported that 80% and 91% of HeartMate II® and other LVAD patients reached transplant, cardiac recovery, or ongoing LVAD support by six months.[27] One report, however, compared HeartMate I and HeartMate II® recipients at a single center, finding the same one year survival and similar rates of subsequent development of right heart failure.[22] Serious adverse events occurring after HeartMate II® implantation included bleeding episodes requiring reoperation, stroke, infection, and device failure. A European study that included 67 bridge to transplant patients and 31 destination therapy patients found similar one-year survival rates in the two groups: 63% and 69%, respectively. A report on HeartMate II® recipients at a single institution found that out of 250 LVAD patients between November 2011 and June 2016, 6% (16) required a device pump exchange during the study period, and all but one patient survived until hospital discharge.[28]

Pediatric Patients

Publications on children using VADs as a bridge to transplantation have reported positive outcomes. For example, a retrospective study of all children listed for a heart transplant at a single center between 1993 and 2009 found that mortality dropped significantly after the availability of VADs.[29] Davies (2008) reported that pediatric patients requiring a pretransplantation VAD had similar long-term survival to those not receiving mechanical circulatory support.[30]

A retrospective registry study by Jeewa (2018) assessed long-term outcomes for pediatric VAD use as a bridge to transplantation in patients from the Berlin Heart investigational device exemption trial.[31] These patients (n=109) were compared with matched controls from the Pediatric Heart Transplant Study who did not require mechanical circulatory support (n=166). There was no significant difference between the groups for five-year survival (81% for VAD, 88% for non-VAD, $p=0.09$) or for rates of infection or rejection.

Bulic (2017) identified all U.S. children between 1 and 21 years of age at heart transplant between 2006 and 2015 for dilated cardiomyopathy who were supported with an LVAD or

vasoactive infusions alone at the time of heart transplant from the Organ Procurement and Transplant Network registry (n=701).[32] Children receiving LVAD were older, on a higher level of hemodynamic support, more likely to be on dialysis and waited long to receive a donor heart than children receiving vasoactive infusions. Functional status as measured by the median Karnofsky Performance Scale at heart transplant was higher for children receiving LVAD compared with vasoactive infusion (6 vs 5, p<0.001) and children receiving LVAD were more likely to be discharged from the hospital at the time of transplant. The percent of children having stroke at the time of transplant was higher in those receiving LVAD (3% vs 1%, p=0.04).

Almond (2013) reported results from a prospective, multicenter registry to evaluate outcomes in children who received the Berlin Heart EXCOR® device as a bridge to transplant.[33] All patients were followed up from the time of EXCOR® implantation until transplantation, death, or recovery. The study included 204 children, 67% of whom received the device under compassionate use. Survival at 12 months on EXCOR® support was 75%, including 64% who survived to transplantation, 6% who recovered (device explanted and patient survived 30 days), and 5% alive with the device in place. In a follow-up study which evaluated 204 children from the same registry, Jordan reported relatively high rates of neurologic events in pediatric patients treated with the EXCOR® device (29% of patients), typically early in the course of device use.[34] A 2016 report on this group included 358 bridge-to-transplant EXCOR® patients, and found that short- and mid-term post-transplant survival in these patients was similar to that of patients who did not receive pre-transplant mechanical circulatory support.[35]

Wehman (2016) reported on post-transplant survival outcomes for pediatric patients who received a VAD, extracorporeal membrane oxygenation (ECMO), or no mechanical circulatory support, in the pre-transplant period.[36] The study included 2,777 pediatric patients who underwent heart transplant from 2005 to 2012, who were identified through the United Network for Organ Sharing Database, of whom 428 were bridged with VADs and 189 were bridged with ECMO. In unadjusted analysis, the actuarial five-year survival was highest in the direct-to-transplant group (77%), followed by the VAD group (49%) and then the ECMO group (35%). In a proportional hazards model to predict time to death, restricted to the first four months post-transplant, ECMO bridging was significantly associated with higher risk of death (adjusted hazard ratio [HR] 2.77 vs direct-to-transplant, 95% CI 2.12 to 3.61, p<0.0001). However, a model to predict time to death excluding deaths in the first four months post-transplant, the bridging group was not significantly associated with risk of death.

Section Summary

In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of numerous nonrandomized studies comparing different LVADs devices among patients who have no other treatment options. In children, the evidence consists of several nonrandomized studies. These studies report that substantial numbers of patients survive the transplant in situations in which survival would not be otherwise expected. Despite the lack of high-quality studies, this evidence is sufficient to determine that outcomes are improved in patients who have no other options for survival.

VENTRICULAR ASSIST DEVICES AS BRIDGE TO RECOVERY

VADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle. Several additional studies have investigated the role of VADs in bridging patients to decision.

Nonrandomized Studies

Support from VADs was originally indicated for the treatment of postcardiotomy cardiogenic shock in patients who could not be weaned from cardiopulmonary bypass. VAD use in this setting is temporary and brief, lasting between 1.4 and 5.7 days. The overall salvage rate for this indication is low, at approximately 25%; however, without VAD support, patients with refractory postcardiotomy cardiogenic shock would experience 100% mortality.[6, 37, 38]

Agrawal (2018) published a retrospective cohort study evaluating the 30-day readmissions of 2,510 patients undergoing LVAD implantation.[39] Of the patients who met the inclusion criteria, 788 (31%) were readmitted within 30 days after surviving initial index hospitalization. Cardiac causes accounted for 23.8% of readmissions, 13.4% due to heart failure, and 8.1% to arrhythmias. Infection (30.2%), bleeding (17.6%), and device-related causes (8.2%) comprised the 76.2% of non-cardiovascular causes for readmission. The study's limitations relate to the nature of nonclinical data collection and gaps in current subject knowledge.

A retrospective cohort study by Adesyiun (2017) assessed LVAD complications and overall effect on mortality to determine factors associated with development of early and long-term complications.[40] Utilizing logistic regression and Cox proportional hazards analyses at univariable and multivariable stages, the study found 24% of patients developed early complications and 18.5% developed both early and late complications. There was a significant association between death and early complications (p=0.017), while the additional presence of two or more complications produced a 2.7-fold increase in mortality odds (p=0.016). Mortality odds increased by 20% with each subsequent complication (p=0.004). The study was limited in that, during its long, 13-year team span, practice associated with LVAD maintained had changed but were not address by the study. Further limitations include the difficulty in determining the strictness to which a patient might have met the complication definitions, as well as the small sample size of the study.

Kawajiri (2017) evaluated the outcomes of patients with end-stage heart failure who had conventional surgery as opposed to transplant or mechanical support.[41] A total of 133 patients of this retrospective cohort study were identified with left ventricular ejection fraction (LVEF) less than 20% and VO2 max < 14 mL/min/m^2 and, after initial referral for advanced therapies, were instead offered a conventional procedure. Of the originally identified 133 patients, 68 were determined transplant eligible. Actuarial survival at 5 and 10 years was 72% and 39%, respectively, after 12% in-hospital mortality. Outcomes were acceptable for conventional cardiac surgery in highly selected patients with end-stage HF, and long-term survival was comparable with advanced surgical therapies. The study was limited by a small study population, its nonclinical nature, and the potential underestimation the VAD/transplant mortality by measuring survival dates starting from first surgery as opposed to date of decision.

Raju (2017) focused their retrospective cohort study on consecutive LVAD patients who received more than one year of total LVAD support time.[42] During the study period, 103 patients received LVADs, 37 received LVAD support for more than one year, and 18 received support for more than two years. Average support time was 786 days. Mortality and hospital readmissions were used to determine the efficacy of continuous-flow LVADs. During a median follow-up of two years, the one-year conditional survival was 74%. Readmission reasons were due to major infection (24%), major bleeding (19%), and device malfunction/thrombosis (13%), and totaled 112 completed readmission procedures, 60% of which were done in 13% (n=5) of patients. The study had the limitations of a descriptive retrospective analysis and small sample

size, and quality of life (QOL) self-assessments would have provided necessary patient perspective.

Takayama (2014) reported outcomes for a retrospectively-defined cohort of 143 patients who received a CentriMag® VAD as a “bridge to decision” for refractory cardiogenic shock due to a variety of causes.[43] Patients were managed with a bridge-to-decision algorithm. Causes of cardiogenic shock included failure of medical management (n=71), postcardiotomy shock (n=37), graft failure post-heart transplantation (n=2), and right ventricular failure post-implantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated left VAD in 8%. After a mean duration of support of 14 days (interquartile range 8 to 26 days), 30% of patients had myocardial recovery, 15% had device exchange to an implantable VAD, and 18% had a heart transplantation.

Acharya (2016) reported on patients who underwent VAD placement in the setting of acute myocardial infarction (AMI) who were enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, a prospective national registry of FDA-approved durable mechanical circulatory support devices.[44] Patients who had an AMI as the admitting diagnosis or a major myocardial infarction (MI) as a hospital complication that resulted in VAD implantation (n=502) were compared with patients who underwent VAD implantation for non-AMI indications (n=9,727). Patients in the AMI group were generally sicker at baseline, with higher rates of smoking, severe diabetes, and peripheral vascular disease, but had fewer cardiac surgeries and recent cardiovascular hospitalizations. Most AMI patients (53.8%) were implanted with a “bridge-to-candidacy” strategy. At one-month post VAD, 91.8% of the AMI group were alive with the device in place. At one-year post-VAD, 52% of the AMI group were alive with the device in place, 25.7% had received a transplant, 1.6% had their VAD explanted for recovery, and 20.7% died with the device in place. Another retrospective study of 15,138 patients in the INTERMACS registry found that the incidence of recovery was significantly higher in bridge-to-recovery patients than in non-bridge-to-recovery patients (11.2% vs 1.2%, $p<0.0001$).[45]

Topkara (2016) reported a similar analysis of 13,454 INTERMACS adults with implants between June 2006 and June 2015 without TAH, pulsatile-flow LVAD, or heart transplant.[46] Device explant rates for cardiac recovery were 0.9% at one-year, 1.9% at two-year, and 3.1% at three-year follow-up. An additional 9% of patients demonstrated partial cardiac recovery.

In a smaller single-center retrospective cohort study, Mohamedali (2015) reported outcomes for 48 patients treated with biventricular support with the CentriMag® device as a “bridge to decision”, 18 of whom had biventricular support with venoarterial (VA) extracorporeal membrane oxygenation (ECMO), while the remainder received just biventricular VAD support.[47] Overall, 23 patients were explanted, nine to recovery, 14 to a durable LVAD, with three additional patients explanted for withdrawal of care. However, given that the study included patients who received VA ECMO, it is difficult to assess the relative impact of VAD support alone.

Six studies using the Centrimag® RVAD included between 12 and 32 patients, the majority of whom received biventricular devices.[38, 48-52] Indications and numbers of patients in these five studies were: support for post-cardiotomy cardiogenic shock (bridge to recovery), bridge to long-term device implantation (n=9), treatment of right heart failure in patients who previously received LVADs, bridge to later decision when neurologic status is clarified, and acute donor graft failure. The mean time on mechanical circulatory support ranged from 9.4 days to 46.9

days. The 30-day mortality rates were between 17% and 63%. The proportion of patients discharged from the hospital was between 30% and 83%. Major complications included bleeding requiring reoperation, sepsis, and stroke. No device failures were observed in these studies.

In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum (2007) evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure.[53] After 30 days, patients demonstrated significant improvements compared with pre-LVAD state in LVEF (17.1% vs 34.12%, p<0.001), left ventricular end-diastolic diameter (7.1 cm vs 5.1 cm, p<0.001), and left ventricular mass (320 g vs 194 g, p<0.001). However, only 9% of patients demonstrated enough recovery to have their LVAD explanted.

In a 2006 study, a series of 15 patients with severe heart failure due to nonischemic cardiomyopathy underwent implantation of LVADs, along with medical management designed to enhance myocardial recovery.[54] Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; two patients died after explantation. Among those who survived, the cumulate rate of freedom from recurring heart failure was 100% and 88.9%, respectively, at one- and four-years post explantation. The same group subsequently reported results of their LVAD explantation protocol among patients with severe heart failure due to nonischemic cardiopathy who had nonpulsatile LVADs implanted.[55] They included 20 patients who received a combination of angiotensin converting enzyme ACE inhibitors, beta blockers, and adosterol antagonists followed by the β2-agonist clenbuterol. One patient was lost to follow-up and died after 240 days of support. Of the remaining 19 patients, 12 (63.2%) were successfully explanted after a mean 286 days; estimated survival without heart failure recurrence was 83.3% at one and three years.

Section Summary

The studies previously outlined indicate that a subset of patients who receive a VAD as a bridge to transplant demonstrate improvements in their cardiac function, sometimes to the point that they no longer require the VAD. However, questions remain about defining and identifying the population most likely to experience cardiac recovery with VAD placement. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. Finally, current evidence is insufficient to allow the identification of other heart failure patient populations who might benefit from the use of a VAD as a specific bridge-to-recovery treatment strategy. Ongoing research studies are addressing this question, along with protocols for transitioning patients off VAD use.

LEFT VENTRICULAR ASSIST DEVICES AS DESTINATION THERAPY

Technology Assessment

The policy statement regarding LVADs as destination therapy was initially based on a 2002 TEC assessment[56] that offered the following observations and conclusions:

- The available evidence comes from a single, well-designed and rigorously conducted randomized trial, known as the REMATCH study.[57] The study was a cooperative effort of Thoratec, Columbia University and the National Institutes of Health.

- The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have significantly better survival on an LVAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this group's better outcomes on function. NYHA Class was significantly improved, as was quality of life among those living to 12 months.

- LVAD patients spend a greater relative proportion of time inside the hospital than medical management patients do, but the survival advantage would mean a longer absolute time outside the hospital.

Randomized Controlled Trials

Park published a further follow-up of patients in the REMATCH trial, mentioned in the above TEC assessment, which found that survival and quality of life benefits were still apparent with extended two-year follow-up.[58]

Nonrandomized Studies

Jorde (2014) published results from an FDA-required postapproval study of the HeartMate II® device for destination therapy.[59] The study included the first 247 HeartMate II® patients identified as eligible for the device as destination therapy, outcomes and adverse events did not differ significantly from those treated in the original trial, which compared patients who received the HeartMate II® to earlier generation devices (Slaughter [2009], described below).[60] Survival in the postapproval cohort was 82% and 69% at one and two years postoperatively, respectively.

A subsequent prospective observational study comparing LVAD support (n=97) with optimal medical therapy (n=103) for patients with heart failure not requiring inotropes also reported superior survival and health-related quality of life in LVAD-treated patients.[61] Twelve-month survival was 80% in the LVAD group, compared with 63% in the best medical therapy group (p=0.022).

In addition, other case series suggest continuing improvement in outcomes related to ongoing improvements in the device and in patient management.[62] However, the durability of the HeartMate device used in the REMATCH trial is a concern; for example, at one participating institution, all six long-term survivors required device change-outs. Next generation devices consisting of smaller continuous flow devices are eagerly anticipated.

Section Summary

The primary evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is from the REMATCH study. This study reported that the use of LVADs led to improvements in survival, quality of life, and functional status.

DEVICE COMPARISONS

The mechanism of operation of LVADs has changed since their introduction. The earliest devices were pulsatile positive displacement pumps. The pulsatile pumps have been largely replaced by axial continuous-flow pumps. More recently centrifugal continuous-flow pumps have also been introduced.

The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of two RCTs of two different centrifugal continuous-flow devices.[63-65] The MOMENTUM3 trial compared HeartMate 3™ centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as a bridge to transplant or destination therapy. HeartMate 3™ received PMA approval in August 2017 but was recalled in April 2018. The ENDURANCE trial compared HeartWare® centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare® is FDA-approved for bridge to transplantation. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke, and freedom from device failure. While there are fewer device failures with the centrifugal devices without significant increase in disabling stroke, the HeartWare® device was associated with increased risk of any stroke over a period of two years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of an RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous-flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes.[60] Other nonrandomized comparative studies, including a database study with large numbers of patients, have not reported important differences in clinical outcomes between devices.

Slaughter (2009) published data from an unblinded randomized multicenter trial.[60] Subjects were randomized to continuous-flow or pulsatile-flow devices on a 2:1 block-randomization basis. The primary outcome measured was a composite endpoint of two-year survival, free of disabling stroke or need for device replacement. Continuous-flow patients (n=134) reached the primary outcome at a rate of 46% (95% CI 38 to 55) compared to pulsatile-flow patients (n=66) rate of 11% (95% CI 3 to 18), which was a significant difference ($p<0.001$). Analysis of constituent factors indicated that a lower rate of devices needing replacement in the continuous-flow group had the largest effect on the composite endpoint; two-year death rate also favored this device (58% vs. 24%, $p=0.008$). Stroke and death (within two years of implantation) were similar in the two groups (stroke rate 12% and death rate 36%). Quality of life scores were also similar in the two groups. Although unblinded, this randomized trial adds to the evidence favoring continuous-flow devices.

Nonrandomized Studies

Dell'Aquila (2014) compared outcomes for patients treated with a third-generation continuous flow device, the HeartWare® device, with those for patients treated with earlier generation devices in a single-center study.[66] Comparison-group patients received either an earlier generation continuous flow device or a pulsatile flow device. Of 287 patients who received VAD support from 1993 to 2012, 52 received a HeartWare® device, 76 an earlier generation continuous flow device, and 159 a pulsatile device. Survival was significantly better for patients who received a third-generation device, with 24 months survival of 70.4%, compared with 33.7% for patients who received an earlier generation continuous flow device and 33.8% for patients who received a pulsatile flow device ($p=0.013$). The difference in survival associated with third generation devices was more pronounced for higher scores on the INTERMACs scale.

Nativi (2011) published a nonrandomized comparison of pulsatile versus continuous flow devices using data from the registry of the International Society for Heart and Lung Transplantation on 8,557 patients undergoing transplant.[67] Comparisons were made among patients receiving a pulsatile LVAD, a continuous flow LVAD, and no LVAD. Two time periods were used for analysis, the first was pre-2004, when nearly all LVADs were pulsatile devices, and post-2004 when continuous use devices began to be used in clinical care. There was a significantly greater risk of mortality in the first time period compared to the second time period (RR 1.30, 95% CI 1.03 to 1.65, p=0.03). When analysis was confined to the second time period, there was no significant improvement in survival for the continuous group compared to the pulsatile group (RR 1.25, 95% CI 1.03 to 1.65, p=0.03).

Other nonrandomized studies that have compared outcomes from different types of LVADs have been smaller and/or focused on physiologic outcomes.[68-71] In some of these studies, the continuous flow devices exhibit greater improvement in physiologic measures, but none of these studies have reported significant differences between devices in clinical outcomes.

Section Summary

The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of two RCTs of two different centrifugal continuous-flow devices. The MOMENTUM3 trial compared HeartMate 3™ centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as a bridge to transplantation or destination therapy. HeartMate 3™ has been recalled. The ENDURANCE trial compared HeartWare® centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare® is FDA-approved for bridge to transplantation. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke and freedom from device failure. While there are fewer device failures with the centrifugal devices without significant increase in disabling stroke, the HeartWare® device was associated with increased risk of any stroke over a period of two years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of one RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes. Other nonrandomized comparative studies, including one database study with large numbers of patients, have not reported differences between devices on clinical outcomes.

AORTIC COUNTERPULSATION DEVICES

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved, and therefore the evidence for these devices is not reviewed in detail.

TOTAL ARTIFICIAL HEARTS

BRIDGE TO TRANSPLANTATION

Nonrandomized Studies

In 2004, the CardioWest Total Artificial Heart (now called the SynCardia Total Artificial Heart) received FDA approval for use as a bridge to transplant. The approval was based on the results of a nonrandomized, prospective study of 81 patients.[72] Patients had failed inotropic therapy and had biventricular failure and thus were not considered appropriate candidates for an LVAD. The rate of survival to transplant was 79%, which was considered comparable to the experience with LVAD in patients with left ventricular failure. The mean time from entry into the study until transplantation or death was 79.1 days.

Other case series have been reported on outcomes of the TAH as a bridge to transplant. For example, Copeland reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant.[73] All patients either met established criteria for mechanically assisted circulatory support or were failing medical therapy on multiple inotropic drugs. The mean support time was 87 days, with a range of 1 to 441 days. Survival to transplant was 68.3% (69/101). Of the 32 deaths prior to transplant, 13 were due to multiple organ failure, 6 were due to pulmonary failure, and four were due to neurologic injury. Survival after transplant at 1, 5, and 10 years, respectively, was 76.8%, 60.5%, and 41.2%.

DESTINATION THERAPY

In currently available studies, the AbioCor® Implantable Replacement Heart has only been used as destination therapy for end-stage patients with congestive heart failure.

Nonrandomized Studies

Torregrossa (2014) reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than one year.[74] Patients were implanted for dilated cardiomyopathy (n=23), ischemic cardiomyopathy (n=15), and “other” reasons (n=9). Over a median support time of 554 days (range, 365-1373 days), 34 patients (72%) were successfully transplanted, 12 patients (24%) died while on device support, and one patient (2%) was still supported. Device failure occurred in five patients (10%). Major complications were common, including systemic infection in 25 patients (53%), driveline infections in 13 patients (27%), thromboembolic events in nine patients (19%) and hemorrhagic events in seven patients (14%). Two of the deaths occurred secondary to device failure

Dowling (2004) reported on the first seven patients in the AbioCor® clinical trial.[75] The 30-day survival rate was 71% compared with the predicted survival rate of 13% with only medical therapy. At 60 days, 43% were still alive and as of July 2006 two patients were still alive 234 and 181 days postoperatively and remain hospitalized. Deaths were due to intraoperative bleeding at the time of implantation, cerebrovascular accidents, pulmonary embolism, and multiorgan failure. No reports of serious device malfunction have been reported for the seven patients. Frazier (2004) reported information on four additional patients receiving the AbioCor®.[76] Using the same inclusion criteria as in the above RCT the device supported three patients for greater than 100 days, whereas a fourth patient expired at 53 days. There were no device related problems reported.

SECTION SUMMARY

There is little evidence on the use of TAH as a bridge to transplantation, or as destination therapy, compared with the use of LVADs. The type of evidence on bridge to transplant is similar to that for LVADs (i.e., case series reporting substantial survival rates in patients without other alternatives). Therefore, this evidence is sufficient to conclude that TAH improves outcomes for these patients similar to LVADs and is a reasonable alternative for patients who require bridge to transplantation but who are ineligible for other types of support devices. Although TAHs show promise for use as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. There is insufficient evidence on the use of TAH as destination therapy to support conclusions about the efficacy of TAH in this setting.

PRACTICE GUIDELINE SUMMARY

SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

In 2015, the Society for Cardiovascular Angiography and Interventions (SCAI), the Heart Failure Society of America (HFSA), the Society of Thoracic Surgeons (STS), the American Heart Association (AHA), and the American College of Cardiology (ACC) published a clinical expert consensus statement on the use of percutaneous mechanical circulatory support (MCS) devices in cardiovascular care.[77] This statement addressed intra-aortic balloon pumps (IABPs), left atrial (LA)-to-aorta assist device (eg, TandemHeart), left ventricle (LV)-to-aorta assist devices (eg, Impella), extracorporeal membrane oxygenation (ECMO), and methods of right-sided support. Specific recommendations are not made, but the statement reviews the use of MCS in patients undergoing high-risk percutaneous intervention (PCI), those with cardiogenic shock, and those with acute decompensated heart failure.

AMERICAN ASSOCIATION FOR THORACIC SURGERY/INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION[78]

In 2020, the American Association for Thoracic Surgery/International Society for Heart and Lung Transplantation published guidelines on selected topics in mechanical circulatory support. The guidelines noted that “Compared with IABP, contemporary percutaneous circulatory support devices provide a significant increase in cardiac index and mean arterial pressure; however, reported 30-day outcomes are similar.” The level of evidence was graded at B and class of evidence was graded IIA.

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION / AMERICAN HEART ASSOCIATION / HEART FAILURE SOCIETY OF AMERICA (ACCF/AHA/HFSA)[79]

The 2013 ACCF/AHA practice guidelines for the management of heart failure included the recommendations below related to MCS which includes LVADs. All of these recommendations were rated II.a., level of evidence B, defined as a recommendation in favor of the treatment being useful, with some conflicting evidence from a single RCT or nonrandomized studies.

- MCS is considered beneficial in carefully selected patients with stage D heart failure with reduced ejection fraction (HFrEF) as a bridge to transplantation or recovery.
- Nondurable mechanical cardiac support including percutaneous and extracorporeal VADs are considered “reasonable” as a bridge to recovery or a bridge to decision for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.

- Durable (permanent) MCS is considered reasonable to prolong survival for carefully selected patients with stage D HFrEF.

The guidelines note that, although optimal patient selection for MCS is an area of investigation, general indications for referral for MCS therapy include patient with LVEF<25% and NYHA class III-IV functional status despite guideline-directed medical therapy (GDMT) including cardiac resynchronization therapy (CRT), when indicated, with either high predicted one- to two-year mortality or dependence on continuous parenteral inotropic support.

In 2017, the ACCF/AHA/HFSA published a focused update of the 2013 recommendations released by the ACCF and AHA.[80] LVAD was one of several treatment options recommended for patients with refractory NYHA class III or IV heart failure (stage D). If symptoms were not improved after guideline-directed management and therapy, which included pharmacologic therapy, surgical management and/or other devices, then LVAD was presented as an additional treatment option. The 2017 update focused on changes in sections regarding biomarkers, comorbidities, and prevention of heart failure, while many of the previous recommendations remained unchanged.

THE HEART FAILURE SOCIETY OF AMERICA (HFSA)

The HFSA published guidelines in 2010 on surgical approaches to the treatment of heart failure. The guidelines are based on evidence and expert opinion.[72] The following recommendations were made regarding ventricular assist devices:

- Bridge to transplantation: Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant. (Strength of Evidence B - cohort and case-control studies)
- Bridge to recovery: Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a "bridge to decision." These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence C - expert opinion)
- Destination Therapy: Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center. (Strength of Evidence B - cohort and case-control studies)

SUMMARY

VENTRICULAR ASSIST DEVICES

There is enough research to show that implantable ventricular assist devices (VADs) as a bridge to transplantation or recovery, or as destination therapy, improve health outcomes in some patients with heart failure who might not otherwise survive. Therefore, implantable VADs may be considered medically necessary when the policy criteria are met.

There is not enough research to show that ventricular assist devices or aortic counterpulsation devices improve health outcomes for people with heart failure or other heart conditions when policy criteria are not met. Therefore, the use of ventricular assist devices or aortic counterpulsation devices when policy criteria are not met is considered investigational.

TOTAL ARTIFICIAL HEARTS

There is enough research to show that the use of a total artificial heart (TAH) as a bridge to heart transplantation improves survival and quality of life for patients in some specific situations. Therefore, total artificial hearts may be considered medically necessary as a bridge to heart transplantation when policy criteria are met.

There is not enough research to show that total artificial hearts (TAHs) as destination therapy improves health outcomes for patients. Therefore, the use of TAHs as destination therapy is considered investigational.

REFERENCES

1. FDA Warns of Serious Risks With LVADs. [cited 1/11/2021]. Available from: https://www.medpagetoday.com/cardiology/chf/52948.
2. AC Alba, M McDonald, V Rao, HJ Ross, DH Delgado. The effect of ventricular assist devices on long-term post-transplant outcomes: a systematic review of observational studies. *European journal of heart failure.* 2011;13(7):785-95. PMID: 21551162
3. Blue Cross and Blue Shield Association. Technology Evaluation Center (TEC). Ventricular Assist Devices in Bridging to Heart Transplantation. TEC Assessments 1996. Volume 11, Tab 26. [cited. Available from:
4. DJ Goldstein, MC Oz, EA Rose. Implantable left ventricular assist devices. *N Engl J Med.* 1998;339(21):1522-33. PMID: 9819452
5. JG Rogers, KD Aaronson, AJ Boyle, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol.* 2010;55(17):1826-34. PMID: 20413033
6. J Lahpor, A Khaghani, R Hetzer, et al. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. *Eur J Cardiothorac Surg.* 2010;37(2):357-61. PMID: 19616963
7. GM Wieselthaler, H Schima, AM Lassnigg, et al. Lessons learned from the first clinical implants of the DeBakey ventricular assist device axial pump: a single center report. *Ann Thorac Surg.* 2001;71(3 Suppl):S139-43; discussion S44-6. PMID: 11265849
8. DJ Goldstein. Worldwide experience with the MicroMed DeBakey Ventricular Assist Device as a bridge to transplantation. *Circulation.* 2003;108 Suppl 1:II272-7. PMID: 12970245
9. S Salzberg, M Lachat, G Zund, et al. Left ventricular assist device as bridge to heart transplantation--lessons learned with the MicroMed DeBakey axial blood flow pump. *Eur J Cardiothorac Surg.* 2003;24(1):113-8. PMID: 12853054
10. E Vitali, M Lanfranconi, E Ribera, et al. Successful experience in bridging patients to heart transplantation with the MicroMed DeBakey ventricular assist device. *Ann Thorac Surg.* 2003;75(4):1200-4. PMID: 12683563

11. JM Grinda, CH Latremouille, P Chevalier, et al. Bridge to transplantation with the DeBakey VAD axial pump: a single center report. *Eur J Cardiothorac Surg.* 2002;22(6):965-70. PMID: 12467821
12. OH Frazier, TJ Myers, S Westaby, ID Gregoric. Use of the Jarvik 2000 left ventricular assist system as a bridge to heart transplantation or as destination therapy for patients with chronic heart failure. *Ann Surg.* 2003;237(5):631-6; discussion 36-7. PMID: 12724629
13. N Aissaoui, M Morshuis, H Maoulida, et al. Management of end-stage heart failure patients with or without ventricular assist device: an observational comparison of clinical and economic outcomes. *Eur J Cardiothorac Surg.* 2018;53(1):170-77. PMID: 28950304
14. JC Grimm, JT Magruder, TC Crawford, et al. Duration of Left Ventricular Assist Device Support Does Not Impact Survival After US Heart Transplantation. *Ann Thorac Surg.* 2016;102(4):1206-12. PMID: 27319984
15. JC Grimm, CM Sciortino, JT Magruder, et al. Outcomes in Patients Bridged With Univentricular and Biventricular Devices in the Modern Era of Heart Transplantation. *Ann Thorac Surg.* 2016;102(1):102-8. PMID: 27068177
16. A Cheng, JR Trivedi, VH Van Berkel, HT Massey, MS Slaughter. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. *Journal of cardiac surgery.* 2016;31(10):648-53. PMID: 27573150
17. SV Deo, K Sung, RC Daly, et al. Cardiac transplantation after bridged therapy with continuous flow left ventricular assist devices. *Heart, lung & circulation.* 2014;23(3):224-8. PMID: 23954004
18. MS Slaughter, FD Pagani, EC McGee, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant.* 2013;32(7):675-83. PMID: 23796152
19. Aaronson, KD, Slaughter, MS, Miller, LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. United States, 2012. p. 3191-200.
20. LW Miller, FD Pagani, SD Russell, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med.* 2007;357(9):885-96. PMID: 17761592
21. FDA information on the Thoratec HeartMate II device. [cited 1/12/2021]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf.
22. ND Patel, ES Weiss, J Schaffer, et al. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann Thorac Surg.* 2008;86(3):832-40; discussion 32-40. PMID: 18721570
23. R John, F Kamdar, K Liao, M Colvin-Adams, A Boyle, L Joyce. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. *Ann Thorac Surg.* 2008;86(4):1227-34; discussion 34-5. PMID: 18805167
24. M Struber, K Sander, J Lahpor, et al. HeartMate II left ventricular assist device; early European experience. *Eur J Cardiothorac Surg.* 2008;34(2):289-94. PMID: 18571932
25. OH Frazier, C Gemmato, TJ Myers, et al. Initial clinical experience with the HeartMate II axial-flow left ventricular assist device. *Tex Heart Inst J.* 2007;34(3):275-81. PMID: 17948075
26. JK Kirklin, DC Naftel, LW Stevenson, et al. INTERMACS database for durable devices for circulatory support: first annual report. *J Heart Lung Transplant.* 2008;27(10):1065-72. PMID: 18926395
27. Starling, RC, Naka, Y, Boyle, AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a

bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). United States, 2011. p. 1890-8.
28. AF Shaikh, SM Joseph, B Lima, et al. HeartMate II Left Ventricular Assist Device Pump Exchange: A Single-Institution Experience. *The Thoracic and cardiovascular surgeon.* 2016. PMID: 27903010
29. D Zakaria, E Frazier, M Imamura, et al. Improved Survival While Waiting and Risk Factors for Death in Pediatric Patients Listed for Cardiac Transplantation. *Pediatric cardiology.* 2016. PMID: 27803956
30. RR Davies, MJ Russo, KN Hong, et al. The use of mechanical circulatory support as a bridge to transplantation in pediatric patients: an analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg.* 2008;135(2):421-7, 27 e1. PMID: 18242279
31. A Jeewa, M Imamura, C Canter, et al. Long-term outcomes after transplantation after support with a pulsatile pediatric ventricular assist device. *J Heart Lung Transplant.* 2018. PMID: 30466802
32. A Bulic, K Maeda, Y Zhang, et al. Functional status of United States children supported with a left ventricular assist device at heart transplantation. *J Heart Lung Transplant.* 2017;36(8):890-96. PMID: 28363739
33. Almond, CS, Morales, DL, Blackstone, EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. United States, 2013. p. 1702-11.
34. LC Jordan, RN Ichord, O Reinhartz, et al. Neurological complications and outcomes in the Berlin Heart EXCOR(R) pediatric investigational device exemption trial. *Journal of the American Heart Association.* 2015;4(1):e001429. PMID: 25613996
35. R Bryant, 3rd, F Zafar, C Castleberry, et al. Transplant Survival Following Berlin Heart EXCOR(R) Support. *ASAIO J.* 2016. PMID: 27660899
36. B Wehman, KA Stafford, GJ Bittle, et al. Modern Outcomes of Mechanical Circulatory Support as a Bridge to Pediatric Heart Transplantation. *Ann Thorac Surg.* 2016;101(6):2321-7. PMID: 26912304
37. E Braunwald, DP Zipes, P Libby. *Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Philadelphia: W.B. Saunders Company, 2001, pp.
38. R John, JW Long, HT Massey, et al. Outcomes of a multicenter trial of the Levitronix CentriMag ventricular assist system for short-term circulatory support. *J Thorac Cardiovasc Surg.* 2010. PMID: 20605026
39. S Agrawal, L Garg, M Shah, et al. Thirty-Day Readmissions After Left Ventricular Assist Device Implantation in the United States: Insights From the Nationwide Readmissions Database. *Circ Heart Fail.* 2018;11(3):e004628. PMID: 29519902
40. TA Adesiyun, RC McLean, RJ Tedford, et al. Long-term follow-up of continuous flow left ventricular assist devices: complications and predisposing risk factors. *The International journal of artificial organs.* 2017;40(11):622-28. PMID: 28777392
41. H Kawajiri, C Manlhiot, H Ross, et al. High-risk cardiac surgery as an alternative to transplant or mechanical support in patients with end-stage heart failure. *J Thorac Cardiovasc Surg.* 2017;154(2):517-25. PMID: 28495061
42. S Raju, J MacIver, F Foroutan, C Alba, F Billia, V Rao. Long-term use of left ventricular assist devices: a report on clinical outcomes. *Canadian journal of surgery Journal canadien de chirurgie.* 2017;60(4):236-46. PMID: 28730986

43. H Takayama, L Soni, B Kalesan, et al. Bridge-to-decision therapy with a continuous-flow external ventricular assist device in refractory cardiogenic shock of various causes. *Circ Heart Fail.* 2014;7:799-806. PMID: 25027874
44. D Acharya, RY Loyaga-Rendon, SV Pamboukian, et al. Ventricular Assist Device in Acute Myocardial Infarction. *J Am Coll Cardiol.* 2016;67(16):1871-80. PMID: 27102502
45. O Wever-Pinzon, SG Drakos, SH McKellar, et al. Cardiac Recovery During Long-Term Left Ventricular Assist Device Support. *J Am Coll Cardiol.* 2016;68(14):1540-53. PMID: 27687196
46. VK Topkara, AR Garan, B Fine, et al. Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices: Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). *Circ Heart Fail.* 2016;9(7). PMID: 27402861
47. B Mohamedali, G Bhat, G Yost, A Tatooles. Survival on biventricular mechanical support with the Centrimag(R) as a bridge to decision: a single-center risk stratification. *Perfusion.* 2015;30:201-8. PMID: 25524992
48. FDA information on Levitronix Centrimag RVAS device. [cited 1/12/2021]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf7/H070004b.pdf.
49. JH Shuhaiber, D Jenkins, M Berman, et al. The Papworth experience with the Levitronix CentriMag ventricular assist device. *J Heart Lung Transplant.* 2008;27(2):158-64. PMID: 18267221
50. F De Robertis, EJ Birks, P Rogers, G Dreyfus, JR Pepper, A Khaghani. Clinical performance with the Levitronix Centrimag short-term ventricular assist device. *J Heart Lung Transplant.* 2006;25(2):181-6. PMID: 16446218
51. F De Robertis, P Rogers, M Amrani, et al. Bridge to decision using the Levitronix CentriMag short-term ventricular assist device. *J Heart Lung Transplant.* 2008;27(5):474-8. PMID: 18442711
52. R John, K Liao, K Lietz, et al. Experience with the Levitronix CentriMag circulatory support system as a bridge to decision in patients with refractory acute cardiogenic shock and multisystem organ failure. *J Thorac Cardiovasc Surg.* 2007;134(2):351-8. PMID: 17662772
53. Maybaum, S, Mancini, D, Xydas, S, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. United States, 2007. p. 2497-505.
54. Birks, EJ, Tansley, PD, Hardy, J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. United States, 2006. p. 1873-84.
55. Birks, EJ, George, RS, Hedger, M, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. United States, 2011. p. 381-90.
56. TEC Assessment 2002. "Left Ventricular assist devices as destination therapy for end-stage heart failure." BlueCross BlueShield Association Technology Evaluation Center, Vol. 17
57. EA Rose, AC Gelijns, AJ Moskowitz, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med.* 2001;345(20):1435-43. PMID: 11794191
58. SJ Park, A Tector, W Piccioni, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg.* 2005;129(1):9-17. PMID: 15632819
59. UP Jorde, SS Kushwaha, AJ Tatooles, et al. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist

device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol.* 2014;63(17):1751-7. PMID: 24613333
60. MS Slaughter, JG Rogers, CA Milano, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 2009;361(23):2241-51. PMID: 19920051
61. JD Estep, RC Starling, DA Horstmanshof, et al. Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients: Results From the ROADMAP Study. *J Am Coll Cardiol.* 2015;66(16):1747-61. PMID: 26483097
62. JW Long, AG Kfoury, MS Slaughter, et al. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. *Congest Heart Fail.* 2005;11(3):133-8. PMID: 15947534
63. MR Mehra, Y Naka, N Uriel, et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med.* 2017;376(5):440-50. PMID: 27959709
64. JG Rogers, FD Pagani, AJ Tatooles, et al. Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure. *N Engl J Med.* 2017;376(5):451-60. PMID: 28146651
65. PC Colombo, MR Mehra, DJ Goldstein, et al. Comprehensive Analysis of Stroke in the Long-Term Cohort of the MOMENTUM 3 Study. *Circulation.* 2019;139(2):155-68. PMID: 30586698
66. AM Dell'Aquila, SR Schneider, J Stypmann, et al. Survival results after implantation of intrapericardial third-generation centrifugal assist device: an INTERMACS-matched comparison analysis. *Artificial organs.* 2014;38(5):383-90. PMID: 24117675
67. JN Nativi, SG Drakos, AY Kucheryavaya, et al. Changing outcomes in patients bridged to heart transplantation with continuous- versus pulsatile-flow ventricular assist devices: an analysis of the registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2011;30(8):854-61. PMID: 21571550
68. RV Pruijsten, SI Lok, HH Kirkels, C Klopping, JR Lahpor, N de Jonge. Functional and haemodynamic recovery after implantation of continuous-flow left ventricular assist devices in comparison with pulsatile left ventricular assist devices in patients with end-stage heart failure. *European journal of heart failure.* 2012;14(3):319-25. PMID: 22294758
69. KM Lim, J Constantino, V Gurev, R Zhu, EB Shim, NA Trayanova. Comparison of the effects of continuous and pulsatile left ventricular-assist devices on ventricular unloading using a cardiac electromechanics model. *The journal of physiological sciences : JPS.* 2012;62(1):11-9. PMID: 22076841
70. TS Kato, A Chokshi, P Singh, et al. Effects of continuous-flow versus pulsatile-flow left ventricular assist devices on myocardial unloading and remodeling. *Circ Heart Fail.* 2011;4(5):546-53. PMID: 21765125
71. PA Ventura, R Alharethi, D Budge, et al. Differential impact on post-transplant outcomes between pulsatile- and continuous-flow left ventricular assist devices. *Clinical transplantation.* 2011;25(4):E390-5. PMID: 21401721
72. Lindenfeld, J, Albert, NM, Boehmer, JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. United States, 2010. p. e1-194.
73. JG Copeland, H Copeland, M Gustafson, et al. Experience with more than 100 total artificial heart implants. *J Thorac Cardiovasc Surg.* 2012;143(3):727-34. PMID: 22245242
74. G Torregrossa, M Morshuis, R Varghese, et al. Results with SynCardia total artificial heart beyond 1 year. *ASAIO J.* 2014;60(6):626-34. PMID: 25158888

75. RD Dowling, LA Gray, Jr., SW Etoch, et al. Initial experience with the AbioCor implantable replacement heart system. *J Thorac Cardiovasc Surg.* 2004;127(1):131-41. PMID: 14752423
76. OH Frazier, RD Dowling, LA Gray, Jr., NA Shah, T Pool, I Gregoric. The total artificial heart: where we stand. *Cardiology.* 2004;101(1-3):117-21. PMID: 14988633
77. CS Rihal, SS Naidu, MM Givertz, et al. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care (Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie D'intervention). *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* 2015;85(7):E175-96. PMID: 25851050
78. JK Kirklin, FD Pagani, DJ Goldstein, et al. American Association for Thoracic Surgery/International Society for Heart and Lung Transplantation guidelines on selected topics in mechanical circulatory support. *J Heart Lung Transplant.* 2020;39(3):187-219. PMID: 31983666
79. CW Yancy, M Jessup, B Bozkurt, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239. PMID: 23747642
80. CW Yancy, M Jessup, B Bozkurt, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136(6):e137-e61. PMID: 28455343
81. BlueCross BlueShield Association Medical Policy Reference Manual "Ventricular Assist Devices and Total Artificial Hearts." Policy No. 7.03.11

CODES

Note: There is no specific code for reporting prolonged extracorporeal percutaneous transseptal ventricular assist device; the appropriate code for reporting this procedure is 33999.

Codes	Number	Description
CPT	33927	Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy
	33928	Removal and replacement of total replacement heart system (artificial heart)
	33929	Removal of a total replacement heart system (artificial heart) for heart transplantation (list separately in addition to code for primary procedure)
	33975	Insertion of ventricular assist device; extracorporeal, single ventricle
	33976	Insertion of ventricular assist device; extracorporeal, biventricular
	33977	Removal of ventricular assist device; extracorporeal, single ventricle
	33978	Removal of ventricular assist device; extracorporeal, biventricular
	33979	Insertion of ventricular assist device, implantable intracorporeal, single ventricle
	33980	Removal of ventricular assist device, implantable intracorporeal, single ventricular
	33981	Replacement of extracorporeal ventricular assist device, single or biventricular, pump(s), single or each pump

Codes	Number	Description
	33982	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, without cardiopulmonary bypass
	33983	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, with cardiopulmonary bypass
	33990	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; left heart, arterial access only
	33991	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; left heart, both arterial and venous access, with transseptal puncture
	33992	Removal of percutaneous left heart ventricular assist device, arterial or arterial and venous cannula(s), at separate and distinct session from insertion
	33993	Repositioning of percutaneous right or left heart ventricular assist device with imaging guidance at separate and distinct session from insertion
	33995	Insertion of ventricular assist device, percutaneous, including radiological supervision and interpretation; right heart, venous access only
	33997	Removal of percutaneous right heart ventricular assist device, venous cannula, at separate and distinct session from insertion
	33999	Unlisted procedure, cardiac surgery
	~~0451T~~	~~Insertion or replacement of a permanently implantable aortic counterpulsation ventricular assist system, endovascular approach, and programming of sensing and therapeutic parameters; complete system (counterpulsation device, vascular graft, implantable vascular hemostatic seal, mechano-electrical skin interface and subcutaneous electrodes)~~ (Deleted 01/01/2022)
	~~0452T~~	~~;aortic counterpulsation device and vascular hemostatic seal~~ (Deleted 01/01/2022)
	~~0453T~~	~~;mechano-electrical skin interface~~ (Deleted 01/01/2022)
	~~0454T~~	~~;subcutaneous electrode~~ (Deleted 01/01/2022)
	~~0455T~~	~~Removal of permanently implantable aortic counterpulsation ventricular assist system; complete system (aortic counterpulsation device, vascular hemostatic seal, mechano-electrical skin interface and electrodes)~~ (Deleted 01/01/2022)
	~~0456T~~	~~;aortic counterpulsation device and vascular hemostatic seal~~ (Deleted 01/01/2022)
	~~0457T~~	~~;mechano-electrical skin interface~~ (Deleted 01/01/2022)
	~~0458T~~	~~;subcutaneous electrode~~ (Deleted 01/01/2022)
	~~0459T~~	~~Relocation of skin pocket with replacement of implanted aortic counterpulsation ventricular assist device, mechano- electrical skin interface and electrodes~~ (Deleted 01/01/2022)
	~~0460T~~	~~Repositioning of previously implanted aortic counterpulsation ventricular assist device, subcutaneous electrode~~ (Deleted 01/01/2022)
	~~0461T~~	~~;aortic counterpulsation device~~ (Deleted 01/01/2022)
	~~0462T~~	~~Programming device evaluation (in person) with iterative adjustment of the implantable mechano-electrical skin interface and/or external driver to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable aortic counterpulsation ventricular assist system, per day~~ (Deleted 01/01/2022)
	~~0463T~~	~~Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable aortic counterpulsation ventricular assist system, per day~~ (Deleted 01/01/2022)
HCPCS	L8698	Miscellaneous component, supply or accessory for use with total artificial heart system

Codes	Number	Description
	Q0477 – Q0509	Ventricular assist device accessories, code range

Date of Origin: *January 1996*

Regence

Medical Policy Manual Transplant, Policy No. 02

Heart Transplant

Effective: December 1, 2023

Next Review: March 2024
Last Review: October 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A heart transplant consists of replacing a diseased heart with a healthy donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

MEDICAL POLICY CRITERIA

I. Human heart transplantation may be considered **medically necessary** for adults (18 years or older) with end-stage heart failure (see Policy Guidelines) when one or more of the following Criteria is met:

   A. Hemodynamic compromise due to heart failure demonstrated by any one of the following (1. – 5.) accepted indications[1]:

      1. Maximal VO2 (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism; or
      2. Refractory cardiogenic shock; or
      3. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion; or
      4. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or

5. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities; or

B. Hemodynamic compromise due to heart failure demonstrated by one of the following (1. or 2.):

1. Any one of the following (i. – iii.) probable indications of hemodynamic compromise[1]:

i. Maximal VO2 <14 mL/kg/min and major limitation of the patient's activities, or

ii. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or

iii. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction.

2. Patient is on a ventricular assist device (VAD) or artificial heart as a bridge to transplant.

II. Human heart transplantation may be considered **medically necessary** in pediatric patients (see Policy Guidelines) when one of the following Criteria is met:

A. There is a diagnosis of heart failure with persistent symptoms at rest and any one or more of the following Criteria are met:

1. Continuous infusion of intravenous inotropic agents; or
2. Mechanical ventilatory support; or
3. Mechanical circulatory support; or

B. There is a diagnosis of pediatric heart disease with symptoms of heart failure in patients who do not meet Criteria II.A but any one of the following Criteria (1 – 7) is met:

1. Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or
2. Cardiomyopathies or previously repaired or palliated congenital heart disease, and significant growth failure attributable to the heart disease; or
3. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
4. Restrictive cardiomyopathy with reactive pulmonary hypertension; or
5. Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
6. Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
7. Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

III. Human heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in patients who meet criteria for heart transplantation.

IV. Human heart transplantation or retransplantation is considered **not medically necessary** when Criterion I., II., or III. is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Adults with histories of congenital heart disease may be considered under applicable criteria for either Adult Patients (Criteria I) or Pediatric Patients (Criteria II).

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Laboratory Tests for Organ Transplant Rejection, Laboratory, Policy No. 51
2. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
3. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

SOLID ORGAN TRANSPLANTATION

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[2] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life, particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS).

HEART TRANSPLANT

In 2022, 42,887 transplants were performed in the United States procured from almost 36,421deceased donors and 6,467 living donors. Heart transplants were the third most common procedure with 4,111 transplants performed from both deceased donors in 2022. As of March 2023, there were 3,404 patients on the waiting list for a heart transplant.[3]

The majority of heart transplant recipients are now hospitalized Status 1 patients at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Patients initially listed as a Status 2 candidates may deteriorate to a Status 1 candidate before a donor organ becomes available. At the same time, as medical and device therapy for advanced heart failure has improved, some patients on the transplant list will recover enough function to become delisted.

Bakhtiyar (2020) published the results of a retrospective cross-sectional analysis of outcomes in 98,323 candidates wait-listed for heart transplantation between January 1, 1987, and December 29, 2017 in the UNOS database.[4] Overall, the one-year survival on the waiting list increased from 34.1% in 1987-1990 to 67.8% in 2011-2017 (difference in proportions, 0.34%; 95% CI, 0.32%-0.36%; p<0.001). The one-year waiting list survival for candidates with ventricular assist devices (VADs) increased from 10.2% in 1996-2000 to 70.0% in 2011-2017 (difference in proportions, 0.60%; 95% CI, 0.58%-0.62%; p< 0.001) and from 53.9% in 1996-2000 to 66.5% in 2011-2017 (difference in proportions, 0.13%; 95% CI, 0.12%-0.14%; p<0.001) for patients without VADs. Improvement in the latter was attributed to changing mechanical circulatory support indications. In sum, temporally associated increases in heart transplant waiting list survival were found for all patient groups (with or without VADs, UNOS status 1 and status 2 candidates, and candidates with poor functional status).

Magnetta (2019) reported outcomes for children on the heart transplant waiting list, comparing the periods of December 16, 2011 to March 21, 2016 (era 1), and March 22, 2016 to June 30, 2018 (era 2).[5] There was a significant decrease from era 1 to era 2 in the proportion of patients listed as status 1 (70% vs 56%; p<0.001), while the proportion of patients with congenital heart disease (CHD) significantly increased across eras (49% to 54%; p=0.018). The median time on the waitlist increased from 68 days to 78 days (p=0.005). There were no significant differences across eras in the cumulative incidence of death on the waitlist among all candidates (subdistribution hazard ratio, 0.96; 95% CI, 0.80 to 1.14; p=0.63) and among those listed status 1A (subdistribution hazard ratio, 1.16; 95% CI, 0.95 to 1.41; p= 0.14). Graft survival at 90 days was also similar across eras in the overall population and in those with CHD (p>0.53 for both).

Alshawabkeh (2018) reported on the one-year probability of the combined outcome of death or delisting due to clinical worsening for patients on the heart transplant waiting list, comparing the periods of April 1, 1986 to January 19, 1999, (early era) and January 20, 1999 to June 2, 2014 (current era).[6] For adults without CHD, the probability of the combined outcome was lower in the current era compared with the early era, regardless of whether the patient was listed in status I (14.5% vs 22.7%; p<0.0001) or 2 (9.0% vs 12.8%, p<0.0001). When comparing the current and early eras in adults with CHD, a reduction in the probability of the combined outcome was demonstrated in those listed in status I (17.6% vs 43.3%, respectively; p<0.0001), whereas the outcome remained unchanged for those listed in status 2 (10.6% vs 10.4%, respectively; p=0.94).

In adults with CHD, factors associated with waitlist death or delisting due to clinical worsening within one year were also examined by Alshawabkeh (2016).[7] A multivariate analysis identified that an estimated glomerular filtration rate less than 60 ml/min/1.73 m2 (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.0 to 1.9; p=0.043), albumin less than 3.2 g/dl (HR, 2.0; 95% CI, 1.3 to 2.9; p<0.001), and hospitalization at the time of listing in the intensive care unit (HR, 2.3; 95% CI, 1.6 to 3.5; p<0.001) or a non-intensive care hospital unit (HR, 1.9; 95%

CI, 1.2 to 3.0; p=0.006) were associated with waitlist death or delisting due to clinical worsening within one year.

Johnson (2010) reported on waiting list trends in the U.S. between 1999 and 2008.[8] An increasing trend of adult patients with congenital heart disease and retransplantation was noted. The proportion of patients listed as Status 1 continued to increase, even as waiting list and post-transplant mortality for this group decreased. Meanwhile, Status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years. This is an update to what Lietz and Miller published in 2007, where they reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005.[9] One year survival for UNOS Status 1 candidates improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared to 81.8% in the earlier time period.

As a consequence of improved survival in those on transplant waiting lists, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (VO2), which is measured during maximal exercise, is one measure that has been suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology (ACC) has adopted maximal VO2 as one criterion for patient selection.[1] Studies have suggested that transplantation can be safely deferred in those patients with a maximal VO2 of greater than 14 mL/kg/min. The importance of maximal VO2 has also been emphasized by an American Heart Association Scientific Statement addressing heart transplant candidacy.[10] In past years, a left ventricular ejection fraction (LVEF) of less than 20% or a New York Heart Association (NYHA) Class III or IV status may have been used to determine transplant candidacy. However, as indicated by the ACC criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than maximal VO2 have been proposed as predictive models in adults.[11-14] The Heart Failure Survival Scale (HFSS) and Seattle Heart Failure Model (SHFM) are two examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information regarding pharmacologic and device usage is incorporated into the model, permitting some estimation of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy and colleagues[15] introduced the model using multivariate analysis of data from the PRAISE1 heart failure trial (n=1,125). Applied to the data of five other heart failure trials, the SHFM correlated well with actual survival (r: 0.98, standard error of the estimate=$\pm$3). The SHFM has been validated in both ambulatory and hospitalized heart failure populations[16-18] but with a noted underestimation of mortality risk, particularly in Black adults and device recipients.[19, 20] None of these models have been universally adopted by transplant centers.

INITIAL HEART TRANSPLANT

In the U.S., over 6 million people 20 years of age and older have heart failure and 1 in 8 deaths have heart failure mentioned on the death certificate.[21, 22] The reduction of cardiac

output is considered to be severe when systemic circulation cannot meet requirements under minimal exertion.

Heart failure may be due to a number of etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart disease (CHD). The leading indication for a heart transplant has shifted over time from ischemic to nonischemic cardiomyopathy. From 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18 to 39 years (64%) and 40 to 59 years (51%) undergoing transplant operations.[23] Ischemic cardiomyopathy was the dominant underlying primary diagnosis among heart transplant recipients 60 to 69 years (50%) and 70 years and older (55%). Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of heart transplants during this time period were in adults with CHD.

HEART RETRANSPLANTATION

From 2008 to 2015, approximately 4% of heart transplants were repeated transplantations.[3] As of June 2020, there were 106 patients on the waitlist for a repeat heart transplant. Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The United Network for Organ Sharing does not have separate organ allocation criteria for repeat heart transplant recipients.

REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse

events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. Due to the nature of the population discussed herein, there are no RCTs comparing heart transplantation with alternatives, including left ventricular assist devices (LVADs). Systematic reviews are based on case series and registry data. RCTs published on related topics (e.g., comparing surgical technique, infection prophylaxis regimens, or immunosuppressive therapy) are not relevant to this evidence review.

INITIAL HEART TRANSPLANT

Survival after heart transplant

According to the Organ Procurement and Transplantation Network (OPTN), Kaplan-Meier survival rates for heart transplants performed during 2008-2015 based on available U.S. data as of June 11, 2021, the one-year survival after heart transplant was 90.3% (95% confidence interval [CI], 89. 6% to 90.9%) and 90.7% (95% CI, 89.6% to 91.7% for men and women, respectively.[3] Three-year survival rates were 84.7% (95% CI, 83.8% to 85.5%) and 84.1% (95% CI, 82.7% to 85.4%)for men and women, respectively, and five-year survival rates were 77.8% (95% CI, 76.8% to 78.8%) and 75.9% (95% CI, 74.2% to 77.6%), respectively.

A systematic review by Almarsi (2019) was conducted to identify new variables associated with transplant outcomes that are not currently collected by the Organ Procurement and Transplantation Network (OPTN).[24] Eighty-one unique studies including 1,193, 410 transplant patients with median follow-up of 36 months posttransplant were included. Among the 108 unique risk factors identified, 104 were recipient-related and 4 were donor-related. The strongest relative association measure for a heart transplant outcome with a risk factor was 8.6 (recipient with the previous Fontan operation).

A retrospective case-control study by Suarez-Pierre (2021) was published that compared survival after heart transplantation with that of the general population.[25] Data from 31,883 adults in the OPTN who had undergone heart transplantation between 1990 and 2007 were matched (5:1) to control subjects (n=159,415) based on age, sex, race, and state of permanent residency. The ten-year survival of heart transplant recipients was 53%. The population expected mortality rate was 15.9 deaths per 100 person-years with an observed rate of 45.1 deaths per 100 person-years (standardized mortality rate [SMR] 2.84; 95% confidence interval, 2.82 to 2.87). Over time, the standardized mortality ratios declined (1990 to 1995, 3.09; 1996 to 2000, 2.90; 2001 to 2007, 2.58) and the largest discrepancies between observed and expected survival were in female (SMR 3.63), black (SMR 3.67), and Hispanic (SMR 4.12) transplant recipients.

A systematic review by Almarsi (2019) was conducted to identify new variables associated with transplant outcomes that are not currently collected by the Organ Procurement and Transplantation Network (OPTN).[24] Eighty-one unique studies including 1,193, 410 transplant patients with median follow-up of 36 months posttransplant were included. Among the 108 unique risk factors identified, 104 were recipient-related and four were donor-related. The strongest relative association measure for a heart transplant outcome with a risk factor was 8.6 (recipient with the previous Fontan operation).

Nguyen (2017) investigated the benefit of heart transplantation compared with waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in the OPTN between July 2006 and December 2015.[26] Net benefit

from heart transplantation was evident across all estimates of donor-recipient status 1A and 1B candidates: status 1A (lowest-risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR=0.52; 95% CI, 0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR=0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR=0.66; 95% CI, 0.58 to 0.74). Status 2 candidates showed a benefit from heart transplantation; however, survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Lund (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation during 2000-2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.[23] Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR=1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR=1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR=1.16; 95% CI: 1.10 to 1.23; n=7822), congenital (HR=1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR=1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs non-ischemic cardiomyopathy), and retransplant (HR=1.18; 95% CI, 1.02 to 1.35; n=489) were associated with post-transplant mortality risk at 10 years.

Ting (2016) published a report that retrospectively evaluated outcomes of 134 patients one month to 78 years old (average 28) who received mechanical circulatory support for acute myocarditis with cardiogenic shock, between 1994 and 2014.[27] Patients recovering without a transplant were compared to those who received a transplant under mechanical circulatory support. 54% of patients survived on mechanical circulatory support, without transplant. Only 5% of the patients underwent transplant. The authors concluded transplant survival under mechanical circulatory support had favorable mid- and long-term outcomes.

Starling (2016) and Svobodova (2016) published studies evaluating transplant outcomes based on biomarkers and/or antibodies. Sterling published a one year observational, multicenter, cohort study in which 200 heart transplant patients were evaluated for biomarkers that could predict heart transplant outcomes.[28] Laboratory tests included anti-AHL antibody analysis, ELISPOT Panel of reactive T cell (PRT) assays, plasma angiogenesis-related proteins, peripheral blood and tissue gene expression profiling. Svobodova published a single-center retrospective study that evaluated antibody-mediated rejection (AMR).[29] Data was analyzed for pre- and post-transplant antibodies and antigens in transplant recipients and/or donors. Median follow-up was 39 months. Starling concluded it is still difficult to find reliable biomarkers that can determine heart transplant outcomes. Svobodova stated monitoring pre- and post-transplant antigens and antibodies may predict rejection.

Rana (2015) conducted a retrospective analysis of solid organ transplant recipients registered in the UNOS database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.[30] Transplant recipients were compared with patients listed for transplant, but who did not receive a transplant after propensity score matching based on a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

A 2013 study examined characteristics of patients who survived longer than 20 years after heart transplantation at a single center.[31] Thirty-nine heart transplant recipients who survived over 20 years post-transplant were compared to 98 patients who died between one and 20-years post-transplant. Independent factors associated with long-term survival were younger

recipient age i.e., <45 years versus 45 years and older (OR: 3.9, 95% CI: 1.6-9.7) and idiopathic cardiomyopathy i.e. versus other etiologies (OR: 3.3, 95% CI: 1.4-7.8).

Bhama (2013) published results from study that reported on survival outcomes for heart transplantation in a cohort of adults with congenital heart disease (CHD) and identified risk factors for mortality that would help guide recipient and donor selection.[32] A retrospective analysis identified 19 patients that had transplantation for CHD and compared to 428 transplant patients that underwent transplantation for conditions other than CHD. There was no significant difference in survival (CHD vs control) at 30 days (89% vs 92%, p = 0.5567), one year (84% vs 86%, p = 0.6976), or five years (70% vs 72%, p = 0.8478). The only significant predictor of death in the CHD group was donor organ ischemic time >four hours (HR 13.26, 95% CI 1.3 to 132.2, p = 0.028). Authors suggested that adults with CHD have excellent early and mid-term survival after heart transplantation.

A 2012 study by Kalic analyzed prospectively collected data from the United Network for Organ Sharing (UNOS) registry.[33] The analysis included 9,404 individuals who had survived 10 years after heart transplant and 10,373 individuals who had died before 10 years. Among individuals who had died, mean survival was 3.7 years post-transplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included:

- Age younger than 55 years (odds ratio [OR]: 1.24, 95% confidence interval [CI]: 1.10 to 1.38),
- Younger donor age (OR: 1.01, 95% CI: 1.01 to 1.02),
- Shorter ischemic time (OR: 1.11, 95% CI: 1.05 to 1.18),
- White race (OR: 1.35, 95% CI: 1.17 to 1.56), and
- Annual center volume of nine or more heart transplants (OR: 1.31, 95% CI: 1.17 to 1.47).

Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included:

- Mechanical ventilation (OR: 0.53, 95% CI: 0.36 to 0.78), and
- Diabetes (OR: 0.67, 95% CI: 0.57 to 0.78).

Jalowiec (2011) compared clinical outcomes in sex-matched and sex-mismatched heart transplant recipients.[34] They retrospectively reviewed data from 347 heart transplant recipients; 237 (78.7%) received a heart from a same-sex donor, 40 (11.5%) cases involved a female donor and male recipient, and 34 (9.8%) cases involved a male donor and female recipient. There was not a statistically significant difference in the mortality rate during the first month post-transplant between the sex-matched and either sex-mismatched group. In adjusted analyses, two of the other nine study outcomes differed significantly among the three groups. The male donor-female recipient group had significantly more treated rejection episodes during the first year post-transplant and significantly more days of rehospitalization after the initial discharge than either of the other two groups. The incidence of steroid-induced diabetes, cardiac allograft vasculopathy, non-skin cancers, number of intravenous (IV)-treated infections post-transplant, and initial hospital length of stay were not significantly different among groups.

Pediatric considerations

The highest one- and three- year survival rate among pediatric patients undergoing heart transplant in the US, during 2008-2015, were 11-17 year old patients according to the Organ Procurement and Transplantation Network (OPTN).[3] Patients younger than one-year-old had the lowest one-, three-, and five-year survival among pediatric patients.

Khan (2021) published the results of a retrospective analysis of heart transplant survival in children with congenital heart disease with or without heterotaxy syndrome.[35] Waitlist outcomes and survival post-listing and transplant were analyzed from 4814 children of whom 196 (4%) had heterotaxy. No differences in waitlist outcomes of transplant, death, or removal were found between patients with or without heterotaxy. Post-transplant survival was worse for children with heterotaxy: one-year survival 77.2% vs. 85.1%, with and without heterotaxy, respectively. In addition, heterotaxy was an independent predictor for early mortality in the earliest era (1993-2004), HR 2.09, CI 1.16-3.75, p = 0.014, however, this improved over time. Lower freedom from infection and from severe rejection was found in patients with heterotaxy, but no difference in vasculopathy or malignancy was identified.

Rossano (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry. Among 12,091 pediatric patients undergoing heart transplantation during 1982-2014, the overall median survival was 20.7 years for infants, 18.2 years for children ages 1 to 5 years, 14.0 years for those ages 6 to 10 years, and 12.7 years for those ages 11 to 17 years. As the first year posttransplant represents the greatest risk for mortality, survival conditional on survival to one year was longer.[36]

Kulkami (2016) published an evaluation of a multicenter prospective single ventricle reconstruction trial to determine outcomes of infant patients with a single ventricle who were listed for transplant after the Norwood procedure.[37] A public database was used to compare infants while on the waiting list and after transplant. Risk factors were also evaluated for those patients put on the waiting list for a transplant and for those who survived without a transplant. Of 555 patients 33 were listed and underwent transplant. One-year survival after being put on the waiting list, including those that died after transplant was 48%. Diagnosis for being put on the transplant list after the Norwood procedure, included worsening right ventricular function, non-hypoplastic left heart syndrome, and a complex intensive care unit stay. The authors determined patients having heart transplant as a rescue procedure within a year of the Norwood procedure had a higher risk of complications and mortality.

Garbern (2016) published a study that evaluated transplant outcomes for pediatric patients with myocarditis versus dilated cardiomyopathy (DCM).[38] During the study 137 children with myocarditis and 1,249 children with DCM underwent heart transplant. Data was taken from the Organ Procurement and Transplant Network (OPTN) database. The data for children with myocarditis was evaluated for a higher risk of mortality pre-transplant. The authors noted several study limitations including that they could not confirm data accuracy, but stated after the adjustment for severity of illness, children with myocarditis were not at a higher risk of mortality pre- and post-transplant than patients with DCM.

According to OPTN data, in 2015, 423 heart transplants were performed in children younger than 18 years of age.[3] Five-year survival rates by age group were: less than one year: 68.6% (95% CI, 62.0% to 75.1%); one to five years: 69.4% (95% CI, 64.1% to 74.7%); six to ten years: 73.1% (95% CI, 66.7% to 79.5%); and 11-17 years: 75.1% (95% CI, 72.6% to 77.5%).

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia in 2014.[39] From 1987 to 2011, 99 adolescents (age, 13-18) heart transplants were

performed with myocarditis and 456 adolescents with coronary heart disease (CHD). Among adolescent transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly less than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

According to the International Society for Heart and Lung Transplantation, 532 heart transplants in children younger than 18 years-old were reported worldwide in 2010.[40] This number compares to 543 reported in 2009. Among the pediatric transplants, about 25% were in infants younger than age one year, 37% were in children between the ages of one and 10 years, and 38% were in adolescents between the ages of 11 to 17 years. In infants, the most common indications for heart transplant were congenital heart disease (56%) and cardiomyopathy (40%). For children older than 10 years of age, the most common indication was cardiomyopathy (63%). Median survival has varied with age of the transplant recipient. Median survival was 19.2 years for infants, 15.6 years for one to 10 year-olds, and 11.9 years for 11-17 year-olds.

In 2011, a retrospective review of pediatric cardiac transplantation patients was published by Auerbach.[41] A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at one year and 68% at five years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was 82% at one year and 72% at five years. In multivariate analysis, the authors found that congenital heart disease (HR: 1.6, 95% CI: 1.02-2.64) and requiring mechanical ventilation at the time of transplantation (HR: 1.6, 95% CI: 1.13-3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only one center.

Patel (2010) presented a retrospective review of echocardiography and serum markers as a predictor of death or need for transplantation in newborns, children, and young adults with heart failure.[42] A total of 99 children with 139 admissions were evaluated on LVEF and tricuspid regurgitation, as well as on various serum markers for their predictive ability of death or need for transplantation in a stepwise multivariate Cox regression model. While brain natriuretic peptide (BNP) and tricuspid regurgitation were not predictive of need for transplantation, ejection fraction and lymphocytosis were predictive (ejection fraction odds ratio [OR]: 0.94, 95% CI: 0.90-0.98; for lymphocytosis, OR 5.40, 95% CI: 1.67–17.4). Serum levels of creatinine and sodium were also predictive. Clinical prediction rules based on these findings have not been compared to current strategies and await clinical validation.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.[43] Of 3,098 children (younger than 18 years of age) listed between 1999 and 2006, a total of 1,874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1,943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population

with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR]: 3.1), ventilator support (HR: 1.9), listing status 1A (HR: 2.2), congenital heart disease (HR: 2.2), dialysis support (HR: 1.9), and non-white race/ethnicity (HR: 1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

HEART RETRANSPLANTATION

Chen (2022) evaluated outcomes after heart re-transplantation in recipients > 60 years. A total of 1026 adult patients undergoing isolated heart re-transplantation were identified (> 60 years, n=177; ≤ 60 years, n=849).[44] Older recipients were more likely to be male and have diabetes or previous malignancies with higher baseline creatinine. They more frequently required pre-transplant ECMO (11.9% vs. 6.8%, p=0.02) and received re-transplantation due to primary graft failure (13.6% vs. 8.5%, p=0.03). After transplant, older recipients had a higher incidence of stroke (6.8% vs. 2.6%, p=0.01) and dialysis requirements (20.3% vs. 13.2%) before discharge (both p<0.05), and more frequently died from malignancy-related causes (16.3% vs. 3.9%, p<0.001). After adjustment, recipient age >60 was associated with an increased risk of both 5-year (HR 1.42, 95% CI 1.02-2.01, p=0.04) and 10-year mortality (HR 1.72, 95% CI 1.20-2.45, p=0.003).

Zhu (2022) evaluated outcomes after heart retransplantation for 123 patients (112 adult and 11 pediatric patients) as compared to those who received a primary heart transplant at a single-center over a 50-year period (January 6, 1968 to June 2019).[45] The indications for retransplantation included cardiac allograft vasculopathy (80%), primary graft dysfunction (15%), and refractory acute rejection (5%). The mean time interval between the primary and retransplant was 6.4 years. Patients who underwent a retransplantation were significantly more likely to have hypertension (73.3% vs. 53.3%; p=.0022), hyperlipidemia (66.7% vs. 30.7%; p<.0001), and require dialysis (11.7% vs. 2.9%; p=.0025) as compared to those undergoing a primary heart transplant. After matching, postoperative outcomes and complications including hospital stay (mean 22.9 vs. 25.8 days; p=.49), intensive care unit stay (mean 12.2 vs. 9.9 days; p=.48), respiratory failure (41.7% vs. 20.6%; p=.083), dialysis (21.2% vs. 24.2%; p=.82), pneumonia (12.9% vs. 9.6%; p=.48), septicemia (1.6% vs. 9.4%; p=.10), and rejection within the first year after transplantation requiring hospitalization (21.5% vs. 26.2%; p=.82) were similar between the retransplant and primary transplant groups, respectively. Matched median survival after retransplantation was 4.6 years versus 6.5 years after primary heart transplantation (p=.36).

In a study analyzing UNOS data from January 1996 to November 2017, Miller (2019) reported that 349 (0.6%) early/acute retransplants (occurring ≤ one year after the previous transplant) and 2,202 (3.5%) late retransplants (occurring > one year after the previous transplant) were performed from a sample of 62,112 heart transplants.[46] Compared with a matched group of patients undergoing initial transplantation, patients undergoing late retransplantation were not at an increased risk of death (HR, 1.08; p=0.084) or the combined outcome of death or retransplantation (HR, 1.07; p=0.114). Additionally, patients undergoing late retransplant had comparable rates of one-year all-cause mortality when compared to patients undergoing initial transplant (13.8% vs 14.5%, respectively; p=0.517). Conversely, patients undergoing early/acute transplant had higher rates of one-year all-cause mortality when compared to patients undergoing initial transplant (35% vs 21.6%; p<0.001). Furthermore, early/acute

retransplantation was associated with an increased risk of all-cause mortality (HR, 1.79; p<0.001) and the combined outcome of death or retransplantation (HR, 1.72; p<0.001).

An analysis of OPTN data from 1995 to 2012 by Belli (2014) reported that 987 retransplants were performed (of 28,464 heart transplants, 3.5% of all transplants).[47] Median survival among retransplant recipients was 8 years. The estimated survival at 1, 5, 10, and 15 years following retransplant was 80%, 64%, 47% and 30%, respectively. Compared with primary transplant recipients, retransplant patients had a somewhat higher risk of death (risk ratio [RR]=1.27, 95% CI, 1.13 to 1.42).

A number of studies have reviewed clinical experience with heart retransplantation in adults. In 2013, Saito published a retrospective review of data on 593 heart transplants performed at their institution; 22 of these (4%) were repeat transplantations.[48] The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in seven patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in five patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7 of 22 patients). Among patients who survived the first 30 days (n=15), 1-, 5- and 10-year survival rates were 93.3%, 79% and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82% and 63%, respectively. An interval of one year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of nine patients (33.3%) with less than a year between the primary and retransplantation survived to 30 days. In comparison 12 of 13 patents (92%) with at least one year between primary and retransplantation were alive at 30 days after surgery.

Tjang (2008) published a systematic review of this literature that identified 22 studies reporting clinical outcomes of heart retransplantation in patients over 18 years old.[49] The most common indications for retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range: 5% to 38%). Some of the factors associated with poorer outcome after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure and an initial diagnosis of ischemic cardiomyopathy.

Topkara (2005) reviewed data on 766 adult patients who underwent heart transplantation between 1992 and 2002.[50] Forty-one (5%) of patients underwent repeat transplants; the indication for retransplantation was transplant-related coronary artery disease in 37 of 41 (90%) of these patients. Due to early experience with retransplantation, criteria at this institution were changed in 1993 so that patients with intractable acute rejection within 6 months of the initial transplant were ineligible for repeat transplants. One and five-year survival rates were 85.1% and 72.9%, respectively after primary transplantation and 72.2% and 47.5%, respectively after retransplantation. Survival rates were significantly lower in the retransplantation group, p<0.001. The authors did not report survival rates stratified by the length of time between initial and repeat transplantations.

Pediatric Considerations

Vazquez (2022) published an evaluation of retransplantation patients from the Pediatric Heart Transplant Society (PHTS) database analysis of retransplantation patients <18 years of age over three decades (Era 1: 1993-2001, Era 2: 2002-2010, Era 3: 2011-2018).[51] Survival was lower (p < .0001) for retransplant (n = 222) compared to primary transplant (n = 6548) (median 9.3 vs 20.2 years). Median survival increased from Era 1 to 2 (4.8 vs 9.3 years; p < .0001) with

no incremental change in Era 3. Era 2 and 3 retransplants had a longer inter-transplant interval (p < .0001), were less frequently for early graft failure (p = .0004) or acute rejection (p = .007), more frequently from a ventricular assist device (p = .0014), and less frequently from extracorporeal membrane oxygenation (p = .0024). Predictors of graft loss included Era 1 (HR 10.55, p = .001), congenital heart disease (HR 4.42, p = .01), inter-transplant interval <1 year (HR 5.34, p = .002), and mechanical support (ventricular assist device HR 7.47, p = .0042; extracorporeal membrane oxygenation HR 10.09, p < .0001). For each 1-year increase in inter transplant interval, graft loss risk decreased by 1.15 (p = .0002). Retransplantation was associated with more rejection, infection, and allograft vasculopathy. The authors conclude that graft survival has improved in pediatric retransplant and that retransplantation should be avoided in the setting of early graft failure especially requiring mechanical support.

Azeka (2020) published a retrospective cohort study reporting on patients who underwent primary heart transplant (PTx) <18 years old and subsequent retransplant (RTx) due to coronary allograft vasculopathy (CAV). [52] The maintenance immunosuppression protocol was double immunosuppression. Between 1992 and 2018, 200 children underwent heart transplantation. Ten re-transplantations were performed, for which 7 (70%) were for CAV. Ages at RTx ranged from 11.5 to 29.3 years (19.1 ± 5.68 years; median 18.2 years). The mean time between PTx and RTx was 12.9 ± 3.4 years (median 13.4 years). The Kaplan-Meier survival rate at 1 month, 3 years, and 5 years was 85.7%, 71.5%, and 47.6%, respectively. The authors conclude that cardiac RTx can be a management option for CAV in patients who have undergone PTx in childhood with double immunosuppression therapy.

As with initial heart transplants, children waiting for heart retransplantation have high waitlist mortality. Alsoufi (2015) published results from a retrospective analysis (1988 to 2013) that examined their experience with heart transplantations in pediatric patients with underlying congenital heart disease.[53] The study included sixteen patients who underwent primary heart transplantation. Participants were predominately male, and had a median age of 3.8 years. Competing risks analysis showed that at 10 years after heart transplantation, 13% of patients had undergone retransplantation, 43% of patients had died without retransplantation, and 44% of patients were alive without retransplantation. After retransplantation, 52% of patients were alive and 18% of patients had undergone a second retransplantation. Overall 15-year survival after initial heart transplantation was 41%. It is important to note this study has methodological considerations, which include but are not limited to, a small sample size; therefore, generalizability of results is limited.

Bock (2014) evaluated data on 632 pediatric patients who were listed for a heart retransplant at least one year (median, 7.3 years) after the primary transplant.[54] Patients' median age was four years at the time of the primary transplant and 14 years when they were relisted. Median waiting time was 75.3 days and mortality was 25.2% (159 of 632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<0.01).

Copeland (2014) published results from a retrospective chart review (n=183) and evaluated late survival among pediatric heart transplant patients, living for more than 15 years after transplant.[55] A total of 32 deaths were reported due to the following conditions: cardiac allograft vasculopathy (CAV); 11 (34.3%); posttransplant lymphoproliferative disease, 18.8%; acute rejection, 12.5%; sepsis, 6.3%; multiorgan failure, 3.1%; and unknown reasons, 25%. A total of 30 patients required cardiac retransplantation due to CAV. The authors concluded that heart transplantation in pediatric patients results in acceptable long-term survival. In patients

who develop CAV and renal dysfunction, heart retransplantation is an acceptable form of palliative treatment.

Friedland-Little (2014) published results from a retrospective analysis (1985-2011) of pediatric and young adult survivors who had undergone repeat heart transplantations.[56] Patients were included in the review who had a primary heart transplant before the age of 21, and had undergone a third transplant. Patients were matched 1:3 with a control group of second heart transplant patients by age, era and re-transplant indication. The authors found no difference between third heart transplant patients (n=27) and the control second heart transplantation patients (n=79) with respect to survival (76% vs 80% at one year, 62% vs 58% at five years and 53% vs 34% at 10 years, p = 0.75). However, generalizability of the study's results may be limited due to methodological limitations, such as small sample size.

Mahle (2005) reviewed data from the United Network for Organ Sharing (UNOS) on heart retransplantation in patients less than 18 years old.[57] A total of 219 retransplantations occurring 1987 to 2004 were identified. The median age at initial transplant was 3 years old and the median age at retransplantation was nine years old. The median interval between initial procedure and retransplantation was 4.7 years. The most common indications for retransplantation were coronary allograft vasculopathy (n=111, 51%), non-specific graft failure (n=34, 18%) and acute rejection (n=19, 9%). Retransplantation was associated with worse overall survival than initial transplantation. One,five, and ten year survival rates were 83%, 70% and 58%, respectively after primary transplantation and 79%, 53% and 44%, respectively after retransplantation. The most common causes of death after retransplantation were acute rejection (14%), coronary allograft vasculopathy (14%) and infections (13%).

In both the adult and pediatric studies, poorer survival after retransplantation than initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events. The increased mortality from retransplantation appears to be mainly from increased short-term mortality. Longer-term survival rates after retransplantation seem reasonable, especially when patients with a higher risk of poor outcomes (e.g., those with a shorter interval between primary and repeat transplantation) are excluded. Also, patients with failed initial transplant have no other options besides a retransplantation.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Pretransplant malignancy is considered a relative contraindication for heart transplantation considering this has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population,

Mistiaen (2015) conducted a systematic review to study the posttransplant outcome of pretransplant malignancy patients.[58] Most selected studies were small case series. Mean patient age varied from 6 years to 52 years. Hematologic malignancy and breast cancer were the most common type of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy was mostly the common reason for transplantation in 4 case series, chemotherapy related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality varied between 0% and 33%, with small sample size potentially explaining the observed variation, One large series reported similar short-term and long-term posttransplant survival of chemotherapy related (N=232) and other nonischemic cardiomyopathy (N=8890) patients. The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients. Similar findings were observed for 1-year survival in smaller series. Two-, 5-, and 10-year survival rates among pretransplant malignancy patients were also comparable with other transplant patients. In addition to the nonmalignancy related factors such as cardiac, pulmonary, and renal dysfunction, two malignancy related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival compared with a longer interval (<60% vs >75%). Patients with prior hematologic malignancies had an increased posttransplant mortality in three small series. Recurrence of malignancy was more frequent among patients with a shorter disease-free interval, 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.

Yoosabai (2015) conducted a retrospective review among 23,171 heart transplant recipient in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of posttransplant malignancy.[59] Posttransplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with increased risk of overall posttransplant malignancy (subhazard ratio [SHR], 1.51; p<0.01), skin (SHR=1.55, p<0.01), and solid organ malignancies (SHR=1.54, p<0.01) on multivariate analysis.

ISHLT guidelines have recommended to stratify each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The guideline also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

OLDER AGE

Jamil (2017) conducted a retrospective study of age as it relates to primary graft dysfunction after heart transplantation.[60] Of the 255 heart transplants studied, 70 (27%) recipients were 65 years and older and 185 were younger; there were no significant differences in post-transplant morbidity (all p>0.12) or one-year survival between groups (p=0.88). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; p=0.037). Study limitations included the single-center design, lack of data on long-term survival, and the potential for selection bias in retrospective studies.

Cooper (2016) published a retrospective cohort study evaluating transplant outcomes in elderly patients, by using data from the United Network for Organ Sharing database. Data on

three groups of patients 18-59, 60-69 and greater than or equal to 70 years of age were compared for five-year survival rates. The authors noted that patients greater than or equal to 70 had more ischemia and renal dysfunction than the 60-69 age group and received transplants from older donors who were more ill or had a history of drug abuse. Five-year survival rates were 26.9% for the 18-59 age group, 29.3% for the 60-69 age group, and 30.8% for the greater than or equal to 70 age group. The authors also noted limitations with this retrospective review including but not limited to potential risk of bias with patient transplant selection and quality of the data. The authors concluded the greater than or equal to 70 age group showed no significant difference in outcomes from the 60-69 age group and should not be excluded from receiving a transplant.

Awad (2016) reported on a single-center retrospective review of 704 adults who underwent heart transplantation from 1988 to 2012 to investigate the mortality and morbidity rates of heart transplantations among recipients 70 years of age and older (n=45) compared with recipients younger than 70 years (n=659).[61] The older and younger groups had similar 1-year (93.0 vs 92.1; p=0.79), 5-year (84.2 vs 73.4; p=0.18), and10-year (51.2 vs 50.2; p=0.43) survival rates, respectively.

Kilic (2012) analyzed data from the UNOS on 5,330 patients age 60 and older (mean age 63.7 years) who underwent heart transplantation between 1995 and 2004.[62] A total of 3,492 individuals (65.5%) survived to five years. In multivariate analysis, statistically significant predictors of five-year survival included younger age (OR: 0.97, 95% CI: 0.95 to 1.00), younger donor age (OR: 0.99, 95% CI: 0.99-1.00), white race (OR: 1.23, 95% CI: 1.02 to 1.49), shorter ischemic time (OR: 0.93, 95% CI: 0.87-0.99), and lower serum creatinine (OR: 0.92, 95% CI: 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly decreased the odds of surviving to five years. Patients with two or more of these factors had a 12% lower rate of five years survival than those with none of them.

Daneshvar (2011) examined data on 519 patients who underwent heart transplantation between 1988 and 2009 at a single institution, with a particular focus on survival differences by age group.[63] There were 37 patients who were at least 70 years-old (group 1), 206 patients between 60 and 69 years (group 2), and 276 patients younger than 60 years (group 3). Median survival was 10.9 years in group one, 9.1 years in group two, and 12.2 years in group three (non-significant difference among groups). The five-year survival rate was 83.2% in group one, 73.8% in group two, and 74.7% in group three.

PULMONARY HYPERTENSION

Findings of several studies published in 2012 and 2013 suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant.[64-67] For example, De Santo (2012) reported on 31 consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization.[64] After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing listing for heart transplant. Oral sildenafil treatment resumed following transplant. One patient died in the hospital. A right heart catheterization at three months post-transplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at one year in the 29 surviving patients. Similarly, in a study by Perez-Villa (2013) , 22 patients considered high-risk for heart transplant due to severe pulmonary hypertension were treated

with bosentan. After four months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of nine patients who refused participation in the study and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation and the one-year survival rate was 93%.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY, AND AMERICAN HEART ASSOCIATION

Guidelines from the American College of Cardiology Foundation and American Heart Association were updated in 2017.[68] Evaluation for heart transplantation was recommended for patients in whom heart failure is assessed as refractory based on New York Heart Association functional class III or IV (stage D) for heart failure after previous guideline-directed medical therapy, use of devices such as an implantable cardioverter defibrillator or a cardiac resynchronization therapy device, or surgical management.

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2016, The International Society for Heart and Lung Transplantation (ISHLT) updated their heart transplantation criteria in and made the following updates to their recommendations:[69]

- 1.2 Use of heart failure prognosis scores. Heart failure prognosis scores should be performed along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated one year survival as calculated by the Seattle Heart Failure Model (SHFM) of <80% or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cut points for listing (Level of Evidence: C; primarily expert consensus opinion).
- 1.4.1 Age, obesity, and cancer as comorbidities and their implications for heart transplantation list.
    - Carefully selected patients >80 years of age may be considered for cardiac transplantation (Level of Evidence: C).
    - Pre-transplantation body mass index (BMI) >35kg/m^2 is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of ≤ 35kg/m^2 before listing for cardiac transplantation (Level of Evidence: C).
- 1.4.2 Diabetes, Renal dysfunction, and peripheral vascular disease.
    - Diabetes with end-stage damage or persistent poor glycemic control (glycosylated hemoglobin >7.5% or 58 mmol/mol) despite optimal effort is a relative contraindication for transplant (Level of Evidence: C).
    - Renal function should be assessed using estimated glomerular filtration rate (eFGR) or creatinine clearance under optimal medical therapy. It is reasonable to consider the presence of irreversible renal dysfunction (eGRF <30 ml/min1.73m2) as a relative contraindication for heart transplantation alone (Level of Evidence: C).
    - Clinically server symptomatic cerebrovascular disease may be considered a contraindication to transplantation when it's presences limits rehabilitation and revascularization is not a viable option (Level of Evidence: C).
- 1.5.3 Psychosocial evaluation. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as

having a relative contraindication to transplant. The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia has not been established, has the potential for harm, and therefore, heart transplantation cannot be recommended for this sub-group of patients (Level of Evidence: C).

- 1.8 Retransplantation. Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Level of Evidence: C).

THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (non-randomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications:[70]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previous repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension,
- The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m2 and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m2 or the transpulmonary gradient to <15 mm Hg.

SUMMARY

There is enough research to show that heart transplantation can improve survival for certain pediatric and adult patients. Guidelines based on research recommend heart transplant for people with certain indications. Therefore, heart transplant may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that heart retransplantation can improve survival for certain pediatric and adult patients who have had a prior transplant. Guidelines based on research recommend heart retransplantation for people with certain indications. Therefore, heart retransplantation may be considered medically necessary in patients who meet the policy criteria.

There is not enough research to show that heart transplantation or retransplantation improves health outcomes for all other indications. Therefore, heart transplantation or retransplantation is considered not medically necessary for indications when the policy criteria are not met.

REFERENCES

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005;112(12):e154-235. PMID: 16160202
2. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21(st) century. *Ann Transl Med.* 2018;6(20):409. PMID: 30498736
3. Organ Procurement and Transplantation Network (OPTN): National Data. [cited 3/21/2023]. 'Available from:' https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
4. Bakhtiyar SS, Godfrey EL, Ahmed S, et al. Survival on the Heart Transplant Waiting List. *JAMA Cardiol.* 2020;5(11):1227-35. PMID: 32785619
5. Magnetta DA, Godown J, West S, et al. Impact of the 2016 revision of US Pediatric Heart Allocation Policy on waitlist characteristics and outcomes. *Am J Transplant.* 2019;19(12):3276-83. PMID: 31544351
6. Alshawabkeh L, Opotowsky AR, Carter KD, et al. Disparities in Wait-List Outcomes for Adults With Congenital Heart Disease Listed for Heart Transplantation Before and Since Revision of Status I Listing. *The American journal of cardiology.* 2018;122(10):1761-64. PMID: 30236623
7. Alshawabkeh LI, Hu N, Carter KD, et al. Wait-List Outcomes for Adults With Congenital Heart Disease Listed for Heart Transplantation in the U.S. *Journal of the American College of Cardiology.* 2016;68(9):908-17. PMID: 27561764
8. Johnson MR, Meyer KH, Haft J, et al. Heart transplantation in the United States, 1999-2008. *Am J Transplant.* 2010;10(4 Pt 2):1035-46. PMID: 20420651
9. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/U.S. United Network of Organ Sharing data, 1990 to 2005. *Journal of the American College of Cardiology.* 2007;50(13):1282-90. PMID: 17888847
10. Costanzo MR, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 1995;92(12):3593-612. PMID: 8521589
11. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation.* 1997;95(12):2660-7. PMID: 9193435
12. Alla F, Briancon S, Juilliere Y, et al. Differential clinical prognostic classifications in dilated and ischemic advanced heart failure: the EPICAL study. *American heart journal.* 2000;139(5):895-904. PMID: 10783225

13. Hansen A, Haass M, Zugck C, et al. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with chronic congestive heart failure. *Journal of the American College of Cardiology.* 2001;37(4):1049-55. PMID: 11263607
14. Lee DS, Austin PC, Rouleau JL, et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA : the journal of the American Medical Association.* 2003;290(19):2581-7. PMID: 14625335
15. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006;113(11):1424-33. PMID: 16534009
16. Gorodeski EZ, Chu EC, Chow CH, et al. Application of the Seattle Heart Failure Model in ambulatory patients presented to an advanced heart failure therapeutics committee. *Circulation Heart failure.* 2010;3(6):706-14. PMID: 20798278
17. Ketchum ES, Moorman AJ, Fishbein DP, et al. Predictive value of the Seattle Heart Failure Model in patients undergoing left ventricular assist device placement. *J Heart Lung Transplant.* 2010;29(9):1021-5. PMID: 20558086
18. Nutter AL, Tanawuttiwat T, Silver MA. Evaluation of 6 prognostic models used to calculate mortality rates in elderly heart failure patients with a fatal heart failure admission. *Congest Heart Fail.* 2010;16(5):196-201. PMID: 20887615
19. Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G, et al. Utility of the Seattle Heart Failure Model in patients with advanced heart failure. *Journal of the American College of Cardiology.* 2009;53(4):334-42. PMID: 19161882
20. May HT, Horne BD, Levy WC, et al. Validation of the Seattle Heart Failure Model in a community-based heart failure population and enhancement by adding B-type natriuretic peptide. *The American journal of cardiology.* 2007;100(4):697-700. PMID: 17697831
21. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation.* 2021;143(8):e254-e743. PMID: 33501848
22. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation.* 2022;145(8):e153-e639. PMID: 35078371
23. Lund LH, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant.* 2016;35(10):1158-69. PMID: 27772668
24. Almasri J, Tello M, Benkhadra R, et al. A Systematic Review for Variables to Be Collected in a Transplant Database for Improving Risk Prediction. *Transplantation.* 2019;103(12):2591-601. PMID: 30768569
25. Suarez-Pierre A, Lui C, Zhou X, et al. Long-term Survival After Heart Transplantation: A Population-based Nested Case-Control Study. *The Annals of thoracic surgery.* 2021;111(3):889-98. PMID: 32739258
26. Nguyen VP, Mahr C, Mokadam NA, et al. The Benefit of Donor-Recipient Matching for Patients Undergoing Heart Transplantation. *Journal of the American College of Cardiology.* 2017;69(13):1707-14. PMID: 28359517
27. Ting M, Wang CH, Tsao CI, et al. Heart Transplantation Under Mechanical Circulatory Support for Acute Fulminant Myocarditis With Cardiogenic Shock: 10 Years' Experience of a Single Center. *Transplantation proceedings.* 2016;48(3):951-5. PMID: 27234777

28. Starling RC, Stehlik J, Baran DA, et al. Multicenter Analysis of Immune Biomarkers and Heart Transplant Outcomes: Results of the Clinical Trials in Organ Transplantation-05 Study. *Am J Transplant.* 2016;16(1):121-36. PMID: 26260101
29. Svobodova E, Gazdic T, Kubanek M, et al. Novel insights into pretransplant allosensitization in heart transplant recipients in the contemporary era of immunosuppression and rejection surveillance. *Transplant international : official journal of the European Society for Organ Transplantation.* 2016;29(1):63-72. PMID: 26340387
30. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg.* 2015;150:252-9. PMID: 25629390
31. Jaramillo N, Segovia J, Gomez-Bueno M, et al. Characteristics of Patients With Survival Longer Than 20 Years Following Heart Transplantation. *Revista espanola de cardiologia.* 2013;66(10):797-802. PMID: 23932221
32. Bhama JK, Shulman J, Bermudez CA, et al. Heart transplantation for adults with congenital heart disease: Results in the modern era. *J Heart Lung Transplant.* 2013. PMID: 23474360
33. Kilic A, Weiss ES, George TJ, et al. What predicts long-term survival after heart transplantation? An analysis of 9,400 ten-year survivors. *The Annals of thoracic surgery.* 2012;93(3):699-704. PMID: 22226494
34. Jalowiec A, Grady KL, White-Williams C. First-Year Clinical Outcomes in Sex-Mismatched Heart Transplant Recipients. *J Cardiovasc Nurs.* 2011. PMID: 21912267
35. Khan A, Pahl E, Koehl DA, et al. Improved heart transplant survival for children with congenital heart disease and heterotaxy syndrome in the current era: An analysis from the pediatric heart transplant society. *J Heart Lung Transplant.* 2021;40(10):1153-63. PMID: 34366230
36. Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant.* 2016;35(10):1185-95. PMID: 27772670
37. Kulkarni A, Neugebauer R, Lo Y, et al. Outcomes and risk factors for listing for heart transplantation after the Norwood procedure: An analysis of the Single Ventricle Reconstruction Trial. *J Heart Lung Transplant.* 2016;35(3):306-11. PMID: 26632030
38. Garbern JC, Gauvreau K, Blume ED, et al. Is Myocarditis an Independent Risk Factor for Post-Transplant Mortality in Pediatric Heart Transplant Recipients? *Circulation Heart failure.* 2016;9:e002328. PMID: 26699389
39. Savla J, Lin KY, Lefkowitz DS, et al. Adolescent age and heart transplantation outcomes in myocarditis or congenital heart disease. *J Heart Lung Transplant.* 2014;33(9):943-9. PMID: 24929645
40. Kirk R, Dipchand AI, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report--2012. *J Heart Lung Transplant.* 2012;31(10):1065-72. PMID: 22975096
41. Auerbach SR, Richmond ME, Chen JM, et al. Multiple risk factors before pediatric cardiac transplantation are associated with increased graft loss. *Pediatr Cardiol.* 2012;33(1):49-54. PMID: 21892650
42. Patel MS, Berg AM, Vincent RN, et al. Serum parameters and echocardiographic predictors of death or need for transplant in newborns, children, and young adults with heart failure. *The American journal of cardiology.* 2010;105(12):1798-801. PMID: 20538133

43. Almond CS, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the United States. *Circulation.* 2009;119(5):717-27. PMID: 19171850
44. Chen Q, Malas J, Chan J, et al. Evaluating age-based eligibility thresholds for heart re-transplantation - an analysis of the united network for organ sharing database. *J Heart Lung Transplant.* 2022. PMID: 36535808
45. Zhu Y, Shudo Y, Lingala B, et al. Outcomes after heart retransplantation: A 50-year single-center experience. *J Thorac Cardiovasc Surg.* 2022;163(2):712-20.e6. PMID: 32798029
46. Miller RJH, Clarke BA, Howlett JG, et al. Outcomes in patients undergoing cardiac retransplantation: A propensity matched cohort analysis of the UNOS Registry. *J Heart Lung Transplant.* 2019;38(10):1067-74. PMID: 31378576
47. Belli E, Leoni Moreno JC, Hosenpud J, et al. Preoperative risk factors predict survival following cardiac retransplantation: analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg.* 2014;147(6):1972-7, 77 e1. PMID: 24636155
48. Saito A, Novick RJ, Kiaii B, et al. Early and late outcomes after cardiac retransplantation. *Can J Surg.* 2013;56:21-6. PMID: 23187039
49. Tjang YS, Tenderich G, Hornik L, et al. Cardiac retransplantation in adults: an evidence-based systematic review. *The Thoracic and cardiovascular surgeon.* 2008;56(6):323-7. PMID: 18704853
50. Topkara VK, Dang NC, John R, et al. A decade experience of cardiac retransplantation in adult recipients. *J Heart Lung Transplant.* 2005;24:1745-50. PMID: 16297775
51. Vazquez Alvarez MDC, Cantor R, Koehl D, et al. The evolution of pediatric heart retransplantation over three decades: An analysis from the PHTS. *J Heart Lung Transplant.* 2022;41(6):791-801. PMID: 35400589
52. Azeka E, Walker T, Siqueira A, et al. Heart Retransplantation for Coronary Allograft Vasculopathy in Children: 25 Years of Single-Center Experience. *Transplantation proceedings.* 2020;52(5):1394-96. PMID: 32387081
53. Alsoufi B, Deshpande S, McCracken C, et al. Outcomes and risk factors for heart transplantation in children with congenital heart disease. *J Thorac Cardiovasc Surg.* 2015;150(6):1455-62 e3. PMID: 26190654
54. Bock MJ, Nguyen K, Malerba S, et al. Pediatric cardiac retransplantation: Waitlist mortality stratified by age and era. *J Heart Lung Transplant.* 2014. PMID: 25016920
55. Copeland H, Razzouk A, Chinnock R, et al. Pediatric recipient survival beyond 15 post-heart transplant years: a single-center experience. *The Annals of thoracic surgery.* 2014;98(6):2145-50; discussion 50-1. PMID: 25443019
56. Friedland-Little JM, Gajarski RJ, Yu S, et al. Outcomes of third heart transplants in pediatric and young adult patients: analysis of the United Network for Organ Sharing database. *J Heart Lung Transplant.* 2014;33(9):917-23. PMID: 24861821
57. Mahle WT, Vincent RN, Kanter KR. Cardiac retransplantation in childhood: analysis of data from the United Network for Organ Sharing. *J Thorac Cardiovasc Surg.* 2005;130:542-6. PMID: 16077425
58. Mistiaen WP. Heart transplantation in patients with previous malignancy. An overview. *Acta cardiologica.* 2015;70(2):123-30. PMID: 26148371
59. Yoosabai A, Mehta A, Kang W, et al. Pretransplant malignancy as a risk factor for posttransplant malignancy after heart transplantation. *Transplantation.* 2015;99(2):345-50. PMID: 25606783
60. Jamil A, Qin H, Felius J, et al. Comparison of Clinical Characteristics, Complications, and Outcomes in Recipients Having Heart Transplants <65 Years of Age Versus >/=65

Years of Age. *The American journal of cardiology.* 2017;120(12):2207-12. PMID: 29056228
61. Awad M, Czer LS, Mirocha J, et al. Similar Mortality and Morbidity of Orthotopic Heart Transplantation for Patients 70 Years of Age and Older Compared With Younger Patients. *Transplantation proceedings.* 2016;48(8):2782-91. PMID: 27788818
62. Kilic A, Weiss ES, Yuh DD, et al. Factors associated with 5-year survival in older heart transplant recipients. *J Thorac Cardiovasc Surg.* 2012;143(2):468-74. PMID: 22248684
63. Daneshvar D, Czer LS, Phan A, et al. Heart transplantation in patients aged 70 years and older: a two-decade experience. *Transplantation proceedings.* 2011;43(10):3851-6. PMID: 22172859
64. De Santo LS, Romano G, Maiello C, et al. Pulmonary artery hypertension in heart transplant recipients: how much is too much? *Eur J Cardiothorac Surg.* 2012;42:864-9; discussion 69-70. PMID: 22402452
65. Perez-Villa F, Farrero M, Cardona M, et al. Bosentan in heart transplantation candidates with severe pulmonary hypertension: efficacy, safety and outcome after transplantation. *Clinical transplantation.* 2013;27(1):25-31. PMID: 22861120
66. Pons J, Leblanc MH, Bernier M, et al. Effects of chronic sildenafil use on pulmonary hemodynamics and clinical outcomes in heart transplantation. *J Heart Lung Transplant.* 2012;31(12):1281-7. PMID: 23127754
67. Bedanova H, Orban M, Vrsansky D, et al. Impact of pulmonary hypertension on early hemodynamics, morbidity and mortality after orthotopic heart transplantation. A single center study. *Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia.* 2013;157(1):35-40. PMID: 23073529
68. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136:e137-e61. PMID: 28455343
69. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant.* 2016;35(1):1-23. PMID: 26776864
70. Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* 2007;115:658-76. PMID: 17261651

CODES

Codes	Number	Description
CPT	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of donor cadaver heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
HCPCS	None	

Date of Origin: *March 2013*

Regence

Medical Policy Manual Transplant, Policy No. 03

Heart-Lung Transplant

Effective: May 1, 2024

Next Review: March 2025
Last Review: March 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The heart/lung transplantation involves a coordinated triple operative procedure consisting of procurement of a donor heart-lung block, excision of the heart and lungs of the recipient, and implantation of the heart and lungs into the recipient. A heart/lung transplantation refers to the transplantation of one or both lungs and heart from a single cadaver donor.

MEDICAL POLICY CRITERIA

I. Heart/lung *transplantation* may be considered **medically necessary** for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:

   A. Irreversible primary pulmonary hypertension with heart failure
   B. Nonspecific severe pulmonary fibrosis, with severe heart failure
   C. Eisenmenger complex with irreversible pulmonary hypertension and heart failure
   D. Cystic fibrosis with severe heart failure
   E. Chronic obstructive pulmonary disease with heart failure
   F. Emphysema with severe heart failure
   G. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

II. Heart/lung transplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

III. Heart/lung *retransplantation* after a failed primary heart/lung transplant may be considered **medically necessary** in patients with end-stage cardiac and pulmonary disease as described in Criterion I above.

IV. Heart/lung retransplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
2. Heart Transplant, Transplant, Policy No. 02
3. Lung and Lobular Transplant, Transplant, Policy No. 08

BACKGROUND

Solid organ transplantation offers a treatment option for patients with different types of endstage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[1] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network (OPTN) and United Network of Organ Sharing (UNOS).

HEART/LUNG TRANSPLANT

The majority of recipients have Eisenmenger syndrome (37%), followed by idiopathic pulmonary artery hypertension (28%) and cystic fibrosis (14%). Eisenmenger syndrome is a form of congenital heart disease in which systemic-to-pulmonary shunting leads to pulmonary vascular resistance. Eventually, pulmonary hypertension may lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation, or cyanosis.[2]

However, the total number of patients with Eisenmenger syndrome has been declining in recent years, as a result of corrective surgical techniques and improved medical management of pulmonary hypertension. Heart/lung transplants have not increased appreciably for other indications either, as it has become more common to transplant a single or double lung and

maximize medical therapy for heart failure, rather than perform a combined transplant. In these, patient survival rates are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication; one, five, and 10-year patient survival rates are 68%, 50%, and 40%, respectively.[2]

In 2021, 45 individuals received heart/lung transplants in the United States. As of March 2022, there were 40 patients on the waiting list for heart/lung transplants.[3]

REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration. The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

EVIDENCE SUMMARY

Due to the nature of the patient population requiring heart/lung transplantation, there were no randomized controlled trials (RCTs) comparing heart/lung transplant to alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, and immunosuppressive therapy and are not germane to this policy. The following is a summary of evidence based on registry data, case series, and expert opinion.

PATIENT SELECTION

Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the United States. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from one based on length of time on the waiting list, to a system that incorporates the severity of the patient's underlying disease, as well as likelihood of survival.[4] However, it has been noted that the individual systems underestimate the severity of illness in patients with both end-stage heart and lung failure, and modification of the lung allocation score can be appealed for patients with pulmonary hypertension who meet the following criteria:

- Deterioration on optimal therapy
- Right arterial pressure greater than 15 mm Hg
- Cardiac index less than 1.8 L/min/m^2.

INITIAL COMBINED HEART/LUNG TRANSPLANT

Sertic (2020) compared outcomes of bilateral lung transplantation with cardiac defect repair to combined heart/lung transplantation in adult patients with Eisenmenger's syndrome using the United Network for Organ Sharing (UNOS) database of heart/lung transplantations performed from 1987 to 2018.[5] Among 442 patients who underwent thoracic transplantation, 316 patients underwent heart/lung transplantation and 126 patients underwent double-lung transplantation with concomitant cardiac defect repair. Overall survival was similar between patients who underwent double-lung transplantation and those who underwent heart/lung transplantation at one year (63.1% vs 68.0%, respectively), five years (38.5% vs 47.3%), and 10 years (30.2% vs 30.5%) posttransplant (p=0.6). Overall survival did not differ among

patients who received transplantation between 1987 to 1999 and those who received transplantation between 2000 to 2018 (p=0.7).

PEDIATRIC CONSIDERATIONS

Riggs (2020) assessed outcomes for pediatric heart/lung transplantation among children with congenital heart disease (CHD) with Eisenmenger syndrome, CHD without Eisenmenger syndrome, primary pulmonary hypertension, and "other" categories using the UNOS database of heart/lung transplantations performed from 1987 to 2018.[6] Among 209 heart/lung transplantations performed during the specified time frame, 37 (17.7%) had CHD with Eisenmenger syndrome, 40 (19.1%) had CHD without Eisenmenger syndrome, 70 (33.5%) had primary pulmonary hypertension, 6 (2.9%) were retransplants, and 56 (26.8%) had another diagnosis. One-year, five-year, and 10-year survival rates post-transplant, respectively, were 75%, 44%, and 32% for pediatric patients with CHD with Eisenmenger syndrome, 56%, 21%, and 16% for patients with CHD without Eisenmenger syndrome, 77%, 41%, and 33% for patients with primary pulmonary hypertension, 40%, 0%, and 0% for retransplanted patients, and 70%, 44%, and 20% for patients with other diagnoses. Compared to the reference group of pediatric patients with primary pulmonary hypertension, patients with CHD without Eisenmenger syndrome (p=0.03) and patients who were retransplanted (p=0.008) had significantly lower survival rates. Other survival comparisons were not significant. Survival rates were not different when comparing patients who received transplants between 1987 to 1999 and 2000 to 2018. Infants (HR, 2.2; 95% CI, 1.04 to 4.55; p=0.04), one to 11 year old patients (HR, 1.78; 95% CI, 1.12 to 2.8; p=0.015), and patients on ECMO (HR, 4.1; 95% CI, 1.3 to 12.8; p=0.016) had the highest risk of mortality post-transplant.

A 2014 analysis of data from the Organ Procurement and Transplantation Network (OPTN) reported on indications for pediatric heart/lung transplantation.[7] The number of pediatric heart/lung transplants has decreased in recent years (i.e., 56 cases in 1993-1997; 21 cases in 2008-2013). The three most common indications for pediatric heart/lung transplant were primary pulmonary hypertension (n=55), congenital heart disease (n=37), and Eisenmenger syndrome (n=30). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, none were performed for this indication since then to the date of the analysis. Pediatric heart/lung transplants have also been performed for other indications including alpha1 antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

In 2012, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) reported on pediatric heart/lung transplant data collected through June 2011.[8] In recent years, the number of heart/lung transplant procedures in children has decreased, and the number of lung transplants has increased. There were no heart/lung transplants in infants between 2007 and the date of the study. Overall, survival rates after heart/lung transplants are comparable in children and adults (median half-life of 4.7 and 5.3 years, respectively). For pediatric heart/lung transplants that occurred between January 1990 and June 2010, the five-year survival rate was 49%. The two leading causes of death in the first year after transplantation were non-cytomegalovirus infection and graft failure. Beyond three years post-transplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report on pediatric lung and heart-lung transplant from the same registry in 2014 did not include updated data on pediatric heart-lung transplants due to the small number of patients available.[9]

RETRANSPLANTATION

Repeat heart-lung transplant procedures have been performed; only three published studies were identified that reported on outcomes after repeat heart-lung transplants. In 2014, the ISHLT described outcomes after retransplantation as compared with primary transplantation, including identifying risk factors leading to retransplantation and both transplant-related morbidities and mortality after retransplantation.[10] The authors reviewed 9,248 primary transplants and 602 retransplants. After retransplantation, early time-related risk of mortality was similar to that after primary transplantation (HR 1.07; 95% CI, 0.92 to 1.25; p=0.40), but both late-phase time-related risk of mortality (HR 1.67; 95% CI, 1.40 to 1.99; p<0.001) and requirement of an additional graft (HR 1.69; 95% CI, 1.18 to 2.43; p=0.004) were higher. Long-term morbidities were significantly more common after retransplantation than with primary transplantation. The authors concluded that retransplantation after primary transplant in the pediatric age group, although feasible with similar early survival, is associated with decreased long-term survival and an increase in transplant-related morbidities.

Yusen (2014) reported outcomes for adult heart-lung transplants, with a focus on retransplantation, using data from the ISHLT Registry.[11] Thirty-three participating centers reported 75 adult heart-lung transplants in 2012, a decline from the peak year for heart-lung transplants (1989) during which 226 heart-lung transplants were performed. From 1982-2012, 90 adults had a first heart–lung retransplant after a previous heart–lung transplant. These 90 patients had a median survival of 0.3 year, with an unadjusted survival rate of 52%, 43%, 36%, and 27% at three months, one year, three years, and five years, respectively. Those who survived to one year had a conditional mean survival of 7.9 years.

Shuhaiber (2008) published results from a review of data from the UNOS registry.[12] The authors identified 799 primary heart-lung and 19 repeat heart-lung transplants. According to Kaplan-Meier survival analysis, the observed median survival times were 2.08 years after primary transplant and 0.34 years after repeat transplants. In addition, the authors analyzed survival data in matched pairs of primary and repeat transplant patients, who were matched on a number of potentially confounding demographic and clinical characteristics. Matches were not available for four repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly in the two groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis is the small number of repeat transplant procedures performed.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure, or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Concerns regarding a potential recipients history of cancer were based on the observation of significantly increased incidence of cancer in kidney transplant patients.[13] In fact, carcinogenesis is two to four times more common, primarily skin cancers, in both heart transplant and lung transplant patients, likely due to the higher doses of immunosuppression necessary for the prevention of allograft rejection.[2, 14] The incidence of *de novo* cancer in heart transplant patients approaches 26% at eight years post-transplant, the rate for lung transplant is 28% at ten years. For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.[15, 16]

In a 2013 retrospective cohort study, *de novo* cancer-related deaths in Australian liver and cardiothoracic transplant recipients were analyzed during a median five year follow-up.[17] *De novo* cancer-related mortality risk in liver and cardiothoracic recipients was significantly elevated compared to the matched general population (n = 171; SMR = 2.83; 95% confidence interval [95%CI], 2.43-3.27). Excess risk was observed regardless of transplanted organ, recipient age group or sex. Risk of death from *de novo* cancer was high in pediatric recipients (n = 5; SMR = 41.3; 95%CI, 13.4-96.5), four of the five deaths were non-Hodgkin lymphoma. Authors suggest that *de novo* cancer was a leading cause of late death, particularly in heart and liver transplantation.

However, it should be noted that the availability of alternate treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage cardiopulmonary failure patients may not have an option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had one, five, and ten-year survival rates of 77%, 64%, and 50%, respectively.[18] By comparison, overall one, five, and ten-year survival rates are expected to be 88%, 74%, and 55%, respectively for the general transplant candidate. The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients in whom cancer is thought to be cured should not be excluded from consideration for transplant. UNOS has not addressed malignancy in current policies.

Human Immunodeficiency Virus

Solid organ transplant for patients who are HIV-positive (HIV+) was historically controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART), has markedly changed the natural history of the disease. A 2009 retrospective case series reported favorable outcomes for seven patients with HIV who received a heart transplant.[19] However, there is little data directly comparing outcomes for patients with and without HIV or for combined heart-lung transplants.

Current Organ Procurement and Transplantation Network (OPTN) policy permits HIV-positive transplant candidates.[20]

OTHER

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart-lung transplantation. For example, cystic fibrosis accounts for the majority of pediatric candidates for heart-lung transplantation, and infection with *Burkholderia* species is

associated with higher mortality in these patients. Also, experience with kidney transplantation in patients infected with HIV in the era of HAART has opened discussion of transplantation of other solid organs in these patients. These topics are addressed more fully in the separate policies on heart transplantation and lung transplantation.

PRACTICE GUIDELINE SUMMARY

THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2021, the International Society for Heart and Lung Transplantation updated their consensus-based guidelines.[21] The guideline states:

"Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

- High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed
- High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."

For combined heart/lung transplant, the guidelines state:

> "Candidates should meet the criteria for lung transplant listing and have significant dysfunction of one or more additional organs, or meet the listing criteria for a non-pulmonary organ transplant and have significant pulmonary dysfunction." The guideline goes on to state: "The primary indication for heart-lung transplant is pulmonary hypertension, either secondary to idiopathic pulmonary arterial hypertension or congenital heart disease (CHD)."

SUMMARY

There is enough research to show that heart/lung transplantation can improve survival for certain patients. Therefore, heart/lung transplant may be considered medically necessary in patients who meet criteria. Similarly, heart/lung retransplantation may improve survival for certain patients who have had a prior transplant. Therefore, heart/lung retransplantation may be considered medically necessary in patients with a failed prior transplant who meet the clinical criteria for heart-lung transplantation.

REFERENCES

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21(st) century. *Ann Transl Med.* 2018;6(20):409. PMID: 30498736
2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report--2011. *J Heart Lung Transplant.* 2011;30(10):1104-22. PMID: 21962018
3. Organ Procurement and Transplantation Network (OPTN). [cited 03/20/24]. 'Available from:' https://optn.transplant.hrsa.gov/.

4. United Network for Organ Sharing (UNOS). Questions and Answers for Transplant Professionals about Lung Allocation. [cited 03/20/24]. 'Available from:' https://www.unos.org/wp-content/uploads/unos/Lung_Professional.pdf.
5. Sertic F, Han J, Diagne D, et al. Not All Septal Defects Are Equal: Outcomes of Bilateral Lung Transplant With Cardiac Defect Repair vs Combined Heart-Lung Transplant in Patients With Eisenmenger Syndrome in the United States. *Chest.* 2020;158(5):2097-106. PMID: 32565271
6. Riggs KW, Chapman JL, Schecter M, et al. Pediatric heart-lung transplantation: A contemporary analysis of outcomes. *Pediatr Transplant.* 2020;24(3):e13682. PMID: 32067330
7. Spahr JE, West SC. Heart-lung transplantation: pediatric indications and outcomes. *Journal of thoracic disease.* 2014;6(8):1129-37. PMID: 25132980
8. Benden C, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart-lung transplantation report--2012. *J Heart Lung Transplant.* 2012;31(10):1087-95. PMID: 22975098
9. Benden C, Goldfarb SB, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report--2014; focus theme: retransplantation. *J Heart Lung Transplant.* 2014;33(10):1025-33. PMID: 25242126
10. Conway J, Manlhiot C, Kirk R, et al. Mortality and morbidity after retransplantation after primary heart transplant in childhood: An analysis from the registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2014;33(3):241-51. PMID: 24462559
11. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. *J Heart Lung Transplant.* 2014;33(10):1009-24. PMID: 25242125
12. Shuhaiber JH, Kim JB, Gibbons RD. Repeat heart-lung transplantation outcome in the United States. *J Heart Lung Transplant.* 2008;27:1122-7. PMID: 18926404
13. Kasiske BL, Snyder JJ, Gilbertson DT, et al. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4(6):905-13. PMID: 15147424
14. Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult heart transplant report--2005. *J Heart Lung Transplant.* 2005;24(8):945-55. PMID: 16102427
15. Otley CC, Hirose R, Salasche SJ. Skin cancer as a contraindication to organ transplantation. *Am J Transplant.* 2005;5(9):2079-84. PMID: 16095486
16. Trofe J, Buell JF, Woodle ES, et al. Recurrence risk after organ transplantation in patients with a history of Hodgkin disease or non-Hodgkin lymphoma. *Transplantation.* 2004;78(7):972-7. PMID: 15480161
17. Na R, Grulich AE, Meagher NS, et al. De novo Cancer-Related Death in Australian Liver and Cardiothoracic Transplant Recipients. *Am J Transplant.* 2013. PMID: 23464511
18. Taylor DO, Farhoud HH, Kfoury G, et al. Cardiac transplantation in survivors of lymphoma: a multi-institutional survey. *Transplantation.* 2000;69(10):2112-5. PMID: 10852607
19. Uriel N, Jorde UP, Cotarlan V, et al. Heart transplantation in human immunodeficiency virus-positive patients. *J Heart Lung Transplant.* 2009;28:667-9. PMID: 19560693

20. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2021. [cited 03/20/24]. 'Available from:' https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
21. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2021;40(11):1349-79. PMID: 34419372

CODES

Codes	Number	Description
CPT	33930	Donor cardiectomy-pneumonectomy, (including cold preparation)
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
HCPCS	None	

Date of Origin: *March 2013*

Regence

Medical Policy Manual Transplant, Policy No. 03

Heart-Lung Transplant

Effective: June 1, 2023

Next Review: March 2024
Last Review: April 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The heart/lung transplantation involves a coordinated triple operative procedure consisting of procurement of a donor heart-lung block, excision of the heart and lungs of the recipient, and implantation of the heart and lungs into the recipient. A heart/lung transplantation refers to the transplantation of one or both lungs and heart from a single cadaver donor.

MEDICAL POLICY CRITERIA

I. Heart/lung *transplantation* may be considered **medically necessary** for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:

   A. Irreversible primary pulmonary hypertension with heart failure
   B. Nonspecific severe pulmonary fibrosis, with severe heart failure
   C. Eisenmenger complex with irreversible pulmonary hypertension and heart failure
   D. Cystic fibrosis with severe heart failure
   E. Chronic obstructive pulmonary disease with heart failure
   F. Emphysema with severe heart failure
   G. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

II. Heart/lung transplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

III. Heart/lung *retransplantation* after a failed primary heart/lung transplant may be considered **medically necessary** in patients with end-stage cardiac and pulmonary disease as described in Criterion I above.

IV. Heart/lung retransplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
2. Heart Transplant, Transplant, Policy No. 02
3. Lung and Lobular Transplant, Transplant, Policy No. 08

BACKGROUND

Solid organ transplantation offers a treatment option for patients with different types of endstage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[1] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network (OPTN) and United Network of Organ Sharing (UNOS).

HEART/LUNG TRANSPLANT

The majority of recipients have Eisenmenger syndrome (37%), followed by idiopathic pulmonary artery hypertension (28%) and cystic fibrosis (14%). Eisenmenger syndrome is a form of congenital heart disease in which systemic-to-pulmonary shunting leads to pulmonary vascular resistance. Eventually, pulmonary hypertension may lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation, or cyanosis.[2]

However, the total number of patients with Eisenmenger syndrome has been declining in recent years, as a result of corrective surgical techniques and improved medical management of pulmonary hypertension. Heart/lung transplants have not increased appreciably for other indications either, as it has become more common to transplant a single or double lung and

maximize medical therapy for heart failure, rather than perform a combined transplant. In these, patient survival rates are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication; one, five, and 10-year patient survival rates are 68%, 50%, and 40%, respectively.[2]

In 2021, 45 individuals received heart/lung transplants in the United States. As of March 2022, there were 40 patients on the waiting list for heart/lung transplants.[3]

REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration. The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

EVIDENCE SUMMARY

Due to the nature of the patient population requiring heart/lung transplantation, there were no randomized controlled trials (RCTs) comparing heart/lung transplant to alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, and immunosuppressive therapy and are not germane to this policy. The following is a summary of evidence based on registry data, case series, and expert opinion.

PATIENT SELECTION

Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the United States. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from one based on length of time on the waiting list, to a system that incorporates the severity of the patient's underlying disease, as well as likelihood of survival.[4] However, it has been noted that the individual systems underestimate the severity of illness in patients with both end-stage heart and lung failure, and modification of the lung allocation score can be appealed for patients with pulmonary hypertension who meet the following criteria:

- Deterioration on optimal therapy
- Right arterial pressure greater than 15 mm Hg
- Cardiac index less than 1.8 L/min/m^2.

INITIAL COMBINED HEART/LUNG TRANSPLANT

Sertic (2020) compared outcomes of bilateral lung transplantation with cardiac defect repair to combined heart/lung transplantation in adult patients with Eisenmenger's syndrome using the United Network for Organ Sharing (UNOS) database of heart/lung transplantations performed from 1987 to 2018.[5] Among 442 patients who underwent thoracic transplantation, 316 patients underwent heart/lung transplantation and 126 patients underwent double-lung transplantation with concomitant cardiac defect repair. Overall survival was similar between patients who underwent double-lung transplantation and those who underwent heart/lung transplantation at one year (63.1% vs 68.0%, respectively), 5 years (38.5% vs 47.3%), and 10 years (30.2% vs 30.5%) posttransplant (p=0.6). Overall survival did not differ among patients

who received transplantation between 1987 to 1999 and those who received transplantation between 2000 to 2018 (p=0.7).

PEDIATRIC CONSIDERATIONS

Riggs (2020) assessed outcomes for pediatric heart/lung transplantation among children with congenital heart disease (CHD) with Eisenmenger syndrome, CHD without Eisenmenger syndrome, primary pulmonary hypertension, and "other" categories using the UNOS database of heart/lung transplantations performed from 1987 to 2018.[6] Among 209 heart/lung transplantations performed during the specified time frame, 37 (17.7%) had CHD with Eisenmenger syndrome, 40 (19.1%) had CHD without Eisenmenger syndrome, 70 (33.5%) had primary pulmonary hypertension, 6 (2.9%) were retransplants, and 56 (26.8%) had another diagnosis. One-year, five-year, and 10-year survival rates post-transplant, respectively, were 75%, 44%, and 32% for pediatric patients with CHD with Eisenmenger syndrome, 56%, 21%, and 16% for patients with CHD without Eisenmenger syndrome, 77%, 41%, and 33% for patients with primary pulmonary hypertension, 40%, 0%, and 0% for retransplanted patients, and 70%, 44%, and 20% for patients with other diagnoses. Compared to the reference group of pediatric patients with primary pulmonary hypertension, patients with CHD without Eisenmenger syndrome (p=0.03) and patients who were retransplanted (p=0.008) had significantly lower survival rates. Other survival comparisons were not significant. Survival rates were not different when comparing patients who received transplants between 1987 to 1999 and 2000 to 2018. Infants (HR, 2.2; 95% CI, 1.04 to 4.55; p=0.04), one to 11 year old patients (HR, 1.78; 95% CI, 1.12 to 2.8; p=0.015), and patients on ECMO (HR, 4.1; 95% CI, 1.3 to 12.8; p=0.016) had the highest risk of mortality post-transplant.

A 2014 analysis of data from the Organ Procurement and Transplantation Network (OPTN) reported on indications for pediatric heart/lung transplantation.[7] The number of pediatric heart/lung transplants has decreased in recent years (i.e., 56 cases in 1993-1997; 21 cases in 2008-2013). The three most common indications for pediatric heart/lung transplant were primary pulmonary hypertension (n=55), congenital heart disease (n=37), and Eisenmenger syndrome (n=30). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, none were performed for this indication since then to the date of the analysis. Pediatric heart/lung transplants have also been performed for other indications including alpha1 antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

In 2012, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) reported on pediatric heart/lung transplant data collected through June 2011.[8] In recent years, the number of heart/lung transplant procedures in children has decreased, and the number of lung transplants has increased. There were no heart/lung transplants in infants between 2007 and the date of the study. Overall, survival rates after heart/lung transplants are comparable in children and adults (median half-life of 4.7 and 5.3 years, respectively). For pediatric heart/lung transplants that occurred between January 1990 and June 2010, the five-year survival rate was 49%. The two leading causes of death in the first year after transplantation were non-cytomegalovirus infection and graft failure. Beyond three years post-transplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report on pediatric lung and heart-lung transplant from the same registry in 2014 did not include updated data on pediatric heart-lung transplants due to the small number of patients available.[9]

RETRANSPLANTATION

Repeat heart-lung transplant procedures have been performed; only three published studies were identified that reported on outcomes after repeat heart-lung transplants. In 2014, the ISHLT described outcomes after retransplantation as compared with primary transplantation, including identifying risk factors leading to retransplantation and both transplant-related morbidities and mortality after retransplantation.[10] The authors reviewed 9,248 primary transplants and 602 retransplants. After retransplantation, early time-related risk of mortality was similar to that after primary transplantation (HR 1.07; 95% CI, 0.92 to 1.25; p=0.40), but both late-phase time-related risk of mortality (HR 1.67; 95% CI, 1.40 to 1.99; p<0.001) and requirement of an additional graft (HR 1.69; 95% CI, 1.18 to 2.43; p=0.004) were higher. Long-term morbidities were significantly more common after retransplantation than with primary transplantation. The authors concluded that retransplantation after primary transplant in the pediatric age group, although feasible with similar early survival, is associated with decreased long-term survival and an increase in transplant-related morbidities.

Yusen (2014) reported outcomes for adult heart-lung transplants, with a focus on retransplantation, using data from the ISHLT Registry.[11] Thirty-three participating centers reported 75 adult heart-lung transplants in 2012, a decline from the peak year for heart-lung transplants (1989) during which 226 heart-lung transplants were performed. From 1982-2012, 90 adults had a first heart–lung retransplant after a previous heart–lung transplant. These 90 patients had a median survival of 0.3 year, with an unadjusted survival rate of 52%, 43%, 36%, and 27% at three months, one year, three years, and five years, respectively. Those who survived to one year had a conditional mean survival of 7.9 years.

Shuhaiber (2008) published results from a review of data from the UNOS registry.[12] The authors identified 799 primary heart-lung and 19 repeat heart-lung transplants. According to Kaplan-Meier survival analysis, the observed median survival times were 2.08 years after primary transplant and 0.34 years after repeat transplants. In addition, the authors analyzed survival data in matched pairs of primary and repeat transplant patients, who were matched on a number of potentially confounding demographic and clinical characteristics. Matches were not available for four repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly in the two groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis is the small number of repeat transplant procedures performed.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure, or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Concerns regarding a potential recipients history of cancer were based on the observation of significantly increased incidence of cancer in kidney transplant patients.[13] In fact, carcinogenesis is two to four times more common, primarily skin cancers, in both heart transplant and lung transplant patients, likely due to the higher doses of immunosuppression necessary for the prevention of allograft rejection.[2, 14] The incidence of *de novo* cancer in heart transplant patients approaches 26% at eight years post-transplant, the rate for lung transplant is 28% at ten years. For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.[15, 16]

In a 2013 retrospective cohort study, *de novo* cancer-related deaths in Australian liver and cardiothoracic transplant recipients were analyzed during a median five year follow-up.[17] *De novo* cancer-related mortality risk in liver and cardiothoracic recipients was significantly elevated compared to the matched general population (n = 171; SMR = 2.83; 95% confidence interval [95%CI], 2.43-3.27). Excess risk was observed regardless of transplanted organ, recipient age group or sex. Risk of death from *de novo* cancer was high in pediatric recipients (n = 5; SMR = 41.3; 95%CI, 13.4-96.5), four of the five deaths were non-Hodgkin lymphoma. Authors suggest that *de novo* cancer was a leading cause of late death, particularly in heart and liver transplantation.

However, it should be noted that the availability of alternate treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage cardiopulmonary failure patients may not have an option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had one, five, and ten-year survival rates of 77%, 64%, and 50%, respectively.[18] By comparison, overall one, five, and ten-year survival rates are expected to be 88%, 74%, and 55%, respectively for the general transplant candidate. The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients in whom cancer is thought to be cured should not be excluded from consideration for transplant. UNOS has not addressed malignancy in current policies.

Human Immunodeficiency Virus

Solid organ transplant for patients who are HIV-positive (HIV+) was historically controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART), has markedly changed the natural history of the disease. A 2009 retrospective case series reported favorable outcomes for seven patients with HIV who received a heart transplant.[19] However, there is little data directly comparing outcomes for patients with and without HIV or for combined heart-lung transplants

Current Organ Procurement and Transplantation Network (OPTN) policy permits HIV-positive transplant candidates.[20]

OTHER

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart-lung transplantation. For example, cystic fibrosis accounts for the majority of pediatric candidates for heart-lung transplantation, and infection with *Burkholderia* species is

associated with higher mortality in these patients. Also, experience with kidney transplantation in patients infected with HIV in the era of HAART has opened discussion of transplantation of other solid organs in these patients. These topics are addressed more fully in the separate policies on heart transplantation and lung transplantation.

PRACTICE GUIDELINE SUMMARY

THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2015, the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation updated their 2006 their consensus-based guidelines [21, 22] The guideline states:

> "Patients with advanced cardiac and lung diseases not amenable to either isolated heart or lung transplant may be candidates for combined heart-lung transplantation. Most commonly, patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH [pulmonary arterial hypertension] are considered for heart-lung transplantation."

The guidelines include criteria for absolute and relative contraindications, as well as special surgical and disease specific considerations for all types of organ transplants.

SUMMARY

There is enough research to show that heart/lung transplantation can improve survival for certain patients. Therefore, heart/lung transplant may be considered medically necessary in patients who meet criteria. Similarly, heart/lung retransplantation may improve survival for certain patients who have had a prior transplant. Therefore, heart/lung retransplantation may be considered medically necessary in patients with a failed prior transplant who meet the clinical criteria for heart-lung transplantation.

REFERENCES

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21(st) century. *Ann Transl Med.* 2018;6(20):409. PMID: 30498736
2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report--2011. *J Heart Lung Transplant.* 2011;30(10):1104-22. PMID: 21962018
3. Organ Procurement and Transplantation Network (OPTN). [cited 04/20/23]. 'Available from:' https://optn.transplant.hrsa.gov/.
4. United Network for Organ Sharing (UNOS). Questions and Answers for Transplant Professionals about Lung Allocation. [cited 04/20/23]. 'Available from:' https://www.unos.org/wp-content/uploads/unos/Lung_Professional.pdf.
5. Sertic F, Han J, Diagne D, et al. Not All Septal Defects Are Equal: Outcomes of Bilateral Lung Transplant With Cardiac Defect Repair vs Combined Heart-Lung Transplant in

Patients With Eisenmenger Syndrome in the United States. *Chest.* 2020;158(5):2097-106. PMID: 32565271
6. Riggs KW, Chapman JL, Schecter M, et al. Pediatric heart-lung transplantation: A contemporary analysis of outcomes. *Pediatr Transplant.* 2020;24(3):e13682. PMID: 32067330
7. Spahr JE, West SC. Heart-lung transplantation: pediatric indications and outcomes. *Journal of thoracic disease.* 2014;6(8):1129-37. PMID: 25132980
8. Benden C, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart-lung transplantation report--2012. *J Heart Lung Transplant.* 2012;31(10):1087-95. PMID: 22975098
9. Benden C, Goldfarb SB, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report--2014; focus theme: retransplantation. *J Heart Lung Transplant.* 2014;33(10):1025-33. PMID: 25242126
10. Conway J, Manlhiot C, Kirk R, et al. Mortality and morbidity after retransplantation after primary heart transplant in childhood: An analysis from the registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2014;33(3):241-51. PMID: 24462559
11. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. *J Heart Lung Transplant.* 2014;33(10):1009-24. PMID: 25242125
12. Shuhaiber JH, Kim JB, Gibbons RD. Repeat heart-lung transplantation outcome in the United States. *J Heart Lung Transplant.* 2008;27:1122-7. PMID: 18926404
13. Kasiske BL, Snyder JJ, Gilbertson DT, et al. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4(6):905-13. PMID: 15147424
14. Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult heart transplant report--2005. *J Heart Lung Transplant.* 2005;24(8):945-55. PMID: 16102427
15. Otley CC, Hirose R, Salasche SJ. Skin cancer as a contraindication to organ transplantation. *Am J Transplant.* 2005;5(9):2079-84. PMID: 16095486
16. Trofe J, Buell JF, Woodle ES, et al. Recurrence risk after organ transplantation in patients with a history of Hodgkin disease or non-Hodgkin lymphoma. *Transplantation.* 2004;78(7):972-7. PMID: 15480161
17. Na R, Grulich AE, Meagher NS, et al. De novo Cancer-Related Death in Australian Liver and Cardiothoracic Transplant Recipients. *Am J Transplant.* 2013. PMID: 23464511
18. Taylor DO, Farhoud HH, Kfoury G, et al. Cardiac transplantation in survivors of lymphoma: a multi-institutional survey. *Transplantation.* 2000;69(10):2112-5. PMID: 10852607
19. Uriel N, Jorde UP, Cotarlan V, et al. Heart transplantation in human immunodeficiency virus-positive patients. *J Heart Lung Transplant.* 2009;28:667-9. PMID: 19560693
20. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2021. [cited 04/20/23]. 'Available from:' https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
21. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34(1):1-15. PMID: 25085497

22. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2006;25(7):745-55. PMID: 16818116

CODES

Codes	Number	Description
CPT	33930	Donor cardiectomy-pneumonectomy, (including cold preparation)
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
HCPCS	None	

Date of Origin: *March 2013*

Regence

Medical Policy Manual Transplant, Policy No. 05

Liver Transplant

Effective: July 1, 2023

Next Review: March 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain, circulatory or cardiac death, or with a liver segment donation from a living donor. Patients are prioritized for transplant according to length of time on the waiting list, mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS).

MEDICAL POLICY CRITERIA

I. A liver transplant, using a cadaver or living donor, may be **medically necessary** for patients with irreversible, end-stage liver failure due to conditions that include, but are not limited to, the following:

   A. Cholestatic Liver Diseases

      1. Biliary atresia; or
      2. Familial cholestatic syndromes; or
      3. Primary biliary cirrhosis; or
      4. Secondary biliary cirrhosis; or

5. Primary sclerosing cholangitis; or
6. Secondary sclerosing cholangitis when the primary etiology is resolved; or
7. Alagille syndrome; or
8. Nonsyndromic paucity of the intrahepatic bile ducts; or
9. Cystic fibrosis; or

B. Hepatocellular Diseases:
1. Alcoholic cirrhosis; or
2. Viral hepatitis (including A, B, C, or non-A, non-B); or
3. Autoimmune hepatitis; or
4. Cryptogenic cirrhosis; or
5. Alpha-1 antitrypsin deficiency; or
6. Hemochromatosis; or
7. Protoporphyria; or
8. Wilson's disease; or
9. Non-alcoholic steatohepatitis; or

C. Malignancies such as the following:
1. Primary hepatocellular carcinoma confined to the liver; or
2. Rare, non-hepatocellular malignancies originating in the liver such as hemangioepitheliomas in young adults and hepatoblastomas in children, and hemangioendotheliomas; or
3. Fibrolamellar hepatocellular carcinoma; or
4. Unresectable hilar cholangiocarcinoma; or

D. Vascular Diseases:
1. Budd-Chiari syndrome (congenital hepatic vein thrombosis); or
2. Veno-occlusive disease; or

E. Inborn errors of metabolism; or

F. Trauma and toxic reactions; or

G. Miscellaneous Diseases:
1. Polycystic disease of the liver in patients who have massive hepatomegaly causing obstruction or functional impairment; or
2. Familial amyloid polyneuropathy (Corino de Andrade's disease, paramyloidosis); or
3. Amyloidosis; or
4. Disorders of branch chain amino acids (e.g., Maple syrup urine disease (MSUD), branched chain a-ketoacid dehydrogenase (BCKD); or
5. Fulminant hepatitic failure; or

6. Glycogen storage disease type IV; or
7. Hyperoxaluria; or
8. Steatohepatitis; or
9. Tyrosinemia; or
10. Urea cycle defects.

II. Liver transplantation is considered **not medically necessary** in the following patients:
   A. Patients with hepatocellular carcinoma that has extended beyond the liver; or
   B. Patients with active alcohol and/or substance abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of three months is required.)

III. Liver transplantation is considered **investigational** in the following patients:
   A. Intrahepatic cholangiocarcinoma; or
   B. Patients with an extrahepatic malignancy, other than those noted above; or
   C. Patients with neuroendocrine tumors metastatic to the liver.

IV. Liver retransplantation may be considered **medically necessary** in patients with one or more of the following diagnoses:
   A. Primary graft nonfunction; or
   B. Hepatic artery thrombosis; or
   C. Chronic rejection; or
   D. Ischemic type biliary lesions after donation after cardiac death; or
   E. Recurrent non-neoplastic disease-causing late graft failure.

V. Liver retransplantation is considered **investigational** in all other situations not described above in Criterion IV.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Small Bowel/Liver and Multivisceral Transplant, Transplant, Policy No. 18

BACKGROUND

LIVER TRANSPLANTATION

Liver transplantation is routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Certain populations are prioritized as Status 1A (e.g., acute liver failure with a life expectancy of fewer than seven days without a liver transplant) or Status 1B (pediatric patients with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient's condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

RECIPIENTS

In March 2019, OPTN and UNOS published its most recent allocation system.[1]

Status 1A Adults

1. The candidate is at least 18 years old at the time of registration
2. The candidate has a life expectancy without a liver transplant of less than 7 days and has at least *one* of the following conditions:
    a. Fulminant liver failure, without pre-existing liver disease and currently in the intensive care unit (ICU), defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease, and has at least *one* of the following criteria:
        i. Is ventilator dependent
        ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iii. Has an international normalized ratio (INR) greater than 2.0
    b. Anhepatic
    c. Primary non-function of a transplanted whole liver within 7 days of transplant, with aspartate aminotransferase (AST) greater than or equal to 3,000 U/L and at least *one* of the following:
        - International normalized ratio (INR) greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25
        - Lactate greater than or equal to 4 mmol/L

    All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

    d. Primary non-function within 7-days of transplant of a transplanted liver segment from a deceased or living donor, evidenced by at least *one* of the following:
        - INR greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25

- Lactate greater than or equal to 4 mmol/L

e. Hepatic artery thrombosis (HAT) within 7-days of transplant, with AST greater than or equal to 3,000 U/L and at least *one* of the following:
   - INR greater than or equal to 2.5
   - Arterial pH less than or equal to 7.30
   - Venous pH less than or equal to 7.25
   - Lactate greater than or equal to 4 mmol/L

All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

Candidates with HAT in a transplanted liver within 14 days of transplant not meeting the above criteria will be listed with a MELD of 40.

f. Acute decompensated Wilson's disease

Status 1A Pediatrics

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.
2. The candidate has at least *one* of the following conditions:
   a. Fulminant liver failure without pre-existing liver disease, defined as the onset of hepatic encephalopathy within 56 days of the first signs and symptoms of liver disease and has at least *one* of the following criteria:
      i. Is ventilator dependent
      ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
      iii. Has an international normalized ratio (INR) greater than 2.0
   b. Diagnosis of primary non-function of a transplanted liver within 7 days of transplant, evidenced by at least *two* of the following:
      i. Alanine aminotransferase (ALT) greater than or equal to 2,000 U/L
      ii. INR greater than or equal to 2.5
      iii. Total bilirubin greater than or equal to 10 mg/dL
      iv. Acidosis, defined as *one* of the following:
         - Arterial pH less than or equal to 7.30
         - Venous pH less than or equal to 7.25
         - Lactate greater than or equal to 4 mmol/L

   All laboratory results reported for any tests required for the primary non-function of a transplanted liver diagnosis above must be from the same blood draw taken between 24 hours and 7 days after the transplant.

   c. Diagnosis of hepatic artery thrombosis (HAT) in a transplanted liver within 14 days of transplant
   d. Acute decompensated Wilson's disease

Status 1B patients

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting

list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.

2. The candidate has *one* of the following conditions:
    a. The candidate has a biopsy-proven hepatoblastoma without evidence of metastatic disease.
    b. The candidate has an organic acidemia or urea cycle defect and a MELD or PELD exception score of 30 points for at least 30 days.
    c. Chronic liver disease with a calculated MELD greater than 25 for adolescent candidates 12 to 17 years old, or a calculated PELD greater than 25 for candidates less than 12 years old, and has at least *one* of the following criteria:
        i. Is on a mechanical ventilator
        ii. Has gastrointestinal bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous 24 hours
        iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.
    d. Chronic liver disease and is a combined liver-intestine candidate with an adjusted MELD or PELD score greater than 25 according to *Policy 9.1.F: Liver-Intestine Candidates* and has at least *one* of the following criteria:
        i. Is on a mechanical ventilator
        ii. Has gastrointestinal bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours
        iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.

Following Status 1, donor livers will be prioritized to those with the highest scores on MELD (model for end-stage liver disease) or PELD (pediatric end-stage liver disease). MELD and PELD are a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (i.e., INR) and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Aside from Status 1, donor livers are prioritized to those with the highest MELD or PELD number; waiting time is only used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet waiting time was found to be a poor predictor of the urgency of liver transplant, since some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation system, patients with a higher mortality risk and higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer.[2]

DONORS

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, the term “split grafts” refers to dividing a donor liver into two

segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and pediatric populations from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively, shortens the preservation time for the donor liver, decreases disease transmission and allows time to optimize the recipient's condition pretransplant.

EVIDENCE SUMMARY

Relevant outcomes for studies on liver transplantation (LT) include waiting time duration, dropout rates, survival time, and recurrence. As experience with LT has matured, patient selection criteria have broadened to include a wide variety of etiologies. The most controversial etiologies include viral hepatitis and primary hepatocellular cancer. In the past, the long-term outcomes in patients with primary hepatocellular malignancies were poor (19%) compared to the overall survival of LT recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors that are three cm or smaller and without extrahepatic spread or macrovascular invasion), has dramatically improved overall survival rates. In a systematic review of LT for hepatocellular carcinoma (HCC), Maggs (2012) found five-year overall survival rates ranged from 65% to 94.7% in reported studies.[3] Transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease and expansion of patient selection criteria. Bridging to transplant, or down-staging of disease, to qualify for LT is frequently studied. Finally, LT cannot be considered curative in patients with locally extensive or metastatic liver cancer, or in patients with isolated liver metastases with extrahepatic primaries.[2]

LIVING DONOR LIVER TRANSPLANTATION: DONOR OUTCOMES

Due to the scarcity of donor organs and the success of living donation, LDLT has become accepted practice. The living donor undergoes hepatectomy of the right lobe, left lobe, or left lateral segment, which is then transplanted into the recipient. Since right hepatectomy involves the resection of 60% to 70% of the total volume of the donor liver, the safety of the donor has been the major concern. The surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia appears to have the most extensive experience and has reported the results of their first 40 adult-to-adult LDLTs, performed between June 1998 and October 1999.[4] There were an equal number of related and unrelated donors. Minor complications occurred in seven donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, four out of five deaths occurred in recipients who were classified as 2A. In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living donor transplant. Other case series have reported similar success rates.[5-7]

Tokodai (2016) published a retrospective review of 56 patients who underwent hepatectomy, between April 2001 and August 2010.[8] Donors were classified as under 50 (average 32) or greater than or equal to 50 (average 58) years of age. The one-, three-, and five-year graft survival rates were 80%, 60%, and 50%, respectively, in the greater than or equal to 50 years of age group compared to the under 50 years of age group with survival rates of 89%, 87%,

and 82%. The authors concluded older patients can undergo hepatectomy safely, but have longer hospital stays and grafts do not survive as long.

Brown (2013) reported on the results of a survey focusing on adult living-related recipients in the United States.[9] The following statistics were reported:

- The survey encompassed 449 adult-to-adult transplantations
- Half of the responding programs already had performed at least one adult-to-adult LDLT, and 32 of the remaining 41 centers were planning to initiate such surgery
- 14 centers had performed more than 10 such transplantations, and these centers accounted for 80% of these transplants
- A total of 45% of those evaluated for living donation subsequently donated a liver lobe; 99% were genetically or emotionally related to the recipient
- Complications in the donor were more frequent in the centers that performed the fewest living-related donor transplantations
- There was one death among the donors, but complications were relatively common (i.e., biliary complications) in 6% and reoperation in 4.5%

Reports of several donor deaths re-emphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team.[10-12] In December 2000, the National Institutes of Health convened a workshop on LDLT. A summary of this workshop was published in 2002.[13] According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. Based on survey results, the workshop reported that donor morbidity was common: 7% required re-exploration, 10% had to be re-hospitalized, and biliary tract complications occurred in 7%. The median complication rate reported by responding transplant centers was 21%. The summary report concluded that the incidence and type of complications encountered, and the mortality associated with LDLT in both donors and recipients needs to be determined and compared with that for patients undergoing cadaveric transplantation.

Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor have a significant long-term and established relationship with the recipient. According to the workshop summary, "At the present time, nearly all centers strive to identify donors who are entirely healthy and at minimal risk during right hepatectomy. As a result, only approximately one third of persons originally interested in becoming a living liver donor complete the evaluation process and are accepted as candidates for this procedure."

Criteria for a recipient of a living-related liver are also controversial, with some groups advocating that living-related donor livers be used only in those most critically ill, while others state that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival.[13]

In 2000 the American Society of Transplant Surgeons issued the following statement:[14]

"Living donor transplantation in children has proven to be safe and effective for both donors and recipients and has helped to make death on the waiting list a less common event. Since its introduction in 1990, many of the technical and ethical issues have been addressed and the procedure is generally applied.

The development of left or right hepatectomy for adult-to-adult living donor liver transplantation has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult living donor liver transplantation has been undertaken at a number of centers. While early results appear encouraging, sufficient data is not available to ascertain donor morbidity and mortality rates. There is general consensus that the health and safety of the donor is and must remain central to living organ donation."

LIVING DONOR VERSUS DECEASED DONOR LIVER TRANSPLANT: RECIPIENT OUTCOMES

Few high-quality studies are available regarding recipient outcomes based upon direct comparison of liver transplantation from living and deceased donors.

A systematic review by Gavrilidis (2019) evaluated differences in outcomes between recipients of living-related adult donor and recipients of split liver transplantation from deceased donors.[15] A meta-analysis revealed differences in age distributions for both donors and recipients, with LDLT donors tending to be older than split donors (mean difference 11.12 years, p<0.001) and LDLT recipients tending to be younger than split transplant recipients (mean difference 2.06 years, p<0.001). However, there were no significant differences in postoperative complications, graft survival or overall survival between groups.

Humar (2019) compared outcomes between LDLT (n=245) and DDLT (n=592) at a single center in the U.S. between 2009 and 2019[16] The authors reported superior three-year survival in LDLT recipients (86% vs. 80% for DDLT, p=0.03), as well as shorter hospital stays (11 vs. 13 days, p=0.03) lower likelihood of intraoperative blood transfusion (52% vs 78%, p<0.01) or need for posttransplant dialysis (1.6% vs 7.4%, p<0.01). No significant differences were seen for early reoperation and biliary/vascular complication rates.

Wong (2019) published a retrospective intention-to-treat (ITT) analysis with propensity score matching comparing living and deceased donor LT.[17] The study included data for 375 patients listed for LT between 1995 and 2014: 188 patients in the ITT-DDLT group, and 187 in the ITT-LDLT group. Of these, 122 patients on the DDLT waitlist and 27 on the LDLT waitlist were delisted. Overall survival at one-, three- and five-years was significantly better in the ITT-LDLT group (94.1 vs. 77.5%, 81.4 vs. 48.7% and 75.9 vs. 40.8%, respectively). After propensity score matching, overall and recurrence-free survival were similar between groups.

Przybyszerski (2018) compared outcomes after LDLT and deceased donor liver transplant (DDLT) in a retrospective cohort of pediatric patients.[18] A total of 241 children were included in the study (DDLT n=177, LDLT n=64). Most of the LDLT donors were haplo-identical parents. The study found that LDLT was generally associated with better outcomes than deceased donor LT, including a lower rate of acute cellular rejection (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.29 to 0.98, p=0.04), chronic rejection (HR 0.12, 95% CI 0.03 to 0.56. p=0.007), and graft loss (HR 0.29, 95% CI 0.10 to 0.88, p=0.03). No difference in mortality by graft type was seen.

Samstein (2017) published a cohort study evaluating complications for recipients receiving DDLT versus LDLT (LDLT).[19] Patients in the study received DDLT (n=471) or LDLT (n=565) from 1998 to 2010 and were followed for up to 10 years post-transplant. The DDLT recipients were found to have higher occurrences of hepatocellular carcinoma, ascites, intra-abdominal bleeding, cardiac complications and pulmonary edema. The LDLT patients had higher biliary-related complications, hepatic artery thrombosis and chronic kidney disease. There was no difference in resolution time, for either group. The authors concluded LDLT outcomes are better than with DDLT, but improvements are needed to lessen complications for both LDLT and DDLT.

Ushigome (2016) published a study evaluating living donor transplants for patients over 60 years of age.[20] Seventy-six adult patients were divided into a greater than 60 years of age group (n=21) or a less than 60 years of age group (n=55). The one-, three-, five-, and 10-year survival rates for the greater than 60 years of age group were 89.9%, 89.9%, 83.0%, and 83.0%, respectively, compared to the less than 60 years of age group with survival rates of 91.1%, 85.2%, 82.8%, and 82.9%. The authors reported no significant differences between the groups' survival rates but noted that the elderly transplant recipients were frailer and needed careful management.

Olthoff (2015) published results from a prospective multicenter National Institutes of Health study comparing recipient outcomes and associated risks from LDLT and DDLT.[21] This was the same cohort evaluated by Samstein (2017), described above. Mortality and graft failure for 1427 liver recipients (963 LDLT and 464 DDLT) enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study who received transplant between 1998 and 2013, at one of twelve North American centers were analyzed at long-term follow-up (median of 6.7 years). Probability of survival at 10 years was higher for recipients of LDLT then DDLT (70% vs. 64%, respectively). For survival, the adjusted hazard ration for recipients of LDLT was 0.98. LDLT recipients had lower mean model for end-stage liver disease compared to deceased donor recipients (15.5 vs. 20.4, respectively) and had better post-transplant outcomes, regardless of type of donated lobe.

Al Sebayel (2015) published results from a single-center retrospective analysis of survival of recipients of LDLT compared to DDLT in relation to their MELD score.[22] Data was assessed from 222 patients for LDLT and 269 patients with deceased donors. HCV recurrence as a cause of death was significantly higher in recipients of LDLT (p=0.023), but the mortality after one year was significantly higher in recipients of DDLT, (p=0.0072). Overall one, three and five-year survival rates of recipients of LDLT and DDLT were 89%, 85%, and 84%, respectively, for MELD score below 25, and 80%,78%, and 77%, respectively, for MELD score greater than or equal to 25. There were no significant differences in survival of recipients of LDLT and those of deceased donors, regardless of MELD score.

Grant (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for HCC.[23] For disease-free survival after living donor liver transplantation, the combined HR was 1.59 (95% CI 1.02 to 2.49) compared to deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Further study is needed to determine any differences between living and deceased liver transplantation outcomes for various etiologies.

MALIGNANCIES

The following two issues were the focus of the literature review regarding liver transplant for malignancy: 1) whether selection criteria for hepatocellular carcinoma should be expanded and 2) whether extrahepatic cholangiocarcinoma should be considered an acceptable indication for liver transplantation.

Hepatocellular Carcinoma

Selection Criteria for Hepatocellular Carcinoma

The patient selection criteria for liver transplantation for hepatocellular carcinoma (HCC) have focused mainly on the number and size of tumors. An editorial by Llovet (2006) noted that the Milan criteria are considered the gold standard.[24] The Milan criteria specify that patients may either have a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors three cm or smaller. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. UNOS adopted the Milan criteria, combined with one additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. A 2001 paper from the University of California, San Francisco (UCSF), proposed expanded criteria to include patients with a single tumor up to 6.5 cm in diameter, three or fewer tumors with maximum size 4.5 cm and a total tumor size of less than or equal to eight cm.[25] It should be noted that either set of criteria can be applied preoperatively with imaging or with pathology of the explanted liver at the time of intended transplant. Preoperative staging often underestimates what is seen on surgical pathology. To apply pathologic criteria a backup candidate must be available in case preoperative staging is inaccurate. Given donor organ scarcity, any expansion of liver transplant selection criteria has the potential to prolong waiting times for all candidates. Important outcomes in assessing expanded criteria include waiting time duration, death or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence or related outcomes such as disease-free survival. Survival time can be estimated beginning when the patient is placed on the waiting list using the intention-to-treat principal or at the time of transplantation. Llovet (2006) stated that one-year dropout rates for patients meeting Milan criteria are 15% to 30%, and five-year survival rates not reported by intention-to-treat should be adjusted down by 10% to 15%.

Guiteau (2010) reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4.[26] On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of one lesion less than six cm, equal to or less than three lesions, none greater than five cm and total diameter less than nine cm. Patient, allograft and recurrence-free survival at three years did not differ significantly between patients meeting Milan criteria versus patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2%, and 90.5% and 86.9%, respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in Region 4 and that similar outcomes may be different in other regions with different waiting times. Additionally, the authors noted that an HCC consensus conference report on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement.[27] The report addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S. Overall, the evidence

base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF or other criteria.

Schwartz (2008) argued that selection based exclusively on the Milan criteria risks prognostic inaccuracy due to the diagnostic limitations of imaging procedures and the surrogate nature of size and number of tumors.[28] They predict that evolution of allocation policy will involve the following:

1. The development of a reliable prognostic staging system to help with allocation of therapeutic alternatives;
2. New molecular markers that might improve prognostic accuracy;
3. Aggressive multimodality neoadjuvant therapy to downstage and limit tumor progression before transplant and possibly provide information about tumor biology based on response to therapy; and,
4. Prioritization for transplantation should consider response to neoadjuvant therapy, time on waiting list, suitability of alternative donor sources.

A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see table below). The largest series was conducted in 14 centers in France including an intention-to-treat total of 44 patients based on preoperative imaging at the time of listing, and a subset of 39 patients meeting pathologic UCSF criteria.[29] The median waiting time was 4.5 months, shorter than the typical six to twelve months in North America. Dropouts composed 11.4%. The post-transplant overall patient five-year survival of 63.6% was more favorable than the intention-to-treat probability of 45.5% but less favorable than among larger numbers of patients meeting Milan criteria. Similar findings were seen for disease-free survival and cumulative incidence of recurrence. Three centers in Massachusetts included ten patients beyond pathologic Milan criteria but within UCSF criteria.[30] Two-year survival post-transplant was 77.1%, with two patients dying and eight alive after a median of 32 months. A group of 74 patients meeting preoperative Milan criteria had a two-year survival probability of about 73%, but it is inadvisable to compare different preoperative and pathologic staging criteria.

From the series of patients from which the expanded UCSF criteria was developed, 14 satisfied those criteria on pathology but exceeded the Milan criteria.[31] UCSF investigators did not provide survival duration data for this subgroup but noted that two patients died. Although the French series suggested that outcomes among patients exceeding Milan criteria and meeting UCSF criteria are worse than for patients meeting Milan criteria, it is unclear if the latter group still achieves acceptable results. A benchmark of 50% five-year survival has been established in the liver transplant community. The French study met this by post-transplant pathologic staging results (63.6%) and fell short by preoperative intention-to-treat results (45.5%). United States centers have published data for only 24 patients exceeding Milan criteria and meeting UCSF criteria; survival and recurrence data are very sparse. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF criteria.

Several groups have worked on identifying predictors of survival and recurrence of disease. Ioannou (2008) analyzed UNOS data pre- and post-adoption of the MELD allocation system finding a six-fold increase in recipients with hepatocellular carcinoma and that survival in the MELD era was similar to survival to patients without HCC.[32] The subgroup of patients with larger (three to five cm) tumors, serum alpha-fetoprotein level equal to or greater than 455

mg/mL, or a MELD score equal to or greater than 20, however, had poor transplantation survival. A cancer recurrence prediction scoring system was developed by Chan (2008), based on a retrospective review and analysis of liver transplants at two centers to determine factors associated with recurrence of HCC.[33] Of 116 patients with findings of hepatocellular carcinoma in their explanted livers, 12 developed recurrent hepatocellular carcinoma. Four independent significant explant factors were identified by stepwise logistic regression: size of one tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio. The accuracy of the method was confirmed in two validation cohorts.

Table 1. Outcomes Among Patients with Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

Study	Outcome	Group	Probability (%)			
			n	1yr	2yr	5yr
Decaens (2006)[29] 14 centers in France, Meeting Milan criteria (Milan+). Exceeding Milan criteria, meeting UCSF criteria (Milan-/UCSF+)	Intention-to-treat, preoperative					
	Overall patient survival	Milan+	279			60.1
		Milan-/UCSF+	44			45.5
	Cumulative incidence of recurrence	Milan+				20.2
		Milan-/UCSF+				27.1
	Disease-free survival	Milan+				60.4
		Milan-/UCSF+				47.8
	Post-transplant, pathologic (p)					
	Overall patient survival	pMilan+	184			70.4
		pMilan-/pUCSF+	39			63.6
	Cumulative incidence of recurrence	pMilan+				9.4
		pMilan-/pUCSF+				16.5
	Disease-free survival	pMilan+				7.02
		pMilan-/pUCSF+				62.7
	Milan-/UCSF+ median waiting time 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)					
Sotiropoulos (2006)[34] Essen, Germany. Unclear if criteria preoperative or pathologic.	Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo.					
Leung (2004)[30] 3 centers in Massachusetts, Meeting preoperative Milan criteria (Milan+)	Post-transplant overall patient survival	Milan+	74	85.9	~73	50.9
		pMilan-/pUCSF+	10		77.1	
	2 patients died at 3 and 22 months, 8 patients alive after median 32 mo follow-up (6.6-73.5)					
Yao (2002)[31] University of California, San Francisco	Post-transplant overall patient survival	pMilan+	46	91	81	72
	pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant					

The use of extended Milan criteria, to include other factors, has recently become an area of investigation. Tosco (2015) conducted a prospective study that recruited 233 patients with HCC according to their proposed total tumor volume (TTV, ≤115 cm^3)/alpha-fetoprotein (AFP, ≤400 ng/mL) score.[35] The Milan group was modified to include only patients with AFP <400 ng/mL (n=195); these patients were compared to patients beyond Milan, but within TTV/AFP (n=38), with an average follow-up of 34 ± 25 months. Risk of dropout was higher for patients beyond Milan (42.1%), than for those within Milan (25.1%, p = 0.033), and intent-to-treat survival was lower in patients beyond Milan (53.8% vs. 71.6% at four years, p<0.001). Post-transplant, patients within Milan criteria and those beyond Milan had similar recurrence rates (4.5% vs. 9.4%, p=0.138) and post-transplant survivals (78.7% vs. 74.6% at four years,

p=0.932). The investigators concluded that expanding the Milan criteria may lead to increased risk of drop-out but does not impact overall post-transplant survival.

Liver Transplantation versus Liver Resection for Hepatocellular Carcinoma

Liver transplantation is the gold standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A.[36] Additionally, current UNOS criteria indicate a liver transplant candidate must not be eligible for resection.[1] However, the best treatment approach for early HCC in well-compensated livers is controversial.

Schoenberg (2017) published a systematic review and meta-analysis of 54 retrospective studies (n=13,794) comparing liver resection (n=7,990) with transplantation (n=5,804) in patients with HCC.[37] At one-year follow-up, survival rates were higher in those receiving resection (86.17%) than in those receiving liver transplant (80.58%) (OR 1.19, 95% CI 0.99 to 1.43, p=0.07). At five-year follow-up, survival rates were better for those who received transplantation (61.26%) than for those receiving surgery (51.9%, OR 0.62, 95% CI 0.50 to 0.76, p<0.001). When a subgroup of patients with early HCC (eight studies) was analyzed, one-year follow-up showed comparable survival rates between surgically-treated patients (92.14%), and transplanted patients (90.38%) (OR 0.97, 95% CI 0.63 to 1.50, p=0.89). At five years, transplanted patients had a significantly higher survival rate (66.67%) than surgically treated patients (60.35%, OR=0.60, 95% CI 0.45 to 0.78, p<0.001). Review limitations included a high level of heterogeneity between studies analyzed.

Chapman (2015) conducted a retrospective analysis of outcomes of liver transplant compared to resection in 1765 HCC patients treated across five U.S. centers.[38] There were 884 patients who underwent resection and 881 who underwent transplantation. Of the resected patients, 248 (28.1%) were eligible for transplantation, according to the MILAN criteria; which were compared with 496 transplant patients, matched based on year of transplantation and tumor status. Five- and 10-year survival rates were significantly higher in transplant patients, compared to resected patients eligible for transplant (74% vs. 53% and 54% vs. 22% respectively, p<0.001). The investigators concluded that although transplantation results in better long-term survival, resection will likely remain a standard therapy in selected patients with HCC due to limited donor availability.

Zheng (2013) reported on a meta-analysis of 62 cohort studies (n=10,170 total patients) comparing liver transplantation to liver resection for HCC.[39] Overall one-year survival was similar between procedures (OR 1.08, 95% CI 0.81 to 1.43, p=0.61). However, three- and five-year overall survival significantly favored liver transplantation over resection (OR 1.47, 95% CI 1.18 to 1.84, p<0.001, and OR 1.77, 95% CI 1.45 to 2.16, p<0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than liver resection patients at one, three, and five years, respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR 0.20, CI 0.15 to 0.28, p<0.001). While liver transplantation outcomes appear favorable compared to liver resection, a shortage of donor organs may necessitate liver resection as an alternative to liver transplantation.

Salvage Liver Transplantation after Liver Resection for Hepatocellular Carcinoma

In patients who have a recurrence of HCC after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection,

chemotherapy or other local therapies such as radiofrequency ablation, transarterial chemoembolization percutaneous ethanol ablation or cryoablation. Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared to primary transplant.

Yadav (2018) published a systematic review and meta-analysis comparing salvage liver transplant (SLT) and primary LT for individuals with hepatocellular carcinoma.[40] Twenty retrospective studies (10 of which were also included in Murali [2017], described below) with a total of 9,879 patients were included in the analysis. One-year overall survival was better for SLT (74.30%) than primary LT (OR 0.86, 95% CI 0.75 to 0.98, p=0.03). SLT also had higher three- (55.69% and 59.07%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.01) and five-year (48.67% and 52.32%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.009) overall survival than primary LT. One- (OR 0.86, 95% CI 0.75 to 0.99, p=0.03), three- (OR 0.56, 95% CI 0.39 to 0.81, p=0.002), and five-year DFS (OR 0.75, 95% CI 0.66 to 0.86, p<0.001) were worse for primary LT (70.03%, 74.08%, and 47.09%, respectively) than for SLT (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the two groups for postoperative biliary complications (p=0.19) or sepsis (p=0.68). No limitations to the analysis were reported.

Murali (2017) published a systematic review and meta-analysis comparing primary LT to locoregional therapy with curative intent (CLRT) followed by SLT.[41] Forty-eight studies with 9,835 patients were included in the review, which found that five-year overall survival and disease-free survival were worse for the CLRT compared with primary LT (OR for overall survival 0.59, 95% CI 0.48 to 0.71, p<0.01), but there was no significant difference between primary LT and CLRT followed by SLT. However, only 32.5% of patients who had disease recurrence after CLRT received SLT, so disease-free survival was worse with CLRT-SLT.

A systematic review of 14 non-randomized comparative studies was published by Zhu (2013) (n=1,272 for primary transplant and n=236 for salvage).[42] Overall survival at one, three, and five years, and disease-free survival at one and three years were not significantly different between groups. Disease-free survival, however, was significantly lower at five years in SLT compared to primary transplantation (OR 0.62, 95% CI 0.42 to 0.92, p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting SLT may be a viable option in these patients.

Chan (2013) systematically reviewed 16 non-randomized studies (n=319) on SLT after primary hepatic resection for HCC.[43] The authors found overall and disease-free survival outcomes with SLT were similar to reported primary LT outcomes. The median overall survival for SLT patients was 89%, 80% and 62% at one, three, and five years, respectively. Disease-free survival was 86%, 68% and 67% at one, three, and five years, respectively. SLT studies had median overall survival rates of 62% (range 41 to 89%) compared to a range of 61% to 80% in the literature for primary LT. Median disease-free survival rates for SLT were 67% (range 29% to 100%) compared to a range of 58 to 89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. UNOS criteria indicate LT candidates with HCC who subsequently undergo tumor resection must be prospectively reviewed by a regional review board for the extension application.

In a meta-analysis, Li (2012) compared primary LT to SLT (liver transplantation after liver resection) for HCC.[44] Included in the meta-analysis were 11 case-controlled or cohort studies totaling 872 primary LTs and 141 SLTs. Survival rates of patients who exceeded the Milan criteria at one, three and five years were not significantly different between the two groups (one-year OR 0.26, 95% CI 0.01 to 4.94, p=0.37, three-year OR 0.41, 95% CI 0.01 to 24.54, p=0.67, and five-year OR 0.55, 95% CI 0.07 to 4.48, p=0.57).

Adenomatosis

Chiche (2016) published a prospective study that evaluated data from the European Liver Transplant Registry (ELTR) for 49 patients who had LT for liver adenomatosis (LA) between January 1, 1986 and July 15, 2013.[45] LA is a rare benign disease that does not affect liver function. It therefore does not increase the MELD score used to determine who should receive a transplant. The most prevalent concern is fear of malignant transformation and severe bleeding. The authors concluded LA is a rare indication for LT and can be handled non-surgically or through other surgical approaches. LT for LA carries an increased risk of morbidity/mortality, and criteria are critical to aid in transplant selection.

Cholangiocarcinoma

Reports on LT for cholangiocarcinoma (CCA), or bile duct carcinoma, generally distinguish between intrahepatic and extrahepatic tumors, the latter including hilar or perihilar tumors. Recent efforts have focused on pretransplant downstaging of disease with neoadjuvant radiochemotherapy. Relevant outcomes included waiting time duration, dropout rates, survival time, and recurrence.

A meta-analysis by Cambridge (2021) assessed survival following neo-adjuvant chemoradiation and orthotopic LT for unresectable perihilar CCA in 20 studies (total n=428).[46] Pooled one-, three-, and five-year overall survival rates following LT for patients who completed neoadjuvant therapy were 82.8% (95% CI 73.0 to 90.8%), 65.5% (95% CI 48.7% to 80.5%), and 65.1% (95% CI 55.1% to 74.5%), respectively. For those without neoadjuvant therapy, survival rates were lower at 71.2% (95% CI 62.2% to 79.4%), 48.0% (95% CI 35.0% to 60.9%), and 31.6% (95% CI 23.1% to 40.7%), respectively. Pooled recurrence at three years with neoadjuvant treatment was 24.1% (95% CI 17.9% to 30.9%), while three-year recurrence without neoadjuvant treatment was 51.7% (95% CI 33.8% to 69.4%).

Lunsford (2018) evaluated neoadjuvant chemotherapy followed by LT in a small, prospective case series of patients with locally advanced, unresectable, intrahepatic CCA at a single center.[47] Of the 21 patients referred between 2010 and 2017, 12 were accepted and six had undergone LT. Three of the transplants were from deceased donors and three were from living donors. All six patients survived to one year after transplant, and five patients survived to three and five years. Three had disease recurrence during follow-up.

Hildebrand (2016) published a multi-center retrospective cohort study to evaluate risk factors, recurrence of biliary strictures, and impact on survival after LT, for patients with primary sclerosing cholangitis (PSC).[48] PSC is a progressive cholestatic disease with inflammation and fibrotic strictures within the hepatic or extrahepatic bile ducts. Progression leads to biliary cirrhosis, recurrent episodes of septic cholangitis, or CCA. The only cure is LT. This study evaluated 2,170 transplant patients with prior PSC. LT was performed at 10 German transplant centers from January 1990 to December 2006. One-, five-, and 10-year recipient survival was 90.7%, 84.8%, and 79.4%, respectively, and one-, five-, and 10-year graft survival was 79.1%,

69.0%, 62.4%. Biliary strictures were found in 36.1% of the recipients after an average of 3.9 years, and recurrent PSC was found in 20.3% of the recipients after 4.6 years post-LT. MELD and Mayo risk score parameters, particularly INR, were higher in patients with biliary stricture after LT. Donor age was also a risk factor for developing strictures after LT.

Gu (2012) reported on a systematic review and meta-analysis of 14 clinical trials on LT for CCA.[49] Overall one-, three-, and five-year pooled survival rates from 605 study patients were 0.73 (95% CI 0.65 to 0.80), 0.42 (95% CI 0.33 to 0.51), and 0.39 (95% CI 0.28 to 0.51), respectively. When patients received adjuvant therapies preoperatively, one-, three-, and five-year pooled survival rates improved and were 0.83 (95% CI 0.57 to 0.98), 0.57 (95% CI 0.18 to 0.92), and 0.65 (95% CI 0.40 to 0.87), respectively.

Darwish Murad (2012) reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar CCA followed by LT.[50] Intent-to-treat survival (after a loss of 71 patients before liver transplantation) was 68% at two years and 53% at five years, and recurrence-free survival rates post-transplant were 78% at two years and 65% at five years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy. ($p<0.001$).

Panjala (2011) published results from a small case series of 22 patients with CCA treated with neoadjuvant chemoradiotherapy and subsequent LT.[51] Estimated rates of one, two, and three year survival, were 90%, 70%, and 63%, respectively, calculated based upon survival after a median follow-up of 601 days. Smaller tumors and those in the earliest stages of disease were associated with the most promising outcomes.

Among the various publications, the Mayo Clinic in Minnesota had the most favorable results.[52, 53] Between 1993 and 2006, 65 patients underwent LT for unresectable perihilar CCA or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and five-year survival was 76%. In a series of 38 patients from the Mayo Clinic, cumulative recurrence was 0% at one year, 5% at three years, and 13% at five years.

The University of California, Los Angeles (UCLA)/Cedars-Sinai reported on 25 cases of both intrahepatic and extrahepatic CCA.[54] One-year survival was 71% and 3-year survival was 35%. The University of Pittsburgh found one-year survival of 70% and 18% five-year survival among 20 patients with intrahepatic CCA.[55] A German study of 24 patients reported the poorest results.[56]

The European Liver Transplant Registry reported that, among 186 patients with intrahepatic CCA, one-year survival was 58% and five-year survival was 29%.[57] In 169 patients with extrahepatic CCA, the probabilities were 63% and 29%. The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic CCA, finding a one-year survival of 72% and a five-year survival of 23%.[58] The multicenter report included 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.[59] One-year survival was 82% and 77%, while five-year survival was 30% and 23%, respectively. Crude recurrence rates were 53% and 36% for extrahepatic and intrahepatic CCA, respectively. The German center at Hannover found a crude recurrence rate of 63%.[56]

Table 2. Outcomes Among Patients with Cholangiocarcinoma

Study	Outcome	Group	n	Probability (%)			
				1yr	2yr	3yr	5yr
Pascher (2003)[30] European Liver Transplant Registry	Overall patient survival	IH-CCA	186	58		38	29
		EH-CCA	169	63		38	29
Meyer (2000)[31] Cincinnati Transplant Registry unresectable CCA, cholangiohepatoma, incidental median follow-up 23 mo (<1-96)	Overall patient survival	IH/EH-CCA	207	72	48		23
Robles (2004)[34] Multiple Centers in Spain 03/88-09/01; hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental	Overall patient survival	Hilar CCA	36	82		53	30
		Peripheral CCA	23	77		65	23
	Crude recurrence rate: EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)						
Heimbach (2006)[52]; Rea (2006)[53] Mayo Clinic, Rochester MN, USA 01/93-01/06, aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis mean follow-up 32 mo (2 d-13 yr)	Overall patient survival	Perihilar CCA	65	91			76
	Cumulative recurrence		38	0		5	13
	Crude recurrence rate: 11/65 (17%) median onset 22 mo (7-65)						
Shimoda (2001)[54] UCLA/Cedars-Sinai, Los Angeles, CA, USA 1984-2000; IH or EH CCA median follow-up 22.3 mo	Overall patient survival	All	25	71		35	
		IH-CCA	16	62		39	
		EH-CCA	9	86		31	
	Disease-free survival	All	25	67		42	
		IH-CCA	16	70		35	
		EH-CCA	9	57		57	
Casavilla (1997)[55] University of Pittsburgh, PA, USA 1981-1994	Overall patient survival	IH-CCA	20	70		29	18
	Tumor-free survival		20	67		31	31
Weimann (2000)[56] Hannover, GER 07/78-12/96; unresectable CCA	Overall patient survival	IH-CCA	24	21	8	4	0
	Crude recurrence rate: 15/24 (63%)						
CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic							

Heimbach (2018) reviewed the published outcomes of the combined protocol in the context of data on outcomes for surgical resection, and concluded that outcomes of neoadjuvant chemoradiotherapy with subsequent LT for patients with early-stage hilar CCA, which is unresectable, or arising in the setting of PSC are comparable to outcomes for patients with hepatocellular carcinoma and other chronic liver diseases, and superior to resection.[60] Intraoperative challenges attributable to the neoadjuvant therapy were described, including severe inflammatory changes and dense fibrosis. The author suggested that key principles for centers considering use of the combined protocol include a multidisciplinary approach, pretransplant staging, inclusion of only patients without lymph node metastasis, replacement of irradiated vessels (when possible), and monitoring for postoperative vascular complications.

Wu (2008) described an extensive surgical procedure combined with radiotherapy.[61] The authors retrospectively reviewed their experience with surveillance and early detection of CCA

and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of patients with early-stage CCA complicating PSC. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with CCA were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. CCA was detected in eight of the 42 patients followed up according the surveillance protocol between 1988 and 2001, and six patients underwent OLT-Whipple. One died at 55 months after transplant of an unrelated cause without tumor recurrence, and five are without recurrence at 5.7 to 10.1 years.

Section Summary

Treatment benefit of liver transplant has been demonstrated for select patients with CCA and evidence on patients with perihilar CCA have shown reasonable survival rates at five years. However, current evidence regarding five-year survival rates for intrahepatic CCA are less certain as most studies which demonstrated lower overall survival rates reported on a combined intra- and extra-hepatic patient population.

Pediatric Hepatoblastoma

Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, tumors aren't often discovered until they are unresectable. In cases of unresectable tumors, LT with pre- and/or post-chemotherapy is a treatment option with reports of good outcomes and high rates of survival.[62] UNOS guidelines list non-metastatic hepatoblastoma as a condition eligible for pediatric LT.[1]

Hamilton (2017) reported on 376 children with hepatoblastoma requiring liver transplantation; this was part of a larger cohort of 544 children receiving a liver transplant from 1987 to 2012, as recorded in the United Network for Organ Sharing database.[63] The five-year patient survival rate after liver transplant for hepatoblastoma was 73%, with five-year graft survival rate of 74%. Recurrent or metastatic disease was the most common (57%) cause of death for this population.

Barrena (2011) reported on 15 children with hepatoblastoma requiring LT.[64] Overall survival after liver transplant was 93.3 (±6.4%) at one-, five- and 10-years. Malek (2010) reported on liver transplantation results for 27 patients with primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007.[65] Tumor recurrence occurred in one patient after LT and overall survival was 93%. Browne (2008) reported on 14 hepatoblastoma patients treated with LT. Mean follow-up was 46 months with overall survival in 10 of 14 patients (71%).[66] Tumor recurrence caused all four deaths. In the 10 patients receiving primary LT, nine survived while only one of four patients transplanted after primary resection survived (90% vs. 25%, p=0.02).

Metastatic Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are relatively rare neoplasms that are generally slow growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In select patients with non-resectable, hormonally active liver metastases refractory to medical therapy, LT has been considered as an option to extend survival and minimize endocrine symptoms.

Moris (2017) published a systematic review on LT for the treatment of NETs with liver metastases.[67] There were 64 studies deemed eligible for inclusion in the review, including four studies using registry data and three multicenter studies. The authors reported an overall recurrence rate ranging from 31.3% to 56.8%, with a five-year survival of 63%. Factors that were associated with worse survival included >50% liver tumor involvement, higher Ki67 (a disease marker) and pancreatic NETs (compared to gastrointestinal NETs).

Sher (2015) conducted a retrospective analysis on LT outcomes of 85 patients with NETs, assessing data from a North American multicenter database.[68] One, three, and five-year patient survival rates were 83%, 60%, and 52%, respectively. These rates are similar to those reported in larger studies. Overall, 40 of 85 patients died, with 20 of 40 deaths due to recurrent disease. In multivariable analysis, predictors of poor overall survival included large vessel invasion (p=0.001), and extent of extrahepatic resection at liver transplant (p=0.015). The investigators reported that the survival outcomes are high enough to merit LT in this patient population.

Fan (2014) reported on a systematic review of 46 studies on LT for NET liver metastases of any origin.[69] A total of 706 patients were included in the studies reviewed. Reported overall five-year survival rates ranged from 0 to 100%, while five-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the five-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after LT were reported in most studies.

Mathe (2011) conducted a systematic review of the literature to evaluate patient survival after LT for pancreatic NETs.[70] Data from 89 transplanted patients from 20 clinical studies were included in the review. Sixty-nine patients had primary endocrine pancreatic tumors, nine patients had carcinoids, and 11 patients were not further classified. Survival rates at one-, three-, and five-years were 71%, 55%, and 44%, respectively. The mean calculated survival rate was 54.45 (±6.31) months, and the median calculated survival rate was 41 months (95% CI 22 to 76 months).

Gedaly (2011) reported on a retrospective analysis of LT conducted on 150 patients with metastatic NETs.[71] Survival rates at one-, three-, and five-years were similar to those reported in the systematic analysis above: 81%, 65%, and 49%, respectively. No significant differences were seen in rates of patient survival between patients with metastatic NETs compared with those with hepatocellular carcinoma. Because longer wait times were associated with improved health outcomes, the authors suggested allowing for disease stabilization before attempting transplantation.

Mazzaferro (2007) performed a literature review to establish transplant selection criteria for patients with metastatic neuroendocrine tumors.[72] Eight studies were reviewed between 1970 and 2006, and all but one study reported either poor or limited five-year survival outcomes. Suboptimal patient selection was reported as the cause for the lower rates of long-term survival. However, the authors reported outcomes for 24 patients who were selected for transplant using the Milan criteria,[73] and found a high five-year survival rate of 77%. Although, the utilization of these criteria to select optimal transplantation candidates in patients with non-resectable metastatic neuroendocrine tumors is promising, the data is limited to a small sample (n=24), from a single study. Larger, long-term studies are required to validate the usefulness of the Milan criteria in improving five-year survival rates for this unique patient population.

Section Summary

While there may be centers that perform LT on select patients with NETs, further studies are needed to determine appropriate selection criteria. Few studies are available, and the quality is limited by their retrospective nature and heterogeneous populations.

HIV POSITIVE RECIPIENTS

The subgroup of HIV positive LT recipients was historically controversial due to the long-term prognosis for HIV positivity, and the impact of immunosuppression on HIV disease. HIV candidates for LT are frequently co-infected with hepatitis B (HBV) or HCV, and viral co-infection can further exacerbate drug-related hepatotoxicities.

Cooper (2011) conducted a systematic review to evaluate LT in patients co-infected with HIV and hepatitis.[74] The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared to those with detectable HIV viremia.

Terrault (2012) reported on a prospective, multicenter study to compare LT outcomes in three groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older.[75] Patient and graft survival reductions were significantly associated with only one factor: HIV infection. At three years, patient and graft survival rates were significantly better in the HCV-only group (79%, 95% CI 72% to 84%, and 74%, 95% CI 66% to 79%, respectively) than in the group with both HIV and HCV infection (60%, 95% CI 47% to 71%, and 53%, 95% CI 40% to 64%, respectively).

Current, OPTN policy permits HIV-positive transplant candidates.[1]

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[76] For liver transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 (CD4) count >100 cells/mL with no history of AIDS-defining illnesses such as opportunistic infection or malignancy or CD4 count >200 cells/mL for at least 3 months
- Undetectable HIV viral load while receiving antiretroviral therapy or a detectable HIV viral load in patients with intolerance to antiretroviral therapy that can be suppressed posttransplant
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring

The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled HBV

infection may be considered for transplant. Caution is recommended in HCV-coinfected patients who have not been initiated on direct acting antiviral therapy.

Section Summary

While HIV infection reduced three-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival. Overall, survival rates are relatively high for patients with viral loads are low at the time of transplantation.

NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (NASH) is a condition where fat build up in the liver causes inflammation of the liver. LT is a treatment option for patients with NASH who progress to liver cirrhosis and failure.

In a systematic review and meta-analysis, Wang (2014) evaluated nine studies comparing LT outcomes in patients with and without NASH.[77] Patients with NASH had similar one-, three- and five-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (OR 0.21, 95% CI 0.05 to 0.89, p=0.03). However, NASH LT patients had a greater risk of death related to cardiovascular disease (OR 1.65, 95% CI 1.01 to 2.70, p=0.05) and sepsis (OR 1.71, 95% CI 1.17 to 2.50, p=0.006) than non-NASH liver transplant patients. Given the relatively equivocal survival rates compared to transplant patients without NASH, transplant in patients with NASH appear to be of benefit.

Cholankeril (2017) published a retrospective cohort analysis of records from 2003 to 2014 in the United Network Organ Sharing and Organ Procurement and Transplantation Network database to evaluate the frequency of NASH-related liver transplantation.[78] In all, 63,061 patients underwent liver transplant from 2003 to 2014. NASH accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to NASH increased by 162.0%, a greater increase than either HCV (33.0% increase) and alcoholic liver disease (55.0% increase). Five-year survival posttransplant in patients who had NASH (77.81%, 95% CI 76.37% to 79.25%) was higher than patients who had HCV (72.15%, 95% CI 71.37 to 72.93, p<0.001). Patients with NASH also demonstrated significantly higher posttransplant survival than patients with HCV (HR 0.75, 95% CI 0.71 to 0.79, p<0.001).

Section Summary

The evidence on LT for hepatocellular disease includes case series, registry studies, and systematic reviews. Long-term survival rates in patients with viral hepatitis are significant in a group of patients who have no other treatment options. Also, survival can be improved by eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival rates are similar to other indications for LT.

VIRAL HEPATITIS

The presence of HBV and HCV have been controversial indications for liver transplantation because of the high potential for recurrence of the virus and subsequent recurrence of liver disease. However, in a review of registry data, Belle (1995) have indicated a long-term survival rate (seven years) of 47% in HBV virus-positive transplant recipients, which is lower than that seen in other primary liver diseases such as primary biliary cirrhosis (71%) or alcoholic liver

disease (57%).[2] Recurrence of HCV infection in transplant recipients, who are not treated pretransplant, has been nearly universal, and 10% to 20% of patients will develop cirrhosis within five years.[79]

Historical data demonstrating inferior survival in transplant recipients with HCV is not applicable to the current treatment landscape with the availability of direct acting antiviral agents, which are associated with sustained virological response rates over 95%.[80] Timing the receipt of direct acting antiviral agents either before or after transplantation is still controversial and the decision should be individualized based the presence of compensated or decompensated disease, Model for End-Stage Liver Disease (MELD) score, current quality of life, and the proportion of HCV-positive donors in the local and regional areas.

ELDERLY DONORS AND RECIPIENTS

Elderly Donors

Gao (2019) evaluated trends in long-term outcomes for LT with donors aged 60 years and above, using data from the OPTN/UNOS database.[81] There were 14,796 adult LT between 1990 and 2014 included in the analysis. There was a steady increase in the number of transplants from older donors found during the first 15 years of period, followed by a leveling off. There were significant improvements in the unadjusted five-year graft and patient survival over time ($p<0.0001$), as well as a reduction in the survival difference between older and younger grafts ($p<0.0001$).

A prospective study by Cascales-Campos (2018) assessed LT outcomes for those with donors aged 80 years and above (n=36) compared to those with donors under 65 years of age (n=283). They reported no significant differences in graft survival and overall survival.[82]

Paterno (2016) published a study that evaluated the outcome of LT from elderly donors.[83] Data from January 2007 to December 2011 was evaluated for patients who received a transplant from donors aged 70 years and older (n=540) or from patients younger than 60 years of age (n=10,473). The authors stated transplants from elderly donors in patients who meet criteria (i.e., no HCV and not on dialysis) had good outcomes and survival rates, but slightly lower graft survival.

A similar study by Dasari (2017) with 4,376 LT recipients compared outcomes for those receiving grafts from deceased donors over 70 years of age (n=880) and below 70 years of age (n=3,496).[84] In this study, graft and patient survival were similar between groups at one year, but there was better graft and patient survival at three and five years in the older donor group.

Elderly Recipients

Chen (2016) published a population-based cohort study that reported age-related LT mortality for patients in Taiwan.[85] Data were collected for patients receiving transplants from July 1, 1998 to December 31, 2012, and patients were followed until the end of the study or death. The authors stated the older a recipient, the higher risk of mortality, particularly for those with comorbidities.

Section Summary

Liver transplants for elderly recipients or from elderly donors can have positive health outcomes. More studies are needed to further identify survival rates and risks of mortality.

RETRANSPLANTATION

A registry analysis of pediatric retransplantation patients from Australia and New Zealand was published by Jeffrey (2020).[86] Between 1986 and 2017, 142 retransplantations in children were performed. Survival was higher in retransplantations performed between 2001 and 2017 compared with those performed between 1986 and 2001 ($p<0.001$), with 5-, 10-, and 15-year patient survival rates of 87%, 87%, and 71%, respectively, for the procedures between 2001 and 2017. There were no significant associations between survival and graft type, cause of graft failure, or number of transplants.

Agüero (2016) published an international cohort study that evaluated retransplantation for HIV patients who had HBV or HCV coinfection.[87] Thirty-seven patients with HBV or HCV coinfection underwent retransplant, with a survival rate of 80%. The authors concluded that patients coinfected with HBV or HCV, without HCV RNA had acceptable outcomes.

Abdelfattah (2015) reported on a retrospective cohort of 466 LT patients, 16 of whom underwent retransplantation.[88] The 16 retransplant patients were divided into those which had retransplantation within 30 days of the primary transplant, and those which had retransplantation more than 30 days after. Although the investigators stated that, overall patient and graft survival were lower after liver retransplant than primary liver transplant, and these outcomes were better in late than early liver retransplant; the study populations in the comparator groups was too small to draw meaningful conclusions. Studies of larger sample size are needed.

Bellido (2012) reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data.[89] Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent versus 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%) related to chronic rejection.

Remiszewski (2011) examined factors influencing survival outcomes in 43 liver retransplantation patients.[90] When compared to primary LT patients, retransplantation patients had significantly lower six-year survival rates (80% vs. 58%, respectively, $p=0.0001$). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong (2011) reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation.[91] Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than one prior liver transplant, need for mechanical ventilation, serum albumin of less than 2.5 g/dL, donor age greater than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful for patient selection.

Section Summary

Recent data regarding liver retransplantation suggest survival rates are not as good as with initial transplantation; however, overall survival rates appear to meet the benchmark of 50% five-year survival.

PRACTICE GUIDELINE SUMMARY

In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for HCC.[92] Consensus criteria for selecting candidates for LT were developed at the conference. Milan criteria were recommended for use as the benchmark for patient selection and as the basis for comparison with other suggested criteria for selecting non-HCC patients. The Milan criteria set limits on the size and quantity of tumors and have been shown to be an independent prognostic factor for outcomes after LT.[92, 93] Panel members did refer to several studies which indicated that in some circumstances, the Milan criteria may be modestly expanded for patients who do not have HCC. It was warned, however, that expanding Milan criteria could result in a variety of outcomes and that patients, "…would need to achieve 5-year survival of 60% or higher to prevent a substantial decrement to the life-years available to the entire population of candidates for liver transplantation."[92] In addition, candidates for LT should also have a predicted survival of five years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

With respect to liver retransplantation, the consensus criteria issued a weak recommendation indicating retransplantation after graft failure of a living donor transplant for HCC is acceptable in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued indicating liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria is not recommended. And the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC is not appropriate. However, a de-novo HCC may be treated as a new tumor and retransplantation may be considered even though data to support this are limited.

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

Evaluation for Liver Transplantation

The AASLD issued separate updated, evidence-based guidelines for evaluating pediatric[94] and adult[95] patients for LT. These guidelines update the 2005 guidelines[96] which addressed all ages. While the disease categories are similar for adult and pediatric (below 18 years of age) patients, separate guidelines were considered warranted because of differences between these age groups in specific etiologies and outcomes. Furthermore, the AASLD guidelines indicate patients should be assessed by a transplantation center to determine whether LT is appropriate. While the AASLD guidelines indicate LT may be appropriate in patients with CCA and metastatic NETs, these recommendations and many of the recommendations in the AASLD guidelines are based on opinion.

- In 2014 the AASLD in conjunction with the American Society of Transplantation (AST) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition issued evidence-based guidelines for the evaluation of pediatric patients for liver transplantation.[94] Each of the 93 recommendations was classified for strength of recommendation and quality of evidence. Strength of recommendation 1 and 2 is defined as a strong or weak recommendation, respectively. Quality of evidence A, B, or C is

defined as high, moderate, or low quality, respectively. Contact of or referral to a liver transplant center was recommended for any of the following indications:

  - Acute liver failure or acute decompensation of an established liver disease (*Strength of recommendation 1; quality of evidence A [1-A])*
  - Liver-based metabolic crises refractory to medical and/or surgical therapy *(1-B)*
  - Unresectable hepatoblastoma or hepatocellular carcinoma *(1-B)*
  - Biliary atresia patients with total bilirubin > 6 mg/dL beyond 3 months post-hepatoportoenterostomy (*1-B*); liver transplant evaluation should be considered in these patients if total bilirubin remains between 2-6 mg/dL. *(1-B)*
  - Anticipate referral for evaluation for children with chronic liver disease and evidence of deteriorating liver function (i.e., poor weight gain, growth failure, variceal hemorrhage, intractable ascites, recurrent cholangitis, or episodes of spontaneous bacterial peritonitis, pruritus, advancing encephalopathy, and/or uncorrectable coagulopathy *(1-B)*

- The 2013 AASLD/ATS guideline for evaluation of adults for LT state that LT is indicated for acute or chronic liver failure when the limits of medical therapy have been reached.[95] The following are some of the included recommendations:

  - Consideration for liver transplantation is recommended for acute liver failure complications of cirrhosis, liver-based metabolic conditions with systemic manifestations, and systemic complications of chronic liver disease (i.e., hepatopulmonary syndrome; portopulmonary hypertension)
  - Liver transplant in combination with neoadjuvant chemoradiation for early-stage unresectable peri-hilar cholangiocarcinoma *(1-B)*.
  - Intrahepatic cholangiocarcinoma is a listed contraindication to liver transplant
  - Extrahepatic malignancy is a contraindication to liver transplant
  - Live donor transplant should be considered only when a deceased donor is unlikely to become available within a reasonable time frame for the recipient's liver disease

Long-term Management after Liver Transplant

The AASLD has also issued joint evidence-based guidelines with the AST for management of pediatric[97] and adult[98] patients following successful LT. Numerous recommendations are included and each is graded for strength of recommendation and quality of the supporting evidence. The stated intent of the guidelines is to provide flexible, preferred approaches to the diagnostic, therapeutic, and preventive aspects of care.

The 2013 guideline for pediatric (age 0 to 18 years) post-LT patients includes 54 recommendations.[97] "Pediatric liver transplant has dramatically changed the prognosis for many infants and children with liver failure and metabolic disease. As survival increases, long-term maintenance resources exceed perioperative care requirements. The most common indication for LT in children is biliary atresia which accounts for 50% of all children requiring transplant in the U.S. and 74% in Europe."

The 2012 AASLD/AST practice guideline for adults after LT includes 93 recommendations.[98] "LT is the treatment of choice for patients with decompensated cirrhosis, acute liver failure, small hepatocellular carcinomas (HCCs), or acute liver failure…long-term survivors are at risk of early death and increased morbidity. The purpose of this guideline is to assist in the management of adult recipients of LT, identify the barriers to maintaining their health, and

make recommendations on the ways to best prevent or ameliorate these barriers. This guideline focuses on management beyond the first 90 days after transplantation."

Alcohol-Associated Liver Disease

The AASLD (2019) guideline on alcohol-associated liver disease provides recommendations on the timing of referral and selection of candidates for liver transplant.[99] The guidance notes that the patient's history of addiction to alcohol is a primary driver in selecting appropriate candidates for liver transplantation. Clinical characteristics that should trigger an evaluation and consideration for liver transplant include decompensated alcohol-associated cirrhosis, Child-Pugh-Turcotte class C cirrhosis, or a MELD-Na score ≥21. Additionally, the guideline notes that candidate selection "should not be based solely on a fixed interval of abstinence" and instead a formal psychological evaluation can help stratify patients into higher- or lesser-risk strata for relapse.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines on hepatobiliary cancers (v1.2022) recommend referral to a liver transplant center or bridge therapy for patients with HCC meeting United Network of Organ Sharing criteria of a single tumor measuring 2 to 5 cm, or two to three tumors 3 cm or less with no macrovascular involvement or extrahepatic disease.[36] Patients should be referred to the transplant center. Patients should be referred to the transplant center before the biopsy. In patients who are ineligible for transplant and in select patients with Child-Pugh class A or B liver function with tumors that are resectable, the NCCN indicates resection is the preferred treatment option; locoregional therapy may also be considered. Patients with unresectable HCC should be evaluated for liver transplantation; if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine and adrenal tumors (v1.2022) indicate that liver transplantation for neuroendocrine tumor metastases in the liver is considered investigational despite "encouraging" five-year survival rate.[100]

SUMMARY

There is enough research to show that liver transplantation can improve survival for patients with irreversible, end-stage liver failure due to certain conditions. Clinical guidelines based on research recommend liver transplantation for some people with irreversible, end-stage liver failure. Therefore, liver transplantation may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that liver transplantation does not improve health outcomes for patients with hepatocellular carcinoma that has extended beyond the liver, or for patients with active alcohol and/or substance abuse. Therefore, liver transplantation is considered not medically necessary for these patients.

There is not enough research to show that liver transplantation improves survival for patients with intrahepatic cholangiocarcinoma, extrahepatic malignancy other than those noted in the policy criteria, or neuroendocrine tumors metastatic to the liver. Therefore, liver

transplantation is investigational for these populations when the policy criteria are not met.

RETRANSPLANTATION

There is enough research to show that liver retransplantation improves survival for pediatric and adult patients for primary graft nonfunction, hepatic artery thrombosis, chronic rejection, ischemic type biliary lesions after donation after cardiac death, or recurrent non-neoplastic disease-causing late graft failure. Therefore, liver retransplantation may be considered medically necessary in patients with one of these diagnoses who meet the policy criteria. There is not enough research to show that liver retransplantation improves survival in patients for other conditions. Therefore, liver retransplantation is investigational when the policy criteria are not met.

REFERENCES

1. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2019. [cited 5/1/2023]. 'Available from:' https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
2. Belle SH, Beringer KC, Detre KM. An update on liver transplantation in the United States: recipient characteristics and outcome. *Clin Transpl.* 1995:19-33. PMID: 8794252
3. Maggs JR, Suddle AR, Aluvihare V, et al. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. *Alimentary pharmacology & therapeutics.* 2012;35(10):1113-34. PMID: 22432733
4. Marcos A, Ham JM, Fisher RA, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. *Liver Transpl.* 2000;6(3):296-301. PMID: 10827229
5. Wachs ME, Bak TE, Karrer FM, et al. Adult living donor liver transplantation using a right hepatic lobe. *Transplantation.* 1998;66(10):1313-6. PMID: 9846514
6. Fan ST, Lo CM, Liu CL, et al. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch Surg.* 2000;135(3):336-40. PMID: 10722038
7. Inomata Y, Uemoto S, Asonuma K, et al. Right lobe graft in living donor liver transplantation. *Transplantation.* 2000;69(2):258-64. PMID: 10670636
8. Tokodai K, Kawagishi N, Miyagi S, et al. Poor Long-Term Outcomes of Adult Liver Transplantation Involving Elderly Living Donors. *Transplantation proceedings.* 2016;48(4):1130-3. PMID: 27320572
9. Brown RS, Jr., Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med.* 2003;348(9):818-25. PMID: 12606737
10. Malago M, Testa G, Marcos A, et al. Ethical considerations and rationale of adult-to-adult living donor liver transplantation. *Liver Transpl.* 2001;7(10):921-7. PMID: 11679994
11. Renz JF, Busuttil RW. Adult-to-adult living-donor liver transplantation: a critical analysis. *Semin Liver Dis.* 2000;20(4):411-24. PMID: 11200412
12. Bak T, Wachs M, Trotter J, et al. Adult-to-adult living donor liver transplantation using right-lobe grafts: results and lessons learned from a single-center experience. *Liver Transpl.* 2001;7(8):680-6. PMID: 11510011
13. Shiffman ML, Brown RS, Jr., Olthoff KM, et al. Living donor liver transplantation: summary of a conference at The National Institutes of Health. *Liver Transpl.* 2002;8(2):174-88. PMID: 11862598

14. American Society of Transplant Surgeons' position paper on adult-to-adult living donor liver transplantation. *Liver Transpl.* 2000;6(6):815-7. PMID: 11084076
15. Gavriilidis P, Azoulay D, Sutcliffe RP, et al. Split versus living-related adult liver transplantation: a systematic review and meta-analysis. *Langenbeck's archives of surgery.* 2019. PMID: 30847599
16. Humar A, Ganesh S, Jorgensen D, et al. Adult Living Donor Versus Deceased Donor Liver Transplant (LDLT Versus DDLT) at a Single Center: Time to Change Our Paradigm for Liver Transplant. *Ann Surg.* 2019;270(3):444-51. PMID: 31305283
17. Wong TCL, Ng KKC, Fung JYY, et al. Long-Term Survival Outcome Between Living Donor and Deceased Donor Liver Transplant for Hepatocellular Carcinoma: Intention-to-Treat and Propensity Score Matching Analyses. *Annals of surgical oncology.* 2019. PMID: 30737669
18. Przybyszewski EM, Verna EC, Lobritto SJ, et al. Durable Clinical and Immunologic Advantage of Living Donor Liver Transplantation in Children. *Transplantation.* 2018. PMID: 29369249
19. Samstein B, Smith AR, Freise CE, et al. Complications and Their Resolution in Recipients of Deceased and Living Donor Liver Transplants: Findings From the A2ALL Cohort Study. *Am J Transplant.* 2016;16(2):594-602. PMID: 26461803
20. Ushigome H, Nakao T, Harada S, et al. Elderly Living Donor Liver Transplant Recipients Over 60 Years Old at a Japanese Single Center. *Transplantation proceedings.* 2016;48(4):1115-8. PMID: 27320569
21. Olthoff KM, Smith AR, Abecassis M, et al. Defining long-term outcomes with living donor liver transplantation in North America. *Ann Surg.* 2015;262:465-75; discussion 73-5. PMID: 26258315
22. Al Sebayel M, Abaalkhail F, Hashim A, et al. Living donor liver transplant versus cadaveric liver transplant survival in relation to model for end-stage liver disease score. *Transplantation proceedings.* 2015;47(4):1211-3. PMID: 26036556
23. Grant RC, Sandhu L, Dixon PR, et al. Living vs. deceased donor liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. *Clinical transplantation.* 2013;27(1):140-7. PMID: 23157398
24. Llovet JM. Expanding HCC criteria for liver transplant: the urgent need for prospective, robust data. *Liver Transpl.* 2006;12(12):1741-3. PMID: 17133574
25. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology.* 2001;33(6):1394-403. PMID: 11391528
26. Guiteau JJ, Cotton RT, Washburn WK, et al. An early regional experience with expansion of Milan Criteria for liver transplant recipients. *Am J Transplant.* 2010;10(9):2092-8. PMID: 20883543
27. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl.* 2010;16(3):262-78. PMID: 20209641
28. Schwartz ME, D'Amico F, Vitale A, et al. Liver transplantation for hepatocellular carcinoma: Are the Milan criteria still valid? *Eur J Surg Oncol.* 2008;34(3):256-62. PMID: 18029133
29. Decaens T, Roudot-Thoraval F, Hadni-Bresson S, et al. Impact of UCSF criteria according to pre- and post-OLT tumor features: analysis of 479 patients listed for HCC with a short waiting time. *Liver Transpl.* 2006;12(12):1761-9. PMID: 16964590

30. Leung JY, Zhu AX, Gordon FD, et al. Liver transplantation outcomes for early-stage hepatocellular carcinoma: results of a multicenter study. *Liver Transpl.* 2004;10(11):1343-54. PMID: 15497158
31. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl.* 2002;8(9):765-74. PMID: 12200775
32. Ioannou GN, Perkins JD, Carithers RL, Jr. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. *Gastroenterology.* 2008;134(5):1342-51. PMID: 18471511
33. Chan EY, Larson AM, Fix OK, et al. Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. *Liver Transpl.* 2008;14(7):956-65. PMID: 18581511
34. Sotiropoulos GC, Molmenti EP, Omar OS, et al. Liver transplantation for hepatocellular carcinoma in patients beyond the Milan but within the UCSF criteria. *Eur J Med Res.* 2006;11(11):467-70. PMID: 17182358
35. Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. *Hepatology.* 2015;62(1):158-65. PMID: 25777590
36. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Hepatobiliary Cancers. v. 1.2023. [cited 5/1/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.
37. Schoenberg MB, Bucher JN, Vater A, et al. Resection or Transplant in Early Hepatocellular Carcinoma. *Deutsches Arzteblatt international.* 2017;114(31-32):519-26. PMID: 28835324
38. Chapman WC, Klintmalm G, Hemming A, et al. Surgical treatment of hepatocellular carcinoma in North America: can hepatic resection still be justified? *J Am Coll Surg.* 2015;220(4):628-37. PMID: 25728142
39. Zheng Z, Liang W, Milgrom DP, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. *Transplantation.* 2014;97(2):227-34. PMID: 24142034
40. Yadav DK, Chen W, Bai X, et al. Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma. *Annals of transplantation.* 2018;23:524-45. PMID: 30072683
41. Murali AR, Patil S, Phillips KT, et al. Locoregional Therapy With Curative Intent Versus Primary Liver Transplant for Hepatocellular Carcinoma: Systematic Review and Meta-Analysis. *Transplantation.* 2017;101(8):e249-e57. PMID: 28282359
42. Zhu Y, Dong J, Wang WL, et al. Short- and long-term outcomes after salvage liver transplantation versus primary liver transplantation for hepatocellular carcinoma: a meta-analysis. *Transplantation proceedings.* 2013;45(9):3329-42. PMID: 24182812
43. Chan DL, Alzahrani NA, Morris DL, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. *Journal of gastroenterology and hepatology.* 2014;29(1):31-41. PMID: 24117517
44. Li HY, Wei YG, Yan LN, et al. Salvage liver transplantation in the treatment of hepatocellular carcinoma: a meta-analysis. *World journal of gastroenterology : WJG.* 2012;18(19):2415-22. PMID: 22654435
45. Chiche L, David A, Adam R, et al. Liver transplantation for adenomatosis: European experience. *Liver Transpl.* 2016;22(4):516-26. PMID: 26919265

46. Cambridge WA, Fairfield C, Powell JJ, et al. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. *Ann Surg.* 2021;273(2):240-50. PMID: 32097164
47. Lunsford KE, Javle M, Heyne K, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *The lancet Gastroenterology & hepatology.* 2018. PMID: 29548617
48. Hildebrand T, Pannicke N, Dechene A, et al. Biliary strictures and recurrence after liver transplantation for primary sclerosing cholangitis: A retrospective multicenter analysis. *Liver Transpl.* 2016;22(1):42-52. PMID: 26438008
49. Gu J, Bai J, Shi X, et al. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. *International journal of cancer Journal international du cancer.* 2012;130(9):2155-63. PMID: 21387295
50. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology.* 2012;143(1):88-98 e3; quiz e14. PMID: 22504095
51. Panjala C, Nguyen JH, Al-Hajjaj AN, et al. The impact of neoadjuvant chemoradiation on the tumor burden prior to liver transplantation in unresectable cholangiocarcinoma. *Liver Transpl.* 2011. PMID: 22140024
52. Heimbach JK, Gores GJ, Haddock MG, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation.* 2006;82(12):1703-7. PMID: 17198263
53. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg.* 2005;242(3):451-8; discussion 58-61. PMID: 16135931
54. Shimoda M, Farmer DG, Colquhoun SD, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. *Liver Transpl.* 2001;7(12):1023-33. PMID: 11753904
55. Casavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma. *J Am Coll Surg.* 1997;185(5):429-36. PMID: 9358085
56. Weimann A, Varnholt H, Schlitt HJ, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. *Br J Surg.* 2000;87(9):1182-7. PMID: 10971425
57. Pascher A, Jonas S, Neuhaus P. Intrahepatic cholangiocarcinoma: indication for transplantation. *J Hepatobiliary Pancreat Surg.* 2003;10(4):282-7. PMID: 14598146
58. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation.* 2000;69(8):1633-7. PMID: 10836374
59. Robles R, Figueras J, Turrion VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg.* 2004;239(2):265-71. PMID: 14745336
60. Heimbach JK. Successful liver transplantation for hilar cholangiocarcinoma. *Curr Opin Gastroenterol.* 2008;24(3):384-8. PMID: 18408469
61. Wu Y, Johlin FC, Rayhill SC, et al. Long-term, tumor-free survival after radiotherapy combining hepatectomy-Whipple en bloc and orthotopic liver transplantation for early-stage hilar cholangiocarcinoma. *Liver Transpl.* 2008;14(3):279-86. PMID: 18306329
62. Czauderna P, Otte JB, Aronson DC, et al. Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). *Eur J Cancer.* 2005;41:1031-6. PMID: 15862752

63. Hamilton EC, Balogh J, Nguyen DT, et al. Liver transplantation for primary hepatic malignancies of childhood: The UNOS experience. *J Pediatr Surg.* 2017. PMID: 29108844
64. Barrena S, Hernandez F, Miguel M, et al. High-risk hepatoblastoma: results in a pediatric liver transplantation center. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie.* 2011;21(1):18-20. PMID: 20938901
65. Malek MM, Shah SR, Atri P, et al. Review of outcomes of primary liver cancers in children: our institutional experience with resection and transplantation. *Surgery.* 2010;148:778-82; discussion 82-4. PMID: 20728194
66. Browne M, Sher D, Grant D, et al. Survival after liver transplantation for hepatoblastoma: a 2-center experience. *J Pediatr Surg.* 2008;43:1973-81. PMID: 18970927
67. Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. *Surgery.* 2017;162(3):525-36. PMID: 28624178
68. Sher LS, Levi DM, Wecsler JS, et al. Liver transplantation for metastatic neuroendocrine tumors: Outcomes and prognostic variables. *Journal of surgical oncology.* 2015;112(2):125-32. PMID: 26171686
69. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. *HPB : the official journal of the International Hepato Pancreato Biliary Association.* 2015;17(1):23-8. PMID: 24992381
70. Mathe Z, Tagkalos E, Paul A, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. *Transplantation.* 2011;91(5):575-82. PMID: 21200365
71. Gedaly R, Daily MF, Davenport D, et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Arch Surg.* 2011;146(8):953-8. PMID: 21844436
72. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *Journal of hepatology.* 2007;47(4):460-6. PMID: 17697723
73. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334(11):693-9. PMID: 8594428
74. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with synthetic cohort. *AIDS.* 2011;25(6):777-86. PMID: 21412058
75. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl.* 2012;18(6):716-26. PMID: 22328294
76. Blumberg EA, Rogers CC. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical transplantation.* 2019;33(9):e13499. PMID: 30773688
77. Wang X, Li J, Riaz DR, et al. Outcomes of Liver Transplantation for Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2014;12(3):394-402 e1. PMID: 24076414

78. Cholankeril G, Wong RJ, Hu M, et al. Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. *Digestive diseases and sciences.* 2017;62(10):2915-22. PMID: 28744836
79. Sheiner P, Rochon C. Recurrent hepatitis C after liver transplantation. *The Mount Sinai journal of medicine, New York.* 2012;79(2):190-8. PMID: 22499490
80. Gadiparthi C, Cholankeril G, Perumpail BJ, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. *World journal of gastroenterology : WJG.* 2018;24(3):315-22. PMID: 29391754
81. Gao Q, Mulvihill MS, Scheuermann U, et al. Improvement in Liver Transplant Outcomes From Older Donors: A US National Analysis. *Ann Surg.* 2019;270(2):333-39. PMID: 29958229
82. Cascales-Campos PA, Ramirez P, Gonzalez-Sanchez MR, et al. Orthotopic Liver Transplantation With Elderly Donors (Over 80 Years of Age): A Prospective Evaluation. *Transplantation proceedings.* 2018;50(10):3594-600. PMID: 30577243
83. Paterno F, Wima K, Hoehn RS, et al. Use of Elderly Allografts in Liver Transplantation. *Transplantation.* 2016;100(1):153-8. PMID: 26154390
84. Dasari BV, Mergental H, Isaac JR, et al. Systematic review and meta-analysis of liver transplantation using grafts from deceased donors aged over 70 years. *Clinical transplantation.* 2017;31(12). PMID: 29044682
85. Chen HP, Tsai YF, Lin JR, et al. Recipient Age and Mortality Risk after Liver Transplantation: A Population-Based Cohort Study. *PLoS One.* 2016;11:e0152324. PMID: 27019189
86. Jeffrey AW, Jeffrey GP, Stormon M, et al. Outcomes for children after second liver transplantations are similar to those after first transplantations: a binational registry analysis. *Med J Aust.* 2020;213(10):464-70. PMID: 33015834
87. Aguero F, Rimola A, Stock P, et al. Liver Retransplantation in Patients With HIV-1 Infection: An International Multicenter Cohort Study. *Am J Transplant.* 2016;16(2):679-87. PMID: 26415077
88. Abdelfattah MR, Al-Sebayel M, Broering D. An analysis of outcomes of liver retransplant in adults: 12-year's single-center experience. *Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation.* 2015;13 Suppl 1:95-9. PMID: 25894135
89. Bellido CB, Martinez JM, Artacho GS, et al. Have we changed the liver retransplantation survival? *Transplantation proceedings.* 2012;44(6):1526-9. PMID: 22841203
90. Remiszewski P, Kalinowski P, Dudek K, et al. Influence of selected factors on survival after liver retransplantation. *Transplantation proceedings.* 2011;43(8):3025-8. PMID: 21996216
91. Hong JC, Kaldas FM, Kositamongkol P, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. *Ann Surg.* 2011;254(3):444-8; discussion 48-9. PMID: 21817890
92. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *The lancet oncology.* 2012;13(1):e11-22. PMID: 22047762
93. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl.* 2011;17 Suppl 2:S44-57. PMID: 21695773
94. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society

for Pediatric Gastroenterology, Hepatology and Nutrition. *Hepatology.* 2014;60(1):362-98. PMID: 24782219
95. Evaluation for Liver Transplantation in Adults: 2013 practice guideline by the AASLD and the American Society of Transplantation. [cited 5/1/2023]. 'Available from:' https://www.aasld.org/sites/default/files/2019-06/141020_Guideline_Evaluation_Adult_LT_4UFb_2015.pdf.
96. Murray KF, Carithers RL, Jr. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology.* 2005;41(6):1407-32. PMID: 15880505
97. Kelly DA, Bucuvalas JC, Alonso EM, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl.* 2013;19(8):798-825. PMID: 23836431
98. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl.* 2013;19(1):3-26. PMID: 23281277
99. American Association for the Study of Liver Diseases. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. [cited 5/1/2023]. 'Available from:' https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30866.
100. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in OncologyTM. Neuroendocrine and Adrenal Tumors. V2.2022. [cited 5/1/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf.

CODES

Codes	Number	Description
CPT	47133	Donor hepatectomy (including cold preservation) from cadaver donor
	47135	Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into two partial liver grafts (i.e., left lateral segment (segments II and III) and right trisegment (segments I and IV through VIII))
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein,

Codes	Number	Description
		hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into two partial liver grafts (i.e., left lobe (segment II, III, and IV) and right lobe (segments I and V through VIII)
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
HCPCS	None	

Date of Origin: *January 1996*

Regence

Medical Policy Manual Transplant, Policy No. 06

Pancreas Transplant

Effective: November 1, 2023

Next Review: August 2024
Last Review: September 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation of a normal pancreas is a treatment method for patients with diabetes.

MEDICAL POLICY CRITERIA

Note: Islet cell transplantation is considered in a separate medical policy (see Cross References).

I. Pancreas transplant may be considered **medically necessary** when both of the following (A. and B.) are met:
   A. Candidates must meet both of the following general criteria:
      1. Adequate cardiopulmonary status; and
      2. Documentation of patient compliance with medical management.
   B. Transplant for any of the following indications:
      1. A combined pancreas-kidney transplant in diabetic patients with uremia; or
      2. Pancreas transplant after a prior kidney transplant in patients with insulin-dependent diabetes mellitus (IDDM); or

3. Pancreas transplant alone in patients with documentation of any of the following conditions, which persist despite optimal medical management:
    a. Severely disabling and potentially life-threatening hypoglycemia unawareness as evidenced by chart notes or emergency room visits; or
    b. Potentially life-threatening labile diabetes as evidenced by documentation of erratic blood glucose levels and hemoglobin A1c equal to or greater than 8% or hospitalization for diabetic ketoacidosis.

II. Pancreas retransplantation may be considered **medically necessary** after one failed primary pancreas transplant.

III. Pancreas transplantation that does not meet Criterion I. or II. is considered **not medically necessary.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

MULTIPLE TRANSPLANTS

Although there are no standard guidelines regarding multiple pancreas transplants, the following information may aid in case review:

- If there is early graft loss resulting from technical factors (e.g., venous thrombosis), a retransplant may generally be performed without substantial additional risk.
- Long-term graft losses may result from chronic rejection, which is associated with increased risk of infection following long-term immunosuppression, and sensitization, which increases the difficulty of finding a negative cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- Pre-transplant evaluation including pulmonary status and pertinent co-morbidities and treatments
- Failed primary pancreas transplant

CROSS REFERENCES

1. Islet Cell Transplantation, Transplant, Policy No. 13

BACKGROUND

Pancreas transplantation can restore glucose control, and is intended to prevent, halt, or

reverse the secondary complications of insulin-dependent Type 1 diabetes mellitus (IDDM). Achievement of insulin independence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. While pancreas transplantation is generally not considered a life-saving treatment, in a small subset of patients who experience life-threatening complications from IDDM, pancreas transplantation could be considered lifesaving. In addition to the immune rejection issues common to all allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.[1]

Pancreas transplantation occurs in several different scenarios such as:

1. Patient with type 1 diabetes with renal failure who may receive a cadaveric simultaneous pancreas/kidney transplant (SPK)
2. Patient with type 1 diabetes who may receive a cadaveric or living-related pancreas transplant after a kidney transplantation (pancreas after kidney, i.e., PAK)
3. Patient with non-uremic type 1 diabetes with specific severely disabling and potentially life-threatening diabetes related problems who may receive a pancreas transplant alone (PTA).

PTA has also been investigated in patients following total pancreatectomy for chronic pancreatitis. The experience with SPK transplants is more extensive than that of other transplant options.

The approach to retransplantation varies according to the cause of failure. Surgical/technical complications such as venous thrombosis are the leading cause of pancreatic graft loss among patients with diabetes. Graft loss from chronic rejection may result in sensitization, increasing both the difficulty of finding a cross-matched donor and the risk of rejection of a subsequent transplant. Each center has its own guidelines based on experience; some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

EVIDENCE SUMMARY

SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANT

The U.S.-based Organ Procurement and Transplant Network (OPTN) reported a one-year patient survival rate of 97.5% (95% confidence interval [CI] 96.9% to 98.0%) for primary simultaneous pancreas/kidney transplant (SPK) procedures performed between 2008 and 2015.[2] Three- and five-year patient survival rates were 94.8% (95% CI 93.9% to 95.5%) and 88.9% (95% CI 87.8% to 89.9%), respectively.

Martin-Gonzalez (2023) published a retrospective observational study was conducted in two cohorts of SPK recipient patients that underwent surgery between 2001 and 2021.[3] The two cohorts represented an initial protocol (cohort 1; n=32) and an updated protocol (cohort 2; n=23). Average survival was 2546 days (95% CI: 1902-3190) for cohort 1 and 2540 days (95% CI: 2100-3204) for cohort 2 ($p > 0.05$). Pancreatic graft failure-free survival had an average of 1705 days (95% CI: 1037-2373) in cohort 1, lower than the average in cohort 2 (2337 days; 95% CI: 1887-2788) ($p = 0.016$). Similarly, renal graft failure-free survival had an average of 2167 days (95% CI: 1485-2849) in cohort 1, lower than the average in cohort 2 (2583 days; 95% CI: 2159-3006) ($p = 0.017$).

Barlow (2017) analyzed U.K. registry data that compared outcomes in patients with type 1 diabetes and end-stage renal disease who had SPK transplants (n=1739) with live donor kidney transplants (n=370).[4] In multivariate analysis, there was not a significant association between type of transplant and patient survival (HR [hazard ratio] 0.71, 95% CI 0.47 to 1.06; p=0.095). SPK recipients with a functioning pancreas graft had significantly better overall survival than those with a living donor kidney transplant (p<0.001).

Pancreas transplant has been found to improve mortality in patients with type 1 diabetes. Van Dellen (2014) reported a retrospective analysis of data on 148 SPK patients and a wait-list control group of 120 patients.[5] The study also included 33 patients who had PAK and 11 PTA patients. All patients had uncomplicated type 1 (insulin dependent) diabetes. Overall mortality was 30% (30/120 patients) on the waiting list and patients who underwent transplantation had a mortality rate of 9% (20/193 patients); the difference between groups was statistically significant (p<0.001). One-year mortality was 13% (n=16) on the waiting list and 4% (n=8) in the transplant group (p<0.001).

There are some data on outcomes in patients with type 2 compared with type 1 diabetes. Sampaio (2011) published an analysis of data from the United Network for Organ Sharing (UNOS) database.[6] The investigators compared outcomes in 6,141 patients with type 1 diabetes and 582 patients with type 2 diabetes who underwent SPK between 2000 and 2007. In adjusted analyses, outcomes were similar in the two groups. After adjusting for other factors such as body weight; dialysis time; and cardiovascular comorbidities, type 2 diabetes was not associated with an increased risk of pancreas or kidney graft survival or mortality compared to type 1 diabetes.

Mora (2010) described the long-term outcome of 12 patients 15 years following SPK transplant.[7] Metabolic measures of glucose control were measured at 1, 5, 10, and 15 years following the procedure. Of this subset of patients, six (50%) had non-diabetic glucose challenge tests. Basal serum insulin levels declined over this period as well, from 24 mU/L to 16 mU/L at 1 and 15 years, respectively. The authors concluded that in a select group of patients whose pancreatic graft continued to function after 15 years, some glycemic control continued, albeit in a diminished fashion. It should be noted that this represented a small fraction of the 367 patients receiving the SPK transplant at this single center (12 of 367 SPK; 3.3%). The number of allograft survivals at five or more, and 10 or more years in this study was 43 (11.7%) and 28 (7.6%), respectively.

The improved glycemic control that may occur in SPK transplant patients, principally in those with labile disease while on medical therapy alone, is purported to reduce risk of complications from diabetes. Davenport (2009) published results of a registry review (n=58) on cardiovascular risk factors in an Irish study of SPK transplant recipients.[8] Glycosylated hemoglobin values fell from a mean of 8.1 to 5.2 (p<0.0001) from pre-transplant levels. Similar statistically significant declines were seen in total cholesterol, triglycerides, and creatinine. Systolic and diastolic blood pressures were likewise improved but with a greater range of pre- and post-transplant variability. These endpoints are commonly accepted as surrogates for cardiovascular risk. The authors compared both a surgical method (bladder vs. enteric drainage) and mode of immunosuppression (cyclosporine vs. tacrolimus) on changes to blood pressure and cholesterol. No significant differences were found in either measure based on surgical drainage method, nor did immunosuppressive therapy have an impact on blood pressure reduction. Cholesterol reduction was greater in the cyclosporine than the tacrolimus group (-1.3 to -0.2, respectively), favoring the less contemporary strategy. The authors noted

that this was in contrast to other recently published studies favoring both enteric drainage and tacrolimus. While this single arm study suggested beneficial cardiovascular effects from transplant, other factors such as rejection rates were more likely to influence the conditions under which transplantations took place.

PANCREAS AFTER KIDNEY TRANSPLANT[9]

Parajuli (2019) described a single center's experience with 635 pancreas and kidney transplant patients (611 SPK, 24 PAK).[10] Transplants were performed between 2000 and 2016. The mean length of time between kidney transplant and pancreas transplant was 23.8 months in the PAK group. Pancreas rejection rates at one-year post-transplant were 4% and 9% with PAK and SPK respectively. During the entire study period, PAK patients were more likely to experience pancreas rejection (38% vs. 16%; p=0.005). Kidney and pancreas graft survival rates did not differ between groups at one year or at last follow-up. Pancreas graft survival rates for PAK and SPK at one year were 100% and 89%, respectively (p=0.09). Death-censored pancreas graft failure rates for PAK and SPK at last follow-up were 13% and 25%, respectively (p=0.17). Patient survival at last follow-up was similar between groups (71% with PAK vs. 68% with SPK; p=0.79).

Gruessner (2016) reported updated patient survival rates for pancreas after kidney (PAK) transplants. According to UNOS and International Registry data, patient survival after PAK from 2010 to 2014 was 97.9% after one year and 94.5% after three years.[11] This compares with one-year and three-year patient survival rates for 2005 to 2009 of 96.4% and 93.1%, respectively.

PAK transplantation allows the uremic patient the benefits of a living-related kidney graft, if available, and the benefits of a subsequent pancreas transplant that is likely to result in improved quality of life compared to a kidney transplant alone. Uremic patients for whom a cadaveric kidney graft is available, but a pancreas graft is not simultaneously available benefit similarly from a later pancreas transplant. Based on international pancreas registry data, at five years post-transplant, the patient survival rate after PAK is 83%.[12]

Bazerbachi (2012) reviewed a single center’s experience with PAK and synchronous pancreas-kidney (SPK) transplantations.[13] Between 2002 and 2010, 172 pancreas transplants were performed in diabetic patients; 123 SPK and 49 PAK. The median length of time between kidney and pancreas transplantation in the PAK group was 4.8 years. Graft and patient survival rates were similar in the two groups. Death-censored pancreas graft survival rates for SPK and PAK were 94% and 90% at one year, 92% and 90% at three years, and 85% and 85% at five years (all respectively, p=0.93). Patient survival rates (calculated beginning at the time of pancreas transplantation) in the SPK versus PAK groups were 98.3% and 100% after one year, 96.4% and 100% after three years, and 94.2% and 100% after five years (all respectively, p=0.09).

Fridell (2009) reported a retrospective review (n=203) of a single center’s experience with PAK and SPK since 2003, when current induction/tacrolimus immunosuppressive strategies became standard.[14] Of the cases studied, 61 (30%) were PAK and 142 (70%) were SPK. One-year patient survival rates were 98% and 95% (PAK and SPK, respectively; p=0.44). Pancreas graft survival rates at one year were observed to be 95% and 90%, respectively (p=0.28). The authors conclude that in the modern immunosuppressive era, PAK should be considered as an acceptable alternative to SPK in candidates with an available living kidney donor.

Kleinclauss (2009) retrospectively examined data from diabetic kidney transplant recipients (n=307) from a single center and compared renal graft survival rates in those who subsequently received a pancreatic transplant to those who did not.[15] The comparative group was analyzed separately depending on whether they were medically eligible (KTA-E) for pancreas transplant, but chose not to proceed for financial or personal reasons, or were ineligible (KTA-I) for medical reasons. The KTA-I (n=57) group differed significantly at baseline from both the PAK group (n=175) and the KTA-E group (n=75) with respect to age, type of diabetes and dialysis experience; kidney graft survival rates were lower than either of the other groups, with 1-, 5-, and 10-year rates of 75%, 54%, and 22%, respectively (p<0.0001). The PAK and KTA-E groups were similar in age, race, type of diabetes, and dialysis experience. The authors compared 1-, 5-, and 10-year kidney graft survival rates in PAK patients with those in the KTA-E group: 98%, 82%, and 67% versus 100%, 84%, and 62%, respectively, and concluded that the subsequent transplant of a pancreas after a living donor kidney transplant did not adversely affect patient or kidney graft survival rates.

PANCREAS TRANSPLANT ALONE[9]

Boggi (2021) reported results of a single-center cohort study of 66 patients with type 1 diabetes who received PTA.[16] After 10 years of follow-up, patient survival was 92.4%. Of these patients surviving to 10 years, 57.4% had optimal graft function (defined as normoglycemia and insulin independence) and 3.2% had good graft function (defined as HbA1c <7%, no severe hypoglycemia, >50% reduction in insulin requirements, and restoration of clinically significant C-peptide production). Four patients (6.0%) developed end-stage renal failure (stage 5, estimated glomerular filtration rate [eGFR] < 15 ml/min/1.73 m2), and 2 additional patients (3.0%) showed stage 4 kidney failure (eGFR 15-30 ml/min/1.73 m2) at the 10-year posttransplant assessment.

Gruessner and Gruessner (2016) reported updated patient survival rates for PTA.[11] According to UNOS and the International Registry data, for the period of 2010 to 2014, patient survival after PTA was 96.3% after one year and 94.9% after three years. This compares with one-year and three-year patient survival rates of 97.5% and 93.3% for 2005 to 2009, respectively.

According to international registry data one-year graft function increased from 51.5% in 1987-1993 to 77.8% in 2006-2010 (p<0.0001).[12] One-year immunologic graft loss remains higher (6%) after PTA than PAK (3.7%) or SPK (1.8%). In carefully selected IDDM patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile diabetes that persists despite optimal medical management, the benefits of PTA were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression. The majority of patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where non-uremic IDDM patients have significant morbidity risks due to secondary complications of diabetes (e.g., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because there is virtually no published evidence regarding outcomes of medical management in this very small group of exceptional diabetic patients, it is not possible to generalize about which circumstances represent appropriate indications for pancreas transplantation alone. Case-by-case consideration of each patient's clinical situation may be the best option for determining the balance of risks and benefits.

Noting that nephrotoxic immunosuppression may exacerbate diabetic renal injury after PTA,

Scalea (2008) reported a single institutional review of 123 patients who received 131 PTA for development of renal failure.[17] Mean graft survival was 3.3 years (range, 0 to 11.3), and 21 patients were lost to follow-up. Mean estimated glomerular filtration rate (eGFR) was 88.9 pre-transplantation versus 55.6 post-transplantation, with mean follow-up of 3.7 years. All but 16 patients had a decrease in eGFR, and mean decrement was 32.1 mg/min/1.73. Thirteen developed end-stage renal disease, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA. Future updates of this policy will continue to follow this clinical topic.

PANCREAS RETRANSPLANTATION[18]

Parajuli (2019) compared outcomes among SPK patients who did or did not receive pancreas retransplantation after isolated pancreas graft failure.[19] Among 109 SPK patients with pancreas graft failure, 25 underwent pancreas retransplantation and 84 did not. Mean follow-up time after pancreas graft failure was longer among patients who underwent pancreas retransplantation (7.6 years vs. 4.6 years). Rates of death-censored kidney graft failure at last follow-up were lower among patients who underwent pancreas retransplantation (24% vs. 48%; p=0.04). However, given the retrospective nature of the study, selection bias may have influenced the observed outcomes. Patient survival was not significantly different between groups. Among patients who underwent retransplantation, one-year pancreas graft survival was 84%.

Rudolph (2015) reported higher graft survival rates, but not patient survival rates, after primary transplant.[20] A total of 2145 pancreas transplants were performed, 415 (19%) of which were retransplants. Death-censored graft survival at one year was 88.2% in initial transplants and 75% in retransplants (p=0.06).

Fridell (2015) reported on 441 initial transplants and 20 late transplants.[21] One-year graft survival rates were 92% after initial transplant and 90% after retransplant (p=0.48). Similarly, one-year patient survival rates were 96% after initial transplants and 95% after retransplants (p=0.53).

Siskind (2015) published the largest comparative study to date which included long-term outcomes for 1149 retransplant patients and 19,705 primary transplant patients.[22] Patient data was collected from the UNOS database (1996-2012) and PAK, PTA, PWK and SPK patients were included in the analysis. Adjusted patient survival rates were compared at 1-, 3-, 5-, 10-, and 15-year follow-up. Analysis of 30-day retransplantation outcomes was not performed due to small sample size. Graft survival was significantly worse in the retransplant group compared to primary transplant at all follow-up points, for all transplant types:

Table 1: Graft Survival

Graft Survival	Primary Transplant, %	Retransplant, %	P
1 year	85.44	37.16	<0.0001
3 year	76.86	21.93	<0.0001
5 year	69.23	14.45	<0.0001
10 year	52.26	2.79	<0.0001
15 year	36.96	0.17	<0.0001

Table 2: Patient Survival

Patient Survival	Primary Transplant, %	Retransplant, %	P
1 year	94.83	98.99	<0.0001
3 year	90.20	96.67	<0.0001
5 year	85.41	93.19	<0.0001
10 year	71.85	79.80	<0.0001
15 year	58.86	54.93	<0.0001

Authors speculated that the improved survival rates in the retransplantation group could be attributed to retransplantation of the kidney with the pancreas versus pancreas alone; however, subgroup analysis did not support this hypothesis. These study findings significantly differ from previous nonrandomized comparative studies which have indicated pancreas retransplantation has comparable graft survival rates to primary transplant.

The OPTN has reported data on transplants performed between 2008 and 2015.[2] Patient survival rates after repeat transplants were similar to survival rates after primary transplants. For example, the one-year survival rate was 91.0% (95% CI, 88.7% to 92.8%) after a primary pancreas transplant and 96.4% (95% CI, 92.1% to 98.4%) after a repeat pancreas transplant. The numbers of patients transplanted were not reported, but OPTN data stated that 663 patients were alive one year after primary transplant and 154 after repeat transplants. The three-year patient survival rate was 87.5% (95% CI, 85.1% to 89.6%) after primary transplants and 91.2% (95% CI, 86.2% to 94.4%) after repeat transplants. The five-year patient survival rate was 79.9% (95% CI, 77.4% to 82.2%) after primary transplants and 83.7% (95% CI, 78.2% to 88.0%) after repeat transplants. The one-year graft survival rate was 81.8% (95% CI, 78.9% to 84.3%) after primary pancreas transplant and 77.7% (95% CI, 70.8% to 83.1%) after repeat transplant.

Data are similar for patients receiving SPK transplants, but follow-up data are only available on a small number of patients who had repeat SPK transplants, so estimates of survival rates in this group are imprecise. Three-year patient survival rate was 94.8% (95% CI, 93.9% to 95.5%) after primary SPK transplant and 87.9% (95% CI, 73.4% to 94.8%) after a repeat SPK transplant. The number of patients living 3 years after transplant was 2871 after a primary combined procedure and 36 after a repeat combined procedure.

Seal (2014) reported on 96 consecutive PTA patients treated at a single center in Canada; 78 were initial transplants, and 18 were retransplants.[23] Pancreas graft survival was similar for primary transplants and retransplants at one year (88% vs 100%, p=0.88) and three years (85% in both groups, p=0.99). Patient survival rates were also similar in the two groups at one year (96% and 100%, p=0.95) and three years (93% and 100%, p=0.93).

Buron (2013) reported on their experience with pancreas retransplantation in France and Geneva.[24] Between 1976 and 2008, 568 pancreas transplants were performed at two centers, including 37 repeat transplants. Patient survival after a repeat pancreas transplant was 100% after one year and 89% after five years. Graft survival was 64% at one year and 46% at five years. Among the 17 patients who underwent a second transplant in a later time period i.e., between 1995 and 2007, graft survival was 71% at one year and 59% at five years. In this more recently transplanted group, graft survival rates were similar to primary pancreas transplants which was 79% at one year and 69% at five years.

Studies for pancreatic retransplantation are limited to retrospective reviews and non-randomized feasibility studies. The evidence for graft and patient survival following the first retransplantation of the pancreas following PAK, PTA, or SPK transplantation has shown

outcomes similar to primary transplantation.[20, 25-29] No clinical trials were found that reported survival outcomes following more than one retransplantation.

HIV+ TRANSPLANT RECIPIENTS

The Organ Procurement Transfer Network (OPTN) permits HIV test positive patients as organ candidates if permitted by the transplant hospital.[25]

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[30] For kidney-pancreas transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 count >200 cells/mL for at least 3 months (insufficient data to recommend for or against transplantation in patients with counts >100 cells/mL and no history of opportunistic infection)
- Undetectable HIV viral load while receiving antiretroviral therapy
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring
- The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled hepatitis B infection may be considered for transplant. Caution is recommended in hepatitis C-coinfected patients who have not been initiated on direct acting antiviral therapy.

A retrospective analysis of all deceased donor pancreas transplants performed in the U.S. between 1988 and 1999 revealed that since the mid-1990's allograft half-lives ranged from eight to nine years for PTA transplants to nearly 13 years for SPK transplants.[31] The data indicates that insulin-independence with functioning grafts can been achieved for longer than 20 years.

AGE

In the past 5 to 10 years, several analyses of outcomes by patient age group have been published and there is now general agreement among experts that age should not be a contraindication; however, age-related comorbidities are important to consider when selecting patients for transplantation.

Siskind (2014) used data from the United Network for Organ Sharing (UNOS) database to publish the largest study of pancreas outcomes by recipient age.[32] Investigators included all adult patients who received SPK or PTA between 1996 and 2012 (n=20,854). There were 3160 patients between the ages of 50 and 59 years, and 280 patients age 60 or older. Overall, Kaplan-Meier survival analysis found statistically significant differences in patient survival ($p<0.001$) and graft survival ($p<0.001$) among age categories. Graft survival was lowest in the 18- to-29 age group at 1, 5, and 10 years, which the authors noted might be due to early immunological graft rejection due to more robust immune responses. However, 10 and 15 year graft survival was lowest in the 60 and older age group. Patient survival rates decreased with increasing age, and the differential between survival in older and younger ages increased with

longer follow-up intervals. Lower survival rates in patients 50 and older could be due in part to comorbidities at the time of transplantation. Also, as patient age, they are more likely to die from other causes. Still, patient survival at 5 and 10 years was relatively high, as shown in Table 3.

Table 3: Patient Survival by Age Group[32]

	Age 18-29, %	Age 30-39, %	Age 40-49, %	Age 50-59, %	Age 60+, %
1 year	95.4	96.0	94.9	93.3	91.0
5 years	86.3	87.8	85.7	81.6	71.4
10 years	73.5	76.8	71.8	61.5	42.5

Shah (2013) reviewed data on 405 patients who underwent PTA between 2003 and 2011.[33] One-year patient survival was 100% for patients younger than age 30, 98% for patients age 30 to 39 years, 94% for patients 40 to 49 years, 95% for patients 50 to 59 years and 93% for patients age 60 or older. There was not a statistically significant difference in the rate of patient survival by age (p=0.38). Findings were similar for one-year graft survival; there was not a statistically significant difference in outcomes by age of the transplant recipients (p=0.10).

Afaneh (2011) reviewed data on 17 individuals at least 50-years-old and 119 individuals younger than 50 who had a pancreas transplant at a single institution in the U.S.[34] The two groups had similar rates of surgical complications, acute rejection and non-surgical infections. Overall patient survival was similar. Three- and five-year survival rates were 93% and 90% in the younger group and 92% and 82% in the older group.

Schenker (2011) in Germany compared outcomes in 69 individuals at least 50-years-old and 329 individuals younger than 50 years who had received a pancreas transplant.[35] Mean duration of follow-up was 7.7 years. One-, five-, and 10-year patient and graft survival rates were similar in the two groups. For example, the five-year patient survival rate was 89% in both groups. The five-year pancreas grant survival rate was 76% in the older group and 72% in the younger group. The authors of both studies, as well as the authors of a commentary accompanying the Schenker article,[36] agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

PRACTICE GUIDELINE SUMMARY

AMERICAN DIABETES ASSOCIATION

The American Diabetes Association (ADA) Position Statement made the following recommendations on kidney and pancreas transplantation for patients with type 1 diabetes:[37]

- “Consider solid organ pancreas transplantation simultaneously with kidney transplantation in patients with type 1 diabetes who have an indication for kidney transplantation and are poorly controlled with large glycemic excursions. (B)”
- “Consider solid organ pancreas transplantation after kidney transplantation in adult patients with type 1 diabetes who have already received a kidney transplant. (C)”
- “Judiciously consider solid organ pancreas transplantation alone in adults with type 1 diabetes, unstable glucose control, hypoglycemia unawareness, and an increased risk of diabetes-related mortality, who have attempted all of the more traditional approaches to glycemic control and have remained unsuccessful, yet are judged responsible enough to manage the antirejection medication regimen, risks, and follow-up required with an organ transplant. (C)”

ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK

The Board of Directors of the Organ Procurement and Transplantation Network (OPTN) issues an updated comprehensive list of transplant related policies regularly, most recently June 2023.[25]

Each candidate registered on the pancreas waiting list must meet *one* of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency
- Require the procurement or transplantation of a pancreas as part of a multiple organ transplant for technical reasons

Each candidate registered on the kidney-pancreas waiting list must meet *one* of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency, with renal insufficiency

In addition, waiting time criteria indicated that for kidney-pancreas transplant candidates 18 years and older, candidates must meet *all* of the following conditions:

1. The candidate is registered for a kidney-pancreas.
2. The candidate qualifies for kidney waiting time according to *Policy 8.4: Waiting Time*.
3. The candidate is on insulin.

The OPTN policy also delineated pancreas, kidney-pancreas, and islet allocation, classifications, and rankings.

SUMMARY

SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION (SPK)

There is enough research to show that simultaneous pancreas kidney (SPK) improves outcomes (e.g., normalizes insulin production and kidney function, improves quality of life, and improves diabetic complications) for patients with diabetes. Therefore, SPK transplantation for patients with diabetes may be medically necessary when policy criteria are met.

PANCREAS AFTER KIDNEY TRANSPLANT (PAK)

There is enough research to show that pancreas after kidney transplant (PAK) improves health outcomes for patients with diabetes. The International Pancreas Transplant Registry provides information that PAK improves health outcomes in some patients with diabetes who have previously received a successful kidney transplant. Therefore, PAK transplantation for patients with diabetes may be considered medically necessary when policy criteria are met.

PANCREAS TRANSPLANT ALONE (PTA)

There is enough research to show that pancreas transplantation improves health outcomes including quality of life and reduce short complications for patients with diabetes. Therefore,

pancreas transplantation for patients with diabetes that have conditions which persist after optimal medical management may be considered medically necessary when policy criteria are met.

RETRANSPLANTATION

There is enough research to show that the health outcomes for pancreas retransplantation recipients appear similar to those reported for initial transplants. Therefore, retransplantation after one failed primary pancreas transplant may be considered medically necessary when policy criteria are met.

There is not enough research to show that a third or subsequent pancreas transplant improves health outcomes and there are documented safety concerns. Therefore, a third or subsequent pancreas transplant including simultaneous kidney-pancreas transplant, pancreas after kidney transplant, or pancreas alone transplant are considered not medically necessary when policy criteria are not met.

REFERENCES

1. Hirshberg B. The cardinal features of recurrent autoimmunity in simultaneous pancreas-kidney transplant recipients. *Curr Diab Rep.* 2010;10(5):321-2. PMID: 20640940
2. Organ Procurement and Transplantation Network (OPTN). National Data. [cited 09/12/2023]. 'Available from:' https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
3. Martin-González ID, Barrera-Lozano LM, Villada-Ochoa OA, et al. Comparison of Outcomes and Survival of Two Cohorts of Patients with Simultaneous Pancreas-Kidney Transplantation: A Retrospective Cohort Study in a Latin American Hospital. *Biomed Res Int.* 2023;2023:2734072. PMID: 37359049
4. Barlow AD, Saeb-Parsy K, Watson CJE. An analysis of the survival outcomes of simultaneous pancreas and kidney transplantation compared to live donor kidney transplantation in patients with type 1 diabetes: a UK Transplant Registry study. *Transplant international : official journal of the European Society for Organ Transplantation.* 2017. PMID: 28319322
5. van Dellen D, Worthington J, Mitu-Pretorian OM, et al. Mortality in diabetes: pancreas transplantation is associated with significant survival benefit. *Nephrol Dial Transplant.* 2013;28:1315-22. PMID: 23512107
6. Sampaio MS, Kuo HT, Bunnapradist S. Outcomes of simultaneous pancreas-kidney transplantation in type 2 diabetic recipients. *Clinical journal of the American Society of Nephrology : CJASN.* 2011;6(5):1198-206. PMID: 21441123
7. Mora M, Ricart MJ, Casamitjana R, et al. Pancreas and kidney transplantation: long-term endocrine function. *Clin Transplant.* 2010;24(6):E236-40. PMID: 20529096
8. Davenport C, Hamid N, O'Sullivan EP, et al. The impact of pancreas and kidney transplant on cardiovascular risk factors (analyzed by mode of immunosuppression and exocrine drainage). *Clin Transplant.* 2009;23(5):616-20. PMID: 19732096
9. TEC Assessment 1998. "Pancreas Transplantation." BlueCross BlueShield Association Technology Evaluation Center, Vol. 13, Tab 7.

10. Parajuli S, Arunachalam A, Swanson KJ, et al. Outcomes after simultaneous kidney-pancreas versus pancreas after kidney transplantation in the current era. *Clin Transplant.* 2019;33(12):e13732. PMID: 31628870
11. Gruessner AC, Gruessner RW. Pancreas Transplantation of US and Non-US Cases from 2005 to 2014 as Reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). *The review of diabetic studies : RDS.* 2016;13(1):35-58. PMID: 26982345
12. Gruessner AC. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *The review of diabetic studies : RDS.* 2011;8(1):6-16. PMID: 21720668
13. Bazerbachi F, Selzner M, Marquez MA, et al. Pancreas-after-kidney versus synchronous pancreas-kidney transplantation: comparison of intermediate-term results. *Transplantation.* 2013;95(3):489-94. PMID: 23183776
14. Fridell JA, Mangus RS, Hollinger EF, et al. The case for pancreas after kidney transplantation. *Clin Transplant.* 2009;23(4):447-53. PMID: 19453642
15. Kleinclauss F, Fauda M, Sutherland DE, et al. Pancreas after living donor kidney transplants in diabetic patients: impact on long-term kidney graft function. *Clin Transplant.* 2009;23(4):437-46. PMID: 19496790
16. Boggi U, Baronti W, Amorese G, et al. Treating Type 1 Diabetes by Pancreas Transplant Alone: a Cohort Study on Actual Long-Term (10 Years) Efficacy and Safety. *Transplantation.* 2021. PMID: 33909390
17. Scalea JR, Butler CC, Munivenkatappa RB, et al. Pancreas transplant alone as an independent risk factor for the development of renal failure: a retrospective study. *Transplantation.* 2008;86(12):1789-94. PMID: 19104423
18. TEC Assessment 2001. "Pancreas Retransplantation." BlueCross BlueShield Association Technology Evaluation Center, Vol. 16, Tab 23.
19. Parajuli S, Arunachalam A, Swanson KJ, et al. Pancreas Retransplant After Pancreas Graft Failure in Simultaneous Pancreas-kidney Transplants Is Associated With Better Kidney Graft Survival. *Transplantation direct.* 2019;5(8):e473. PMID: 31576369
20. Rudolph EN, Finger EB, Chandolias N, et al. Outcomes of pancreas retransplantation. *Transplantation.* 2015;99(2):367-74. PMID: 25594555
21. Fridell JA, Mangus RS, Chen JM, et al. Late pancreas retransplantation. *Clin Transplant.* 2015;29(1):1-8. PMID: 25284041
22. Siskind E, Maloney C, Jayaschandaran V, et al. Pancreatic Retransplantation Is Associated With Poor Allograft Survival: An Update of the United Network for Organ Sharing Database. *Pancreas.* 2015;44(5):769-72. PMID: 25931257
23. Seal J, Selzner M, Laurence J, et al. Outcomes of pancreas retransplantation after simultaneous kidney-pancreas transplantation are comparable to pancreas after kidney transplantation alone. *Transplantation.* 2015;99(3):623-8. PMID: 25148379
24. Buron F, Thaunat O, Demuylder-Mischler S, et al. Pancreas retransplantation: a second chance for diabetic patients? *Transplantation.* 2013;95(2):347-52. PMID: 23222920
25. Organ Procurement and Transplantation Network (OPTN) Policies. [cited 09/12/2023]. 'Available from:' https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.
26. LaMattina JC, Sollinger HW, Becker YT, et al. Simultaneous pancreas and kidney (SPK) retransplantation in prior SPK recipients. *Clin Transplant.* 2012;26(3):495-501. PMID: 22032238
27. Hollinger EF, Powelson JA, Mangus RS, et al. Immediate retransplantation for pancreas allograft thrombosis. *American journal of transplantation : official journal of the American*

Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(4):740-5. PMID: 19298453
28. Genzini T, Crescentini F, Torricelli FC, et al. Pancreas retransplantation: outcomes of 20 cases. *Transplantation proceedings.* 2006;38(6):1937-8. PMID: 16908328
29. Stratta RJ, Lowell JA, Sudan D, et al. Retransplantation in the diabetic patient with a pancreas allograft. *American journal of surgery.* 1997;174(6):759-62; discussion 63. PMID: 9409613
30. Blumberg EA, Rogers CC. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33(9):e13499. PMID: 30773688
31. Sutherland DE, Gruessner AC. Long-term results after pancreas transplantation. *Transplantation proceedings.* 2007;39(7):2323-5. PMID: 17889177
32. Siskind E, Maloney C, Akerman M, et al. An analysis of pancreas transplantation outcomes based on age groupings--an update of the UNOS database. *Clin Transplant.* 2014;28(9):990-4. PMID: 24954160
33. Shah AP, Mangus RS, Powelson JA, et al. Impact of recipient age on whole organ pancreas transplantation. *Clin Transplant.* 2013;27(1):E49-55. PMID: 23228216
34. Afaneh C, Rich BS, Aull MJ, et al. Pancreas transplantation: does age increase morbidity? *Journal of transplantation.* 2011;2011:596801. PMID: 21766007
35. Schenker P, Vonend O, Kruger B, et al. Long-term results of pancreas transplantation in patients older than 50 years. *Transplant international : official journal of the European Society for Organ Transplantation.* 2011;24(2):136-42. PMID: 21039944
36. Gruessner AC, Sutherland DE. Access to pancreas transplantation should not be restricted because of age: invited commentary on Schenker et al. *Transplant international : official journal of the European Society for Organ Transplantation.* 2011;24(2):134-5. PMID: 21208293
37. Chiang JL, Kirkman MS, Laffel LM, et al. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care.* 2014;37(7):2034-54. PMID: 24935775

CODES

Codes	Number	Description
CPT	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomosis from the iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
HCPCS	S2065	Simultaneous pancreas kidney transplantation
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

Date of Origin: *January 1996*

Regence

Medical Policy Manual Transplant, Policy No. 08

Lung and Lobar Lung Transplant

Effective: June 1, 2023

Next Review: March 2024
Last Review: April 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A lung transplant consists of replacing all or part of diseased lungs with healthy lung(s). Transplantation is an option for patients with end-stage lung disease.

MEDICAL POLICY CRITERIA

I. Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy.

II. A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease.

III. Lung or lobar lung retransplantation after a failed lung or lobar lung transplant may be considered **medically necessary** in patients who meet either criterion I or II.

IV. Lung or lobar lung transplantation is considered **not medically necessary** in all other situations.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

End-stage pulmonary disease may include, but is not limited to, the following diagnoses:

- Alpha-1 antitrypsin deficiency
- Bilateral bronchiectasis
- Bronchiolitis obliterans
- Bronchopulmonary dysplasia
- Chronic obstructive pulmonary disease
- Cystic fibrosis (both lungs to be transplanted)
- Eisenmenger's syndrome
- Emphysema
- Eosinophilic granuloma
- Idiopathic/interstitial pulmonary fibrosis
- Lymphangiomyomatosis
- Postinflammatory pulmonary fibrosis
- Primary pulmonary hypertension
- Pulmonary hypertension due to cardiac disease
- Recurrent pulmonary embolism
- Sarcoidosis
- Scleroderma

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Heart/Lung Transplant, Transplant, Policy No. 3

BACKGROUND

End-stage lung disease may be the consequence of a number of different conditions. The most common indications for lung transplantation are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. Prior to the consideration for transplant, patients should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung-volume reduction surgery for COPD. Lung or lobar lung transplantation is an option for patients with end-stage lung disease despite these measures.

A lung transplant refers to single-lung or double-lung replacement. In a single-lung transplant, only one lung from a deceased donor is provided to the recipient. In a double-lung transplant, both the recipient's lungs are removed and replaced by the donor's lungs. In a lobar transplant, a lobe of the donor's lung is excised, sized appropriately for the recipient's thoracic dimensions, and transplanted. Donors for lobar transplant have primarily been living-related

donors, with one lobe obtained from each of two donors (e.g., mother and father) in cases for which bilateral transplantation is required. There are also cases of cadaver lobe transplants. Combined lung-pancreatic islet cell transplant is being studied for patients with cystic fibrosis.[1]

Potential recipients who are 12 years of age and older are ranked according to the Lung Allocation Score (LAS).[2] A score may range between 1 and 100 and incorporates predicted survival after transplantation and predicted survival on the waiting list; the LAS takes into consideration the patient's disease and clinical parameters. Waiting list incorporates the LAS, geography, and blood type classifications. Children younger than age 12 years old receive a priority for lung allocation. Under this system, children younger than 12 years old with respiratory lung failure and/or pulmonary hypertension who meet criteria are considered "priority 1" and all other candidates in the age group are considered "priority 2." A lung review board has the authority to adjust scores on appeal for adults and children.

EVIDENCE SUMMARY

Due to the nature of the population, there are no randomized controlled trials (RCTs) that compare lung transplantation with alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, or immunosuppressive therapy and are not germane to this policy. Therefore, the following is a summary of the evidence based on registries, case series, and expert opinion.

SURVIVAL

The Registry of the International Society for Heart and Lung Transplantation (ISHLT) contains data from 49,453 adult recipients who received lung transplantation (including lung retransplantation) through June 30, 2015, at 134 transplant centers.[3] A total of 55,795 lung transplants were performed, of which 53,522 (95.9%) were primary transplants and 2,273 (4.1%) were retransplants. The overall median survival of patients who underwent lung transplantation was 5.8 years. Estimated unadjusted survival rates were 89% at three months, 80% at one year, 65% at five years, and 32% at 10 years. Patients who survived a year after primary transplantation had a median survival of 8.0 years. In the first 30 days after transplantation, the major reported causes of mortality were graft failure (24.5%) and non-cytomegalovirus (CMV) infections (19.1%), while non-CMV infections became the major cause of death for the remainder of the first year. Beyond the first year, the most common reported causes of mortality were obstructive bronchiolitis/bronchiolitis obliterans syndrome (OB/BOS), graft failure, and non-CMV infections. Beyond 10 years post-transplant, the major causes of mortality were OB/BOS (21.5%), non-CMV infection (16.5%) and non-lymphoma malignancy (13.7%).

The ISHLT registry contains a total of 2,229 pediatric lung transplants performed through 2014.[4] Most transplants (73%) were done in older children between the ages of 11 to 17 years. Median survival in children who underwent lung transplantation was 5.4 years, similar to survival in adults (mean survival, 5.7 years). However, median survival in children was lower (2.2 years) than in adults (5.6 years) for single-lung transplants.

Black (2014) published results from an analysis of lung transplants using data from the United Network for Organ Sharing's (UNOS) Scientific Registry of Transplant Recipients from 1994 to June 2012.[5] The goal of the analysis was to evaluate how survival was affected in patients who had a high lung allocation score (LAS) and received a single versus a double lung

transplant. In all, there were 8,778 patients identified; however, just 8,050 had a LAS less than 75, and 728 has a LAS greater than or equal to 75. Kaplan-Meier survival curves stratified by high and low LAS, and by single versus double lung transplants, showed a significant decrease in survival ($p<0.001$) in those with a high LAS who received a single lung transplant when compared with those with a high LAS who received a double lung transplant. The authors, that despite a higher operative morbidity, patients who had a high LAS did substantially better in terms of survival if two lungs were transplanted rather than only one, with a larger difference in survival than for patients with a lower LAS.

Yu (2019) compared double-lung with single-lung transplantations for outcomes of survival, pulmonary function, surgical indicators, and complications in a meta-analysis of 30 studies (n=1,980 recipients of single-lung transplants and n=2,112 recipients of double-lung transplants).[6] Overall survival, in-hospital mortality, and postoperative complications besides bronchiolitis obliterans syndrome were similar between the two groups. Recipients of double-lung transplants had lower rates of bronchiolitis obliterans syndrome, better postoperative lung function, improved long-term survival, while recipients of single-lung transplants spent less time in surgery, postoperative intensive care unit, and postoperative hospital stay.

Thabut (2009) reported on a comparison of patients undergoing single- and double-lung transplantation for idiopathic pulmonary fibrosis.[7] A retrospective review was conducted of 3,327 patients with data in the UNOS registry. More patients underwent single-lung as compared to double-lung transplant (64.5 vs. 35.5%, respectively). Median survival time was greater for the double-lung group at 5.2 years (95% CI 4.3 to 6.7 years) versus 3.8 years (95% CI 3.6 to 4.1 years, $p<0.001$). After adjustment for baseline differences, however, survival times were not statistically different. The authors concluded that overall survival did not differ between the two groups: single-lung transplants offered improved short-term survival but long-term harm, whereas double-lung transplant increased short-term harm but was associated with a long-term survival benefit. Later, Black (2014) reported on the LAS and single- versus double-lung transplant in 8,778 patients (8,050 had an LAS less than 75 and 728 had an LAS of 75 or higher).[5] A significant decrease in survival was seen in single-lung transplant patients with a high LAS compared with double-lung transplant patients with a high LAS, even though operative morbidity was higher ($p<0.001$).

Hayanga (2016) analyzed lung transplantation data from the UNOS registry between 2005 and 2013.[8] Survival was analyzed in relation to the annual volume of lung transplants performed at each center: less than 20, 20-29, 30-39, and 40 or more. During the study period, 13,506 adults underwent lung transplantation. Approximately 40% of the transplants were performed in centers with a volume of 40 or more, with the remaining transplants spread relatively equally across lower volume center groups. Both one- and five-year patient survival tended to increase with increasing volume, but the authors noted that it was a relatively small effect.

Kistler (2014) reported on a systematic review of the literature on waitlist and posttransplant survival for idiopathic pulmonary fibrosis.[9] Estimated median survival of idiopathic pulmonary fibrosis patients posttransplantation is estimated at 4.5 years and is lower than other underlying pretransplant diagnoses. From ISHLT and the Organ Procurement and Transplantation Network (OPTN) data, one-year survival ranged from 75% to 81%; three-year, 59% to 64%, and five-year, 47% to 53%. Limited data were available on posttransplant morbidity outcomes.

Taimeh (2016) reported on post-lung transplant survival in 695 patients with pulmonary sarcoidosis in the U.S.[10] Survival in this group was similar to that of non-sarcoid lung recipients, and in a multivariate analysis, sarcoidosis was not associated with higher mortality. In the sarcoidosis group, LAS and double lung transplantation were both associated with improved survival.

PATIENT SELECTION

Based on concern that the LAS may prioritize lung transplant candidates with a poor expected survival benefit from the procedure, Li (2019) analyzed data from the UNOS registry (n=21,157) to determine whether there was a LAS threshold above which the score did not predict increasing survival benefit.[11] The results of this analysis indicated that the greatest benefit was seen for recipients with scores between 70 and 79 (n=365), with a hazard ratio of death after undergoing transplantation relative to remaining on the waitlist of 0.2 (95% CI 0.1 to 0.3). Survival for patients with LAS scores above this range was not significantly increased. The authors noted that the survival benefit threshold for patients with cystic fibrosis was quite a bit lower, at a score of approximately 50.

Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation, and 426 who underwent primary lung transplantation between 2005 and 2010.[12] Patients on the waitlist who had a higher LAS had a higher rate of mortality ($p<0.001$). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival ($p=0.05$) but not late posttransplant survival ($p=0.4$). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality ($p=0.12$).

Russo (2011) analyzed a dataset of 6,082 patients who received a lung transplant between May 4, 2005 and May 4, 2009 in order to describe outcomes and estimate the survival benefit based upon patient lung allocation score.[13] Authors found that although lower priority patients comprise the majority of transplants, mid-priority groups with LAS of 50 to 79, seemed to achieve the greatest survival benefit from transplantation (2.81 to 3.49 years). Patients with the highest and lowest LAS score achieved the least survival benefit; however, it was noted that patients with high allocation scores were expected to have worse survival and that patients with lower LAS had the lowest risk of death on the waiting list. Data suggested that transplant centers may be justified in considering patients for lung transplantation who had a mid-range allocation scores before patients with the highest and lowest scores.

Yusen (2010) reviewed the effect of the LAS on lung transplantation by comparing statistics for the period before and after its implementation in 2005.[14] Other independent changes in clinical practice, which may affect outcomes over the same period of time, include variation in immunosuppressive regimens, an increased supply of donor lungs, changes in diagnostic mix, and increased consideration of older recipients. Deaths on the waiting list declined following implementation of the LAS system, from approximately 500 per 5,000 patients to 300 per 5,000 patients. However, it is expected that implementation of the LAS affected patient characteristics of transplant applicants. One-year survival post-transplantation did not improve after implementation of the LAS system: patient survival data before and after are approximately 83%. More recently, Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010.[12] Patients on the waitlist who had a higher LAS

had a higher rate of mortality (p<0.001). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival (p=0.05) but not late posttransplant survival (p=0.4). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality (p=0.12).

Gries (2010) published results from a study on pre-transplant characteristics of 10,128 patients from the Organ Procurement and Transplantation Network (OPTN) database were examined to understand how well LAS post-transplant survival model parameters predict one- and five-year survival.[15] Authors concluded that the LAS system and pre-transplant characteristics in general did not predict long term one- or five-year survival better than chance.

Kozower (2008) performed a retrospective cohort study using data from five academic medical centers to evaluate the impact of the LAS on short-term outcomes after lung transplantation.[16] (The LAS was implemented in May 2005 by the OPTN.) This score changed lung allocation from a system based on waiting time to an algorithm based on the probability of survival for one year on the transplant list and survival one-year post-transplantation. Results were compared for 170 patients who received transplants based on the new lung allocation scores (May 4, 2005 to May 3, 2006) with those of 171 patients who underwent transplants the preceding year before implementation of the scoring system. Waiting time decreased from 681 to 445.6 days (p<0.001). Recipient diagnoses changed, with an increase (15% to 25%) in idiopathic pulmonary fibrosis cases and decreases in emphysema (46% to 34%) and cystic fibrosis (23% to 13%). Hospital mortality and one-year survival were the same between groups (5.3% vs. 5.3% and 90% vs. 89%, respectively). Presumably due to increased severity of illness, the incidence of primary graft dysfunction and postoperative intensive care unit length of stay increased in the year after implementation of the scoring system; graft dysfunction grew from 14.8% (24/170) to 22.9% (39/171); (p=0.04) and length of stay rose from 5.7 to 7.8 days.

PEDIATRIC CONSIDERATIONS

A retrospective cohort study from 150 centers worldwide was conducted by Nelson (2021).[17] The results compared outcomes of 2232 pediatric patients with or without cystic fibrosis that underwent lung transplantation between 1990 and 2017. The primary outcomes were all-cause mortality and graft failure at timepoints of 30 days, one year, five years, and 10 years. The proportion of patients undergoing lung transplantation without cystic fibrosis is increasing where nearly half of primary pediatric lung transplantations are performed for other indications. These patients without cystic fibrosis were younger, more commonly receiving intensive care, were on inotropes and/or extracorporeal membrane oxygenation (ECMO). Mortality was higher for non-cystic fibrosis patients after 30 days compared to patients with cystic fibrosis. A diagnosis of pulmonary arterial hypertension was also a risk factor for pediatric patients without cystic fibrosis at one and five years. However, long-term survival was higher in these patients without cystic fibrosis comparatively.

Paraskeva (2018) analyzed survival rates of adolescent lung transplant recipients using data from the ISHLT registry.[18] Patients between 10 and 24 years old represented 9% of the registry data (n=2,319) and they were compared with both old and young cohorts. Overall survival in the adolescent cohort was 65% at three years, which was similar to that observed in adults between 50 and 65 years of age, but significantly lower than the three-year survival

rate among the pediatric subgroup (73%, p=0.006) and adults 25 to 34 years old (75%, p<0.001) and 35 to 49 years old (71%, p<0.001). Within the adolescent group, patients between 15 and 19 years of age had the poorest survival rates at three years (59%) compared with 10- to 14-year year old patients (73%, p<0.001) and 20- to 24-year old patients (66%, p<0.001). The registry study was biased toward inclusion of North American data and potential data entry errors or missing data. There were no data reported on cause of mortality, differences in regimens, or rates of graft dysfunction between the groups.

Benden (2012) reviewed pediatric lung transplants that have been reported to the international registry.[19] Pediatric patients are defined as those younger than 18 years of age. The authors noted an increase in the number of pediatric lung transplants in recent years; there were 126 transplants in 2010 compared to 73 in 2000. In contrast to adult patients, the most common indication for pediatric patients was cystic fibrosis, accounting for 54% of lung transplants in 6- to 11-year-olds and 72% of lung transplants in 12- to17-year-olds that occurred between 1990 and June 2011. Survival has improved in the recent era, and five-year survival is not significantly different from adult recipients. The half-life, estimated time at which 50% of recipients have died, was 4.7 years for children and 5.3 years for adults. For children receiving allografts between 2002 and June 2010, the five-year survival rate was 54% and seven-year survival was 44%. Patients aged 1 to 11 years had a significantly better survival rate than those between the ages of 12 and 17 years (half-life of 6.2 years and 4.3 years, respectively). In the first year after lung transplantation, non-CMV infection and graft failure were the two leading causes of death. Bronchiolitis obliterans syndrome was the major cause of death beyond three years after transplantation.

Moreno (2016) compared survival and clinical outcomes in pediatric and adult lung transplantation for cystic fibrosis at a single institution.[20] There were 120 patients included in the study: 50 children and 70 adults, who underwent 111 bilateral, four lobar, four combined and one unilateral lung transplant. Overall survival for children at five, ten, and 15 years was 57, 45, and 35% vs, 67, 55, and 43% for adults, respectively (p=0.32). Pediatric patients were significantly more likely than adults to have used cardiopulmonary bypass (56% vs. 28%, p=0.002), have acute rejection episodes (1.4 ± 0.7 vs. 1.2 ± 0.8, p=0.004), and stay longer in intensive care (20 ± 19 vs. 10 ± 9 days, p=0.006). The authors noted that pediatric cystic fibrosis patients presenting for lung transplant tend to have a worse status than adult patients, which might explain some of these differences.

Mangiameli (2016) reported on outcomes of pediatric lung transplantation at a center in France, with a focus on sex matching of donors and recipients.[21] In this study, which included 58 patients below age 18, the 30-day mortality was 10% and survival at one, five, and 10 years was 81%, 60%, and 57%, respectively. Among these patients, female sex and sex mismatching were associate with poor prognosis, with female recipients of male-donated organs having particularly poor outcomes.

A study by Fraser (2019) used information from the UNOS database to examine the role of size mismatch in preadolescent lung transplantation.[22] There were 540 patients included in the analysis, which found that one-year mortality was higher for patients with height and weight mismatching, and for predictive total lung capacity ratios less than 0.9 (p=0.017)

POTENTIAL CONTRAINDICATIONS

Malignancy

Concerns regarding a potential recipient's history of cancer have been based on the observation of significantly increased incidence of cancer in kidney transplant patients.[23] For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.[24, 25] However, it should be noted that the availability of alternative treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage lung disease patients may not have an option to defer.

A 2012 study reported on outcomes in patients with lung cancer who were lung transplant recipients.[26] Ahmad and colleagues identified 29 individuals in the UNOS database who underwent lung transplantation for advanced bronchoalveolar carcinoma (BAC). These patients represented 0.13% of the 21,553 lung transplantations during the study period. BAC and general lung transplant recipients had similar survival rates: the 30-day mortality rate was 7% versus 10% (p=0.44) and five-year survival rate was 50% versus 57% (p=0.66), respectively.

Human Immunodeficiency Virus (HIV)

The current Organ Procurement Transplantation Network (OPTN) policy permits HIV-positive transplant candidates.[27] The 2020 US Public Health Service guideline also allows for transplantations in HIV-positive recipients with proper screenings and effective regimens for HIV infections.[28]

Other Infections

Infection with *Burkholderia cenocepacia* is associated with increased mortality in some transplant centers, a factor that may be considered when evaluating overall risk for transplant survival.[29]

A 2016 analysis of international registry data found that non-CMV infection is a major cause of mortality within 30 days of lung transplant in adults.[3] A total of 655 (19%) of 3,424 deaths after transplants between January 1990 and June 2015 were due to non-CMV infection. Only three (0.1%) of the deaths were due to CMV infection.

Wojarski (2018) assessed the impact of bacterial infection on mortality in 97 lung transplant patients from a single center between 2004 and 2016.[30] The mean hospitalization time was 57 days, and 67 patients had a total of 120 episodes of bacterial infection. The most common sources of infection were *Pseudomonas aeruginosa* (27%), followed by *Acinetobacter baumannii* (21%), and *Stenotrophomonas maltophilia* (11%). There were 39 patients who developed bronchiolitis obliterans syndrome. *A. baumannii* infection was associated with decreased survival, while treatment with mammalian target of rapamycin inhibitors was linked to increased survival.

Lobo (2013) reported on 13 lung transplant patients with *Mycobacterium abscessus* in cystic fibrosis.[31] Survival rates were 77%, 64% and 50% after transplant at one, three, and five years, respectively. These results were not significantly different when compared to 154 cystic fibrosis patients treated with lung transplantation who did not have *M. abscessus* (p=0.8).

Shields (2012) reported on infections in 596 consecutive lung transplant recipients treated at a single center occurring in the first 90 days after transplantation.[32] A total of 109 patients

(18%) developed 138 *Staphylococcus aureus* (*S. aureus*) infections. The most common type of infection was pneumonia (66 of 138, 48%) followed by tracheobronchitis (36 of 138, 26%) and bacteremia (17 of 138, 12%). Thirteen of 109 (12%) of patients with *S. aureus* infection died within 90 days of the onset of infection. The one-year mortality rate was higher for patients with *S. aureus* pneumonia (19 of 66, 29%) but not *S. aureus* tracheobronchitis (8 of 36, 22%) compared with uninfected patients (85 of 487, 17%).

Pinney (2011) published results from a retrospective review of invasive fungal infection rates in lung transplantation patients without cystic fibrosis treated at a single center.[33] Patients were followed for a median of 34 months. Invasive fungal infections were identified in 22 of 242 (9.1%) patients. *Aspergillus* infections were most common, occurring in 11 of 242 (4.5%) of patients. There were also seven cases (3%) of *Candida* infection. Survival rates did not differ significantly in patients with invasive fungal infections compared to the entire cohort of patients. For example, three-year survival was 50% among patients with invasive fungal infection and 66% in the entire cohort (p=0.66). The authors did not compare survival in patients with invasive fungal infections to survival only in those without invasive fungal infections.

In a study published by Murray (2008), multivariate Cox survival models assessing hazard ratios (HRs) were applied to 1,026 lung transplant candidates and 528 transplant recipients.[34] Of the transplant recipients, 88 were infected with *Burkholderia*. Among transplant recipients infected with *Burkholderia cenocepacia,* only those infected with nonepidemic strains (n=11) had significantly greater post-transplant mortality than uninfected patients (HR 2.52, 95% CI 1.04 to 6.12, p=0.04). Transplant recipients infected with *Burkholderia gladioli* (n=14) also had significantly greater post-transplant mortality than uninfected patients (HR 2.23, 95% CI 1.05 to 4.74, p=0.04). When adjustments for specific species/strains were included, lung allocation scores of *Burkholderia multivorans*-infected transplant candidates were comparable to uninfected candidate scores, and scores for patients infected with non-epidemic *B. cenocepacia* or *B. gladioli* were lower. In a smaller study of 22 patients colonized with *Burkholderia cepacia* complex who underwent lung transplantation in two French centers, the risk of death by univariate analysis was significantly higher for the eight patients infected with *B. cenocepacia* than for the other 14 colonized patients (11 of whom had *B. multivorans*).[35]

Coronary Artery Disease (CAD)

Castleberry (2013) reported on a retrospective cohort study of lung transplantation with concurrent CAB or preoperative percutaneous coronary intervention (PCI).[36] Out of 898 lung transplants performed during the period between 1997 and 2010, 49 patients also had concurrent CAB and 38 patients had preoperative PCI. All of the intervention groups, including revascularization, had similar rates of perioperative mortality, overall unadjusted survival and adjusted HR for cumulative risk of death. Postoperative major adverse cardiac event rates were also similar among groups, although postoperative length of stay, intensive care unit time and need for ventilator support increased in patients receiving concurrent CAB with lung transplantation.

Sherman (2011) reported on outcomes in 27 patients with CAD at a single center who underwent lung transplantation and coronary revascularization.[37] Patients needed to be otherwise considered good candidates for transplantation and have discrete coronary lesions (at least 50% in the left main artery or at least 70% in other major vessels) and preserved

ejection fraction. Thirteen patients had single-lung transplantation and 14 had double-lung transplantation. Outcomes were compared with a control group of 81 patients without CAD who underwent lung transplantation; patients were matched for age, diagnosis, lung allocation score and type of procedure. During a mean follow-up of three years, nine of 27 (33%) patients with CAD and 28 of 81 (35%) without CAD died (p=0.91). Bronchiolitis obliterans and infection were the primary causes of death. There was no significant difference between groups in a composite outcome of adverse cardiac events (defined as acute coronary syndrome, redo revascularization or hospital admissions for congestive heart failure), p=0.80.

LOBAR LUNG TRANSPLANTATION

Several case series have reported outcomes after lobar lung transplants in both children and adults.

Eberlein (2017) published a systematic review of studies on lobar lung transplantation from deceased donors.[38] Reviewers identified nine studies comparing outcomes after lobar lung or lung transplant, all of which were single-center retrospective cohort studies. Seven studies were conducted in Europe, one in Australia, and one in North America. One-year survival reported in individual studies ranged from 50% to 100% after lobar lung transplant and from 72% to 88% after conventional lung transplant. In a pooled analysis of data from eight studies, lobar lung transplant recipients (n=284) had a significantly higher risk of one-year mortality than lung transplant recipients (n=2,777) (relative risk [RR] 1.85, 95% CI 1.52 to 2.25, p<0.001, I^2=0%).

Date (2014) reported on a retrospective study comparing 42 living-donor lobar lung transplants and 37 cadaveric lung transplants.[39] Survival rates at one and three years were not significantly different between the groups (89.7 and 86.1% vs 88.3 and 83.1%, respectively, p=0.55), despite living-donor lobar lung transplant patients having poorer health status preoperatively.

Slama (2014) reported on a comparison of outcomes in 138 cadaveric lobar lung transplants (for size discrepancies) to 778 patients who received cadaveric whole-lung transplants, 239 of whom had downsizing by wedge resection of the right middle lobe and/or the left lingula.[40] Survival in the lobar lung transplant group at one and five years was 65.1% and 54.9% versus 84.8% and 65.1% in the whole lung and downsized by wedge resection group (p<0.001). The lobar lung transplantation group experienced significantly inferior early postoperative outcomes, but in patients who were successfully discharged, survival rates were similar to standard lung transplantation (p=0.168).

In 2012, a program in Japan reported on 14 critically ill patients who had undergone single living-donor lobar lung transplants; there were ten children and four adults.[41] Patients were followed for a mean 45 months. The three-year survival rate was 70% and the five-year survival was 56%. Severe graft dysfunction occurred in four patients. Mean forced vital capacity (FVC) was found to be lower in patients experiencing severe graft dysfunction compared to the other patients, mean FVC was 54.5% and 66.5%, respectively. The authors stated that this suggests size mismatching in the patients with severe graft dysfunction. The same year, Inci (2012) published data on 23 patients in Switzerland who received bilateral lobar lung transplants.[42] The mean age was 41 years (range 13 to 66 years). Survival at one and two years was 82% and 64%, respectively; survival rates were comparable with 219 patients who underwent bilateral lung transplantation during the same period (p=0.56).

A review article by Date (2015) stated that, as of 2011, approximately 400 living-donor lobar lung transplants have been performed worldwide.[39] Procedures in the U.S. decreased after 2005 due to changes in the lung allocation system. The author stated that size matching between donor and recipient is important and that, to some extent, size mismatching (oversized or undersized grafts) can be overcome by adjusting surgical technique.

Several studies reported on lobar lung transplantation from living donors. For example, Barr (2005) reported on experience performing living donor lobar lung transplants in the U.S.[43] Ninety patients were adults and 43 were children. The primary indication for transplantation (86%) was cystic fibrosis. At the time of transplantation, 67% of patients were hospitalized and 20% were ventilator dependent. Overall recipient actuarial survival at one, three and five years was 70%, 54% and 45%, respectively. There was not a statistically significant difference in actuarial survival between adults and children who underwent transplantation. Moreover, survival rates were similar to the general population of lung transplant recipients. The authors also reported that rates of postoperative pulmonary function in patients surviving more than three months post-transplant were comparable to rates in cadaveric lung transplant recipients.

RETRANSPLANTATION

Registry data and case series reports have demonstrated favorable outcomes with lung retransplantation in certain populations, such as in patients who meet criteria for initial lung transplantation.[44-47]

OPTN reported data on lung transplants performed between 2008 and 2015.[48] Patient survival rates after repeat transplants were lower than primary transplants, but a substantial number of patients survived. For example, one-year patient survival was 87.9% (95% CI 87.2% to 88.7%) after a primary lung transplant and 76% (95% CI 70.9% to 80.2%) after a repeat transplant. Five-year patient survival was 55.9% (54.7% to 57.2%) after a primary lung transplant and 33.8% (28.5 to 39.1%) after repeat transplant.

The ISHLT registry contains data on 2,273 retransplantations performed through June 2015 (4.4% of all lung transplantations during this period).[3] The major causes of death in the first 30 days after retransplantation were graft failure and non-CMV infection, followed by multiorgan failure, cardiovascular causes and technical factors related to the transplant procedure. Beyond the first year, the most common reported causes of mortality were OB/BOS, graft failure, and non-CMV infections.

Biswas Roy (2018) published a single-center retrospective study comparing survival outcomes in 29 patients who received retransplantation for chronic lung allograft dysfunction with 390 patients receiving primary lung transplant at the same center.[49] Patients receiving retransplantation had significantly higher use of extracorporeal membrane oxygenation support for severe primary graft dysfunction (p=0.019) and underwent cardiopulmonary bypass and re-exploration for bleeding (p=0.019) more frequently than patients receiving primary transplantation (p=0.029). At one-year follow-up, 89.7% of primary transplant patients were living, as were 89.2% of retransplantation patients. At five-year follow-up, a greater percentage of the retransplantation group had survived, compared with the primary transplantation group (64.3% vs 58.2%), although the difference was not statistically significant. While high LAS and extended hospital length of stay were both identified as independent mortality risk factors, retransplantation was not (HR 1.58, 95% CI 0.31 to 8.08, p=0.58). Study limitations included its single-center, retrospective design, the potential selection bias for younger patients, and the

small size of the retransplantation group. Further, follow-up data at three and five years were incomplete for some patients, and patients who were refused retransplantation were not considered in the analyses. However, for appropriately selected patients, retransplantation after chronic lung allograft dysfunction resulted in one- and five-year survival rates comparable to those seen after primary lung transplantation.

Thomas (2015) published results from a retrospective study that compared patient survival after lung retransplantation (LRTx) to primary lung transplantation (LPTx) in the U.S. using data from the UNO registry between 2004 and 2013.[50] A total of 582 LRTx and 13,673 LPTx recipients were included in the analysis. The median survival after LRTx was 2.6 years compared with 5.6 years after LPTx. One-year, three-year, and five-year survival rates were, respectively, 71.1%, 46.3%, and 34.5% for LRTx, and 84.3%, 66.5%, and 53.3% for LPTx ($p<0.001$). On multivariate analysis, patients who had LRTx after a greater than one-year interval survived longer (RR 0.53, 95% CI 0.34% to 0.88%, p=0.008). Lower survival was associated with single-lung transplantations (RR 1.49, 95% CI 1.06% to 2.07%, p=0.021), transplantations done between 2009 and 2013 (RR 1.40, 95% CI 1.01% to 1.94%, p=0.041), multiple retransplantations (RR 2.55, 95% CI 1.14% to 5.72%, p=0.023), and recipients requiring pre-transplantation ventilator support.

Kilic (2013) evaluated data on 390 adult lung retransplantation patients from the UNOS database.[45] Patients received lung retransplantation during the period May 2005 to December 2010, which was after the LAS selection criteria were implemented. Patients with reduced functional status were found to have poorer outcomes than patients with better functional status prior to retransplantation. Using the Karnofsky scale to stratify patients into functional status groups, the authors found the overall one-year survival of 56% for patients requiring total assistance before retransplantation was significantly lower than the overall one-year survival of 82% for patients who only required some assistance before retransplantation ($p<0.001$). The one-year mortality rate after risk adjustment was also increased significantly for patients requiring total assistance prior to retransplantation (odds ratio 3.72, p=0.02). While additional patient selection criteria may be useful for lung retransplantation, current LAS criteria are now used.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2021, the International Society for Heart and Lung Transplantation published updated consensus-based guidelines on the selection of lung transplant candidates.[51]

"Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed.
2. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."

The guideline also notes risk factors to be considered in the evaluation of transplant candidates, along with pediatric and disease-specific considerations.

The 2021 guideline update briefly addressed lung **retransplantation**, with the consensus statement noting that "The outcomes after re-transplants are inferior compared to first lung transplants, particularly if the re-transplant is done within the first year after the original transplant or for patients with restrictive allograft syndrome (RAS) [...] In the pre-transplant evaluation of such patients, particular emphasis should be focused on understanding the possible reasons for the graft failure, such as alloimmunization, poor adherence, gastroesophageal reflux, or repeated infections".

In 2015, the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation (ISHLT) published an update to their 2006 consensus-based guidelines on selection of lung transplant candidates.[52, 53] The guidelines state:

> "… there is general agreement that referral to a lung transplant program should occur early in patients who have a lung disease that is amenable to transplantation. None of the parameters listed in this document informing on the timing of referral or listing should be used in isolation. Instead, the entire clinical situation of the patient should be considered. However, early referral does give the transplant program maximal flexibility in performing the formal evaluation and in making the second more important step—placing the patient on the active waiting list. Listing a patient for a lung transplant is an explicit acknowledgement that a patient has a limited life expectancy without a transplant and an expectation that the risk-to-benefit ratio favors lung transplantation rather than conventional medical treatment."

For lung retransplantation, the guidelines state:

> "Lung retransplantation accounts for a small percentage of lung transplants performed annually. However, its frequency has increased in recent years. The criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation. Survival after lung retransplantation may have improved over time but remains inferior to survival seen after initial transplantation. For the individual patient, retransplantation should be analyzed as a time-dependent survival risk factor. Consideration must also be given to ethical issues surrounding lung allocation to retransplantation candidates."

AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY/JAPANESE RESPIRATORY SOCIETY/LATIN AMERICAN THORACIC ASSOCIATION

Evidence-based recommendations from the American Thoracic Society and three international respiratory/thoracic societies were published in 2011 for the diagnosis and management of patients with idiopathic fibrosis.[54] For appropriately selected patients with idiopathic pulmonary fibrosis, the group recommended lung transplantation (strong recommendation, low-quality evidence). An updated to this document was published in 2015 in which the committee did not make a recommendation regarding single versus bilateral lung transplantation in patients with idiopathic fibrosis.[55] The committee stated that "it is unclear whether single or bilateral lung transplantation is preferential for long-term outcomes".

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

In 2017 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee members performed a literature search and developed guidelines regarding the diagnosis, management and prevention of chronic obstructive pulmonary disease.[56] The committee

suggested that in carefully selected patients with COPD, lung transplantation has been shown to improve quality of life and functional capacity. The guidelines state:

> "In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered. … Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, Pco_2 greater than 50 mm Hg or 6.6 kPa and/or Pao_2 less than 60 mm Hg or 8 kPa, and FEV_1 less than 25% predicted."

These recommendations were made on the basis of evidence collected from observational studies; however, randomized controlled trials are unlikely in this patient population.

SUMMARY

There is enough research to show that lung transplantation can improve survival in certain patients and thus may be considered medically necessary for patients when the policy criteria are met. It may be the only option for some patients with end-stage lung disease.

There is enough research to show that lung retransplantation can improve survival and may be the only option for patients with failed lung transplantation. Therefore, lung retransplantation may be considered medically necessary in selected patients who meet criteria for lung transplantation.

Lung or lobar lung transplantation or retransplantation is considered not medically necessary in all other situations when the policy criteria are not met.

REFERENCES

1. Kessler L, Bakopoulou S, Kessler R, et al. Combined pancreatic islet-lung transplantation: a novel approach to the treatment of end-stage cystic fibrosis. *Am J Transplant.* 2010;10(7):1707-12. PMID: 20642693
2. Organ Procurement and Transplantation Network (OPTN). Organ Distribution: Allocation of Lungs. Policy 10. [cited 3/14/2022]. 'Available from:' https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
3. Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant.* 2016;35(10):1170-84. PMID: 27772669
4. Goldfarb SB, Levvey BJ, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Lung and Heart-Lung Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant.* 2016;35(10):1196-205. PMID: 27772671
5. Black MC, Trivedi J, Schumer EM, et al. Double lung transplants have significantly improved survival compared with single lung transplants in high lung allocation score patients. *Ann Thorac Surg.* 2014;98(5):1737-41. PMID: 25110334
6. Yu H, Bian T, Yu Z, et al. Bilateral Lung Transplantation Provides Better Long-term Survival and Pulmonary Function Than Single Lung Transplantation: A Systematic Review and Meta-analysis. *Transplantation.* 2019;103(12):2634-44. PMID: 31283687

7. Thabut G, Christie JD, Kremers WK, et al. Survival differences following lung transplantation among US transplant centers. *JAMA : the journal of the American Medical Association.* 2010;304(1):53-60. PMID: 20606149
8. Hayanga JA, Lira A, Vlahu T, et al. Procedural volume and survival after lung transplantation in the United States: the need to look beyond volume in the establishment of quality metrics. *American journal of surgery.* 2016;211(4):671-6. PMID: 26830718
9. Kistler KD, Nalysnyk L, Rotella P, et al. Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. *BMC pulmonary medicine.* 2014;14:139. PMID: 25127540
10. Taimeh Z, Hertz MI, Shumway S, et al. Lung transplantation for pulmonary sarcoidosis. Twenty-five years of experience in the USA. *Thorax.* 2016;71(4):378-9. PMID: 26781176
11. Li SS, Miller R, Tumin D, et al. Lung Allocation Score Thresholds Prioritize Survival After Lung Transplantation. *Chest.* 2019;156(1):64-70. PMID: 30664859
12. Shafii AE, Mason DP, Brown CR, et al. Too high for transplantation? Single-center analysis of the lung allocation score. *Ann Thorac Surg.* 2014;98(5):1730-6. PMID: 25218678
13. Russo MJ, Worku B, Iribarne A, et al. Does lung allocation score maximize survival benefit from lung transplantation? *J Thorac Cardiovasc Surg.* 2011;141(5):1270-7. PMID: 21497235
14. Yusen RD, Shearon TH, Qian Y, et al. Lung transplantation in the United States, 1999-2008. *Am J Transplant.* 2010;10(4 Pt 2):1047-68. PMID: 20420652
15. Gries CJ, Rue TC, Heagerty PJ, et al. Development of a predictive model for long-term survival after lung transplantation and implications for the lung allocation score. *J Heart Lung Transplant.* 2010;29(7):731-8. PMID: 20382034
16. Kozower BD, Meyers BF, Smith MA, et al. The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. *J Thorac Cardiovasc Surg.* 2008;135(1):166-71. PMID: 18179935
17. Nelson JS, Maul TM, Aughtman SL, et al. A shifting landscape: Practice patterns and outcomes of cystic fibrosis and non-cystic fibrosis pediatric lung transplantation. *Pediatr Transplant.* 2021;25(7):e14086. PMID: 34275181
18. Paraskeva MA, Edwards LB, Levvey B, et al. Outcomes of adolescent recipients after lung transplantation: An analysis of the International Society for Heart and Lung Transplantation Registry. *J Heart Lung Transplant.* 2018;37(3):323-31. PMID: 28320631
19. Benden C, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart-lung transplantation report--2012. *J Heart Lung Transplant.* 2012;31(10):1087-95. PMID: 22975098
20. Moreno P, Alvarez A, Carrasco G, et al. Lung transplantation for cystic fibrosis: differential characteristics and outcomes between children and adults. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2016;49(5):1334-43. PMID: 26530270
21. Mangiameli G, Arame A, Boussaud V, et al. Lung transplantation in childhood and adolescence: unicentric 14-year experience with sex matching as the main prognosticator. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2016;49(3):810-7. PMID: 26188011

22. Fraser CD, 3rd, Zhou X, Grimm JC, et al. Size Mismatching Increases Mortality After Lung Transplantation in Preadolescent Patients. *Ann Thorac Surg.* 2019;108(1):130-37. PMID: 30763559
23. Kasiske BL, Snyder JJ, Gilbertson DT, et al. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4(6):905-13. PMID: 15147424
24. Otley CC, Hirose R, Salasche SJ. Skin cancer as a contraindication to organ transplantation. *Am J Transplant.* 2005;5(9):2079-84. PMID: 16095486
25. Trofe J, Buell JF, Woodle ES, et al. Recurrence risk after organ transplantation in patients with a history of Hodgkin disease or non-Hodgkin lymphoma. *Transplantation.* 2004;78(7):972-7. PMID: 15480161
26. Ahmad U, Wang Z, Bryant AS, et al. Outcomes for lung transplantation for lung cancer in the United Network for Organ Sharing Registry. *Ann Thorac Surg.* 2012;94(3):935-40; discussion 40-1. PMID: 22835555
27. Organ Procurement and Transplantation Network (OPTN). Identification of Transmissible Diseases, Policy 15. [cited 3/14/2022]. 'Available from:' https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
28. Jones JM, Kracalik I, Levi ME, et al. Assessing Solid Organ Donors and Monitoring Transplant Recipients for Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Infection - U.S. Public Health Service Guideline, 2020. *MMWR Recomm Rep.* 2020;69(4):1-16. PMID: 32584804
29. Alexander BD, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. *Am J Transplant.* 2008;8(5):1025-30. PMID: 18318775
30. Wojarski J, Ochman M, Medrala W, et al. Bacterial Infections During Hospital Stay and Their Impact on Mortality After Lung Transplantation: A Single-Center Study. *Transplantation proceedings.* 2018;50(7):2064-69. PMID: 30177110
31. Lobo LJ, Chang LC, Esther CR, Jr., et al. Lung transplant outcomes in cystic fibrosis patients with pre-operative Mycobacterium abscessus respiratory infections. *Clinical transplantation.* 2013;27(4):523-9. PMID: 23710571
32. Shields RK, Clancy CJ, Minces LR, et al. Staphylococcus aureus infections in the early period after lung transplantation: epidemiology, risk factors, and outcomes. *J Heart Lung Transplant.* 2012;31(11):1199-206. PMID: 22986156
33. Pinney MF, Rosenberg AF, Hampp C, et al. Invasive fungal infections in lung transplant recipients not receiving routine systemic antifungal prophylaxis: 12-year experience at a university lung transplant center. *Pharmacotherapy.* 2011;31(6):537-45. PMID: 21923437
34. Murray S, Charbeneau J, Marshall BC, et al. Impact of burkholderia infection on lung transplantation in cystic fibrosis. *Am J Respir Crit Care Med.* 2008;178(4):363-71. PMID: 18535253
35. Boussaud V, Guillemain R, Grenet D, et al. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with Burkholderia cepacia complex: results from two French centres. *Thorax.* 2008;63(8):732-7. PMID: 18408050
36. Castleberry AW, Martin JT, Osho AA, et al. Coronary revascularization in lung transplant recipients with concomitant coronary artery disease. *Am J Transplant.* 2013;13(11):2978-88. PMID: 24102830
37. Sherman W, Rabkin DG, Ross D, et al. Lung transplantation and coronary artery disease. *Ann Thorac Surg.* 2011;92(1):303-8. PMID: 21718862

38. Eberlein M, Reed RM, Chahla M, et al. Lobar lung transplantation from deceased donors: A systematic review. *World journal of transplantation.* 2017;7(1):70-80. PMID: 28280698
39. Date H, Sato M, Aoyama A, et al. Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2015;47(6):967-72; discussion 72-3. PMID: 25228745
40. Slama A, Ghanim B, Klikovits T, et al. Lobar lung transplantation--is it comparable with standard lung transplantation? *Transplant international : official journal of the European Society for Organ Transplantation.* 2014;27(9):909-16. PMID: 24810771
41. Date H, Shiraishi T, Sugimoto S, et al. Outcome of living-donor lobar lung transplantation using a single donor. *J Thorac Cardiovasc Surg.* 2012;144(3):710-5. PMID: 22717276
42. Inci I, Schuurmans MM, Kestenholz P, et al. Long-term outcomes of bilateral lobar lung transplantation. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2012. PMID: 23091227
43. Barr ML, Schenkel FA, Bowdish ME, et al. Living donor lobar lung transplantation: current status and future directions. *Transplantation proceedings.* 2005;37(9):3983-6. PMID: 16386604
44. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report--2013; focus theme: age. *J Heart Lung Transplant.* 2013;32(10):965-78. PMID: 24054805
45. Kilic A, Beaty CA, Merlo CA, et al. Functional status is highly predictive of outcomes after redo lung transplantation: an analysis of 390 cases in the modern era. *Ann Thorac Surg.* 2013;96(5):1804-11; discussion 11. PMID: 23968759
46. Kawut SM. Lung retransplantation. *Clin Chest Med.* 2011;32:367-77. PMID: 21511096
47. Wallinder A, Danielsson C, Magnusson J, et al. Outcomes and Long-term Survival After Pulmonary Retransplantation: A Single-Center Experience. *Ann Thorac Surg.* 2019;108(4):1037-44. PMID: 31121129
48. Organ Procurement and Transplantation Network (OPTN). National Data. [cited 3/14/2022]. 'Available from:' https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
49. Biswas Roy S, Panchanathan R, Walia R, et al. Lung Retransplantation for Chronic Rejection: A Single-Center Experience. *Ann Thorac Surg.* 2018;105(1):221-27. PMID: 29100649
50. Thomas M, Belli EV, Rawal B, et al. Survival After Lung Retransplantation in the United States in the Current Era (2004 to 2013): Better or Worse? *Ann Thorac Surg.* 2015;100(2):452-7. PMID: 26141777
51. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2021;40(11):1349-79. PMID: 34419372
52. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2006;25(7):745-55. PMID: 16818116
53. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of

the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34(1):1-15. PMID: 25085497
54. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183(6):788-824. PMID: 21471066
55. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2015;192(2):e3-19. PMID: 26177183
56. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2017 Report. GOLD Executive Summary. [cited 3/14/2022]. 'Available from:' http://www.atsjournals.org/doi/abs/10.1164/rccm.201701-0218PP.

CODES

Codes	Number	Description
CPT	32850	Donor pneumonectomy(ies) (including cold preservation), from cadaver donor
	32851	Lung transplant, single; without cardiopulmonary bypass
	32852	;with cardiopulmonary bypass
	32853	Lung transplant, double (bilateral, sequential, or en bloc); without cardiopulmonary bypass
	32854	;with cardiopulmonary bypass
	32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus, unilateral
	32856	;bilateral
HCPCS	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor

Date of Origin: *March 2013*

Regence

Medical Policy Manual Transplant, Policy No. 09

Small Bowel, Small Bowel/Liver, and Multivisceral Transplant

Effective: April 1, 2024

Next Review: January 2025
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Small bowel transplants are performed to treat intestinal failure in patients that require total parenteral nutrition (TPN) and are having serious TPN complications.

Small bowel/liver transplantation is performed in people that have both intestinal and liver failure, and may be combined with the transplantation of other portions of the digestive tract and accessory organs, including the, duodenum, jejunum, ileum, pancreas, or colon. When the small bowel and liver are transplanted in conjunction with other gastrointestinal organs, the procedure is referred to as a multivisceral transplant.

MEDICAL POLICY CRITERIA

I. A small bowel transplant using cadaveric intestine may be considered **medically necessary** for adults and children when ALL of the following are met (A. – E.):

   A. Adequate cardiopulmonary status; and

   B. Documentation of patient compliance with medical management; and

   C. Intestinal failure characterized by the loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance; and

   D. Long-term dependence on total parenteral nutrition (TPN); and

E. One or more of the following severe complications due to TPN:

1. TPN intolerance to the point that multiple and prolonged hospitalizations are required to treat TPN-related complications; or
2. The development of progressive but reversible liver failure; or
3. Inability to maintain venous access.

II. A small bowel transplant using a living donor may be considered **medically necessary** when a cadaveric intestine is not available for transplantation and Criterion I. is met.

III. A small bowel/liver transplant or multivisceral transplant may be considered **medically necessary** for adults and children when all of the following are met (A. – B.)

A. Criterion I. is met; and

B. There is evidence of impending end-stage liver failure.

IV. A small bowel retransplant may be considered **medically necessary** after a failed small bowel transplant.

V. A small bowel/liver or multivisceral retransplant may be considered **medically necessary** after a failed primary small bowel/liver or multivisceral transplant.

VI. A small bowel transplant is considered **not medically necessary** for patients with intestinal failure who are able to tolerate TPN.

VII. A small bowel transplant is considered **not medically necessary** if Criterion I, II, or IV is not met.

VIII. A small bowel/liver, or multivisceral transplant is considered **not medically necessary** if Criterion III or V is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. Liver Transplant, Transplant, Policy No. 5
2. Pancreas Transplant, Transplant, Policy No. 6

BACKGROUND

Intestinal failure is a serious medical condition which results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to

maintain protein-energy, fluid, electrolyte, or micronutrient balance.[1] Short bowel syndrome, one type of intestinal failure, is a condition in which the absorbing surface of the small intestine is inadequate due to extensive disease or surgical removal of a large portion of small intestine. Etiologies of short bowel syndrome include: volvulus, atresias, necrotizing enterocolitis, gastroschisis, desmoid tumors, and trauma. Patients with short bowel syndrome are unable to obtain adequate nutrition from enteral feeding and become dependent upon total parenteral nutrition (TPN). Patients with complications from TPN, such as catheter-related mechanical problems, infections, hepatobiliary disease, and metabolic bone disease, may be considered candidates for small bowel transplant.

Small bowel/liver transplantation is transplantation of an intestinal allograft in combination with a liver allograft, either alone or in combination with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, or colon. Small bowel transplants are typically performed in patients with intestinal failure (IF) due to functional disorders (e.g., impaired motility) or short bowel syndrome (SBS), defined as an inadequate absorbing surface of the small intestine due to extensive disease or surgical removal of a large portion of small intestine. In some instances, short bowel syndrome is associated with liver failure, often due to the long-term complications of total parenteral nutrition (TPN). These patients may be candidates for a small bowel/liver transplant or a multivisceral transplant, which includes the small bowel and liver with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, and/or colon. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant, and the patient requires removal of all of the native gastrointestinal tract and replacement with a multivisceral graft.

Intestinal transplants, including multivisceral and small intestine/liver, represent a small minority of all solid organ transplants. In 2022 and 2023, 82 and 87 intestinal transplants, respectively, were performed in the United States, all of which were from deceased donors. In 2023, 27 multivisceral transplants involving the small intestine/liver/pancreas were performed. Small intestine/liver transplant is rare, with only one performed in 2022 and zero in 2023.[2]

EVIDENCE SUMMARY

Ideally, for intestinal transplant to be considered as a replacement for total parenteral nutrition (TPN), head-to-head comparisons of transplantation versus TPN are needed, preferably in well-designed randomized controlled trials (RCTs). Further, for chronic conditions such as intestinal failure, comparative trials with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects, and to establish guidelines regarding the timing of intestinal transplant. In order to establish the net benefit of using living donors versus cadaveric intestinal transplant for treatment of intestinal failure, clinical trials that compare these therapies are needed, and the impacts on health outcomes for both the donors and recipients must be considered.

The current literature on small bowel transplantation included the following general observations:

- The importance of timely referral for intestinal transplantation was emphasized to avoid the necessity of combined liver and intestine transplantation.
- While outcomes continue to improve, obstacles to long-term survival remain. Recurrent and chronic rejections and complications of immunosuppression are significant issues in bowel transplantation.

- It has been suggested that improvements in survival over the last 10–15 years may justify removing the restriction of intestinal transplantation to patients who have severe complications of TPN.[3] However, as noted by Vianna in their report on the status of intestinal transplantation, no randomized trials compare intestinal transplantation to long-term parenteral nutrition, and optimal timing for earlier transplantation has not been established.[4]

- People with high morbidity from TPN appear to have better outcomes with transplant, but it is unknown whether ongoing home-based TPN or intestinal transplant is superior. Randomized controlled trials comparing the two forms of IF management have not been performed, primarily owing to small numbers of people with IF.[5]

REGISTRY DATA

The most recent published report from the international Intestinal Transplant Registry (ITR) reported on 4103 total intestinal transplants between January 1985 and December 2018. Of these, 2096 transplants were performed in children. Transplant subtypes are: small bowel only (1842), small bowel and liver (1251), multivisceral (small bowel, liver, stomach: 810), and modified multivisceral (small bowel and stomach: 200).[6] Improvements in the management of IF, both with and without intestinal transplant have led to a sharp reduction in the annual number of intestinal transplants being performed. Intestinal transplant volume decreased from a peak of 270 in 2008 to fewer than 50 in 2018.[5, 6] Participation in this registry was considered to be nearly 100% of all intestinal transplants performed in the world since April 1985. The following trends were identified[7]:

- Regional practices and outcomes are now similar worldwide.
- Current actuarial patient survival rates at one-, five-, and 10-years post-transplant are 76%, 56%, and 43%, respectively.
- Outcomes of intestinal transplantation improved modestly over the past decade, but rates of graft loss beyond one year have not improved.
- The reasons for late graft loss have been difficult to identify due to the low case volumes at most centers.
- Better function was found in intestinal grafts that included a colon segment and/or a liver component.

Better graft survival was also seen in patients who waited at home for intestinal transplant, used induction immune-suppression therapy, and had rapamycin maintenance therapy.

SYSTEMATIC REVIEWS

This policy was initially based on 1995 and 1999 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessments.[8, 9] The 1995 assessment concluded that in children, small bowel transplant was associated with improved survival compared to TPN. This assessment also concluded that in adults, the outcomes for small bowel transplant were worse than those associated with TPN.

The 1999 TEC assessment reevaluated the data on adults, specifically focusing on the probability of adult patient and graft survival with small bowel transplant compared to TPN, and whether successful outcome of small bowel transplant improves health outcomes or reduces adverse outcomes.[9] The assessment reported that bowel transplants in adults produce patient survival rates from 27%-58% at 4 or 5 years. Graft survival rates (and presumably

independence from TPN) range from 13%-30%. It is unknown whether this represents a net benefit to these patients, since some patients may survive for long periods of time on TPN. The TEC assessment also indicated that some patients with increasingly severe TPN-associated complications may face a high probability of impending mortality such that the risk of continued medical management is higher than the risk of transplantation. However, at this point in time, it is not possible to predict which patients will survive longer on TPN versus small bowel transplant.

In 2010, Sudan published a systematic review of current literature on long-term outcomes after intestinal transplantation.[10] The author noted that intestinal transplantation has become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series indicate a 1-year patient survival rate of 78-85% and a 5+ year survival rate of 56-61%. With respect to pediatric intestinal transplant patients, the majority achieve normal growth velocity at two years post-transplant. However, oral aversion is a common problem; tube feedings are necessary in 45% of children. Sudan also noted that parental surveys of quality of life in pediatric transplant patients have shown that intestinal transplant patients appear to have modestly improved quality of life compared to patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

RANDOMIZED CONTROLLED TRIALS

No RCTs were identified that compared intestinal transplantation with ongoing parenteral nutrition with or without subsequent small bowel/liver or multivisceral transplantation.

NONRANDOMIZED STUDIES

Despite the lack of RCTs, isolated small bowel transplantation has become an accepted alternative to continued total parenteral nutrition (TPN) to avoid the need for multivisceral transplantation in carefully selected patients with intestinal failure who are developing severe complications related to total parenteral nutrition (TPN).

The following is a summary of non-randomized trials that are representative of the available data on small bowel, small bowel/liver, and multivisceral transplantation, and post-transplantation complications.

Living Donor

The literature related to living-related intestinal transplant consists of small case reports of 1 to 11 patients in which different lengths of the ileum or jejunum were used.[11-18] While there appeared to be minimal complications to the donors, of the cases reported a significant number of recipients remained on TPN for at least part of their nutrition while others remain healthy and off TPN.

Ueno reported on 21 intestinal transplant patients that underwent transplantation between 1996 and 2012 at one of five institutions.[19] Twelve transplants came from living donors. All but one patient received an isolated small bowel transplant for intestinal failure. The overall 1- and 5- year survival rates were 86% and 68%, respectively. In the 15 patients who underwent transplantation after 2006, 1-year survival was 92% and 5-year survival was 83%.

Gangemi and Benedetti published a literature review of living donor small bowel transplantation reports from 2003 to 2006; all of the reports listed Benedetti as author.[20] The

authors commented that, “Due to the excellent result in modern series of deceased donor bowel transplantation, widespread use of the procedure [living donor] should not be recommended, in consideration of the potential risks to donor. Furthermore, few centers have acquired the necessary experience with the procedure.” Benedetti also reported outcomes from four children and seven adults who underwent 12 living-related small bowel transplantations between 1998 and 2004.[21] All donors were reported to have had uneventful recovery following removal of up to 40% of the small intestine. The three-year patient survival was 82%, with graft survival of 75%. Longer follow-up from the earlier cases was not reported.

Complications

Post-transplant lymphoproliferative disorders (PTLD) are a potentially life-threatening complication of the immunosuppression required for solid organ transplant. PTLD is associated with exposure to Epstein-Barr virus (EBV). Chang (2022) performed a retrospective single-institution study of pediatric solid organ transplant recipients to determine risk factors associated with post-transplant EBV DNAemia and PTLD.[22] The study included 275 patients, of whom 20 had multivisceral transplant and 10 had intestinal transplant. Other transplant types were liver, lung, kidney, and heart. Intestinal and multivisceral transplants patients were over-represented in PTLD cases. Intestinal transplants comprised 2% of the total study population but 21% of PTLD cases. Multivisceral transplant recipients represented 3% of the study population but 14% of PTLD cases. While high post-transplant EBV DNAemia levels were a strong risk factor for PTLD ($p<0.0001$), the study found that PTLD incidence in intestinal and multivisceral transplant recipients was not explained by EBV DNAemia levels. Transplant type did not correlate with EBV DNAemia ($p=0.14$).

Santarsieri (2022) published data describing PTLD incidence and outcomes from 5365 solid-organ and hematopoietic stem cell transplants over a 20-year period in the United Kingdom.[23] Multivisceral transplants were defined as intestinal transplant, with or without simultaneous transplant of other abdominal organs. The study included both adult and pediatric cases with the median age at transplant of 52 years (range 0.8 to 79.5 years). In addition to multivisceral transplant, other transplant types were kidney, pancreas, liver, hematopoietic stem cell, heart, lung (single, bilateral, and heart-lung), and simultaneous kidney and pancreas (SPK). A total of 225 cases of PTLD were documented. It was noted that multivisceral transplant follow-up time was the shortest because the procedure was initiated after other transplant types. Despite shorter follow-up, the incidence of PTLD was highest in multivisceral transplant cases. Out of a total of 113 multivisceral transplant cases, 21 (18.6%) were diagnosed with PTLD, which was notably higher than the overall PTLD incidence of 5.9% in all transplant types.

Clouse (2019) reported on the incidence of graft-versus-host disease (GVHD) following intestine transplant at a single center.[24] Of the 236 transplants performed between 2003 and 2015, 37 patients (16%) developed GVHD. Mortality was 54% within one year of diagnosis for these patients. An increased risk of GVDH was seen with liver inclusion and increasing graft volume.

Spence (2020) published on the development of intra-abdominal infections within two years following intestinal and multivisceral transplants in adults at a single center.[25] There were 103 patients that were included, who underwent transplantations between 2003 and 2015, and 46 of these (43%) had intra-abdominal infections with the two-year follow-up. The median time to infection was 23 days post-transplant. Six patients also had concurrent blood stream

infections. While patients with intra-abdominal infections had longer hospital stays than those without (median 35 days vs. 23 days, p=0.0012), there was no difference in all-cause mortality.

A report of thrombotic and hemorrhagic complications associated with visceral transplantation was published by Raveh (2018).[26] Data from 48 adult transplantations (32 multivisceral, 10 isolated intestinal, and six modified multivisceral) between 2010 and 2017 were reviewed retrospectively. There were eight patients who experience intraoperative intracardiac thrombosis (ICT)/pulmonary embolism (PE), all of whom were undergoing multivisceral transplants. Postoperative bleeding complications at one month were found in 11% of multivisceral transplants, 20% of isolated intestinal transplants, and 17% of modified multivisceral transplants.

Danziger-Isakov (2018) evaluated the epidemiology and outcomes of inpatient respiratory virus infection in pediatric patients following solid organ transplant at nine U.S. transplant centers.[27] Among the 42 patients who underwent intestine/multivisceral transplantation, respiratory virus infection occurred in 38%, the highest rate by transplant type. Respiratory virus infection was associated with younger age at transplant.

Vo (2018) reported on the risk of invasive pneumococcal infections among pediatric patients receiving liver-small bowel-pancreas transplants at a single center.[28] Of the 122 patients who underwent this procedure between 2008 and 2016, nine patients experienced 12 invasive pneumococcal infections. The median time to first infection following transplant was three years (range 0.8 to 5.8 years), and the mortality rate was 22%. The authors noted that all patients were on prophylactic oral penicillin and the majority had received at least one dose of pneumococcal conjugate vaccine.

Nagai (2016) reported on cytomegalovirus (CMV) infection after intestinal or multivisceral transplantation at a single center in the US.[29] A total of 210 patients had in intestinal transplant, multivisceral transplant or modified multivisceral transplant between January 2003 and June 2014. The median length of follow-up was 2.1 years. A total of 34 patients (16%) developed CMV infection a median of 347 days after transplantation. Nineteen patients had tissue invasive CMV disease. CMV infection was significantly associated with rejection (odds ratio 2.6, p<0.01) and adversely affected patient survival (hazard ratio 2.7, p<0.001). A report from another center in the US, 16 of 85 (19%) patients undergoing intestinal or multivisceral transplantation developed CMV infection a mean of 139 days (range 14 to 243 days) postoperatively.[30]

Wu (2016) investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (n=175).[31] Acute ABMR was diagnosed by: clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free grafts, 36% included a liver graft, and 6.3% were retransplantations. Eighteen cases of acute ABMR were identified: 14 (14%) among the patients undergoing first liver-free transplantation, two (3%) among patients undergoing liver/small bowel transplantations, and two (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

In 2016, Limketkai published a retrospective study on mortality and graft rejection rates in 1115 cases of intestinal transplants performed from May 1990 through June 2014.[32] Of these, 142

transplants were done for Crohn's disease (CD). Transplants were rejected in 33.3% of patients without CD and 36.9% of patients with CD. The actuarial risk of death for patients with CD at one, five, and ten years post-transplant 22.5%, 50.3%, and 59.7%, respectively. Patients without CD had similar mortality risks.

In a case series by Cromvik (2016), five of 26 patients (19%) were diagnosed with GVHD after intestinal or multivisceral transplantation at a center in Sweden.[33] Risk factors for GVHD were malignancy as a cause of transplantation and neoadjuvant chemotherapy or brachytherapy before transplantation.

A 2015 retrospective review reported a number of parameters for intestinal and multivisceral transplants performed on Nordic patients between 1998 and 2013.[34] Twenty out of the 29 patients (69%) received liver-containing allografts. Nineteen of them were multivisceral grafts, including the stomach, the pancreaticoduodenal complex, the liver and the small intestine. The remaining liver-containing allograft was a combined liver and intestinal graft with a segmental pancreas. Three of eight patients with a spleen included in their multivisceral graft developed GVHD. One patient with GVHD and manifestations with skin rash later developed post-transplant lymphoproliferative disorder (PTLD).

In 2014, Calvo Pulido reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants.[35] Thirteen patients (62%) experienced renal failure; the etiology included high ileostomy output, immunosuppression and medical treatment.

In 2013, Boyer reported that 7 of 12 children who had an isolated small bowel transplant had renal function complications at some point after surgery.[36] Prior to treatment, all of the patients had normal renal functioning.

Florescu have published several articles retrospectively reviewing complications in a cohort of 98 pediatric patients. Twenty-one of these children (21.4%) had an isolated small bowel transplant; the remainder had combined transplants. These articles include a 2012 study that reported that 68 of the 98 patients (69%) developed at least one episode of bloodstream infection.[37] Among the patients with an isolated small bowel transplant, the median time to infection for those who became infected was 4.5 months (95% confidence interval [CI]: 2.4 to 6.7 months). Also in 2012, the researchers reported that 7 of 98 patients (7%) developed cytomegalovirus (CMV) disease; only one of these had an isolated small bowel transplant.[38] A 2010 study by this group retrospectively reported on the incidence of fungal infection after pediatric small bowel transplantation among patients treated between 2003 and 2007 at a single center.[39] The average length of follow-up was not reported. A total of 25 of 98 cases reviewed (26%) developed at least one episode of fungal infection; Candida infection was most common. During the study period, the mortality rate did not differ significantly between patients who did and did not develop a fungal infection (32.3% vs. 29.8%, respectively), but the authors stressed the importance of better screening tools to identify and prevent fungal infections.

As noted previously, Sudan reported oral aversion to be a common problem in pediatric patients with tube feedings necessary in 45% of children following small bowel transplantation.[10]

A 2012 retrospective review focused on the rate of kidney dysfunction, a recognized complication after non-renal solid organ transplantation, in 33 multivisceral and 15 isolated small bowel transplant patients.[40] A significant decline in kidney function was reported in 46% of patients at one year following transplantation. A significant correlation was found for patient

age, pretransplant serum creatinine, estimated GFR (eGFR) at post-transplant day 30, 90, 180, and 270, and tacrolimus level at post-transplant day seven. Lesser decline was found in pediatric patients and patients with multivisceral transplantation compared with adults or isolated small bowel transplantation.

A 2012 retrospective review reported on bloodstream infections among 98 children younger than age 18 years with small bowel/combined organ transplants.[37] Seventy-seven (79%) patients underwent small bowel transplant in combination with a liver, kidney, or kidney-pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients remained alive. The one-year survival rate was similar in patients with combined small bowel transplant (75%) and those with isolated small bowel transplant (81%). In the first year after transplantation, 68 patients (69.4%) experienced at least one episode of bloodstream infection. The one-year survival rate for patients with bloodstream infections was 72% compared to 87% in patients without bloodstream infections (p=0.056 for difference in survival in patients with and without bloodstream infections).

Wu (2011) reported on complications after small bowel and multivisceral transplantation in 241 patients who underwent intestinal transplantation.[41] Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants and 12% had small bowel/liver transplants. There were 151 children (63%) and 90 adults. A total of 22 patients (9%) developed graft-versus-host disease (GVHD). Children younger than five years old were more likely to develop GVHD; the incidence in this age group was 16 of 121 (13.2%) compared to 2 of 30 (6.7%) in children between 5 and 18 years and 9 of 90 (4.4%) in adults over 18 years. Among diseases, patients with intestinal atresia were more likely to develop GVHD than those with other conditions (22.2% vs. 2.6%, respectively, p=0.03).

Transplant Recipients with Tumors

Duchateau (2022) published a systematic review of reported experiences of combined liver-intestinal and multivisceral transplantation (MvTx) for neuroendocrine tumors (NET) extending beyond the liver.[42] Fourteen single-center and three multi-center retrospective studies reported on one combined liver-intestinal and 38 MvTx for NET and nine previously unreported MvTx were added to the analysis by the authors. Overall patient survival up to 51.2% was found with recurrence of 35%, which is similar to recurrence after liver transplantation for NET. In addition, the authors reported that patients with NET with diffuse abdominal presentation, normally considered a contraindication, may benefit from radical resection and MvTx. Additional studies to optimize post-transplant management are needed.

Cruz (2011) published results from a small case series (n=10) of patients with intra-abdominal desmoid tumors secondary to familial adenomatous polyposis who underwent multivisceral transplant.[43] All patients were able to discontinue home parenteral nutrition by an average 30 days after transplant. Estimated survival was 80% at five years, and desmoid tumors reoccurred in one patient 15 months after transplantation. However, conclusions from this study are limited by the small sample size and the lack of a comparison group, factors which do not allow for the isolation of transplant as a causative factor in patient health outcomes.

Retransplantation

Evidence for the use of retransplantation to treat individuals who have failed intestinal transplantations includes several case series, mostly from single institutions. One case series analyzed records from the United Network for Organ Sharing database.[44] Among the case

series described in Table 1, reasons for retransplantation include: acute rejection, chronic rejection, CMV, liver failure, lymphoproliferative disorder, and graft dysfunction. Survival rates for retransplantation are listed in Table 2.

Table 1. Summary of Key Case Series Characteristics for Retransplantation

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up, (Range), mo
				Treatment	n	
Ekser (2018)[45]	United States	18	27 (0.9-57)	oIsolated IT oModified MVT oMultivisceral graft	1 1 16	NR
Kubal (2018)[46]	United States	23	27 (1-58)	oIsolated IT oMultivisceral graft	1 22	NR
Lacaille (2017)[47]	France	10	13 (5-16)	oIsolated IT oCombined liver IT	3 7	4
Desai (2012)[44]	United States	• 72 (adults) • 77 (children)	NR	*Adults:* oIsolated IT oCombined liver IT *Children:* oIsolated IT oCombined liver IT	 41 31 28 49	NR
Abu-Elmagd (2009)[48]	United States	47	NR	oIsolated IT oCombined liver IT oMultivisceral graft	31 7 9	NR
Mazariegos (2008)[49]	United States	14	9.4 (3.2-22.7)	oIsolated IT oCombined liver IT oMultivisceral graft	1 3 10	55.9

IT: intestinal transplantation; NR: not reported.

Table 2. Summary of Key Case Series Results for Retransplantation

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Ekser (2018)	oIsolated IT oMultivisceral graft oModified multivisceral graft	1 1 16	Graft survival: • 71% at 1 y, 56% at 3 y, 44% at 5 y Patient survival: • 71% at 1 y, 47% at 3 y, 37% at 5 y	NR
Kubal (2018)[46]	oIsolated IT oMultivisceral graft	1 22	All transplantations combined: o34% at 1 y	NR
Lacaille (2017)[47]	oIsolated IT oCombined liver IT	3 7	All transplantations combined: o30% at last follow-up	NR
Desai (2012)[44]	*Adults:* oIsolated IT oCombined liver IT *Children:* oIsolated IT oCombined liver IT	 41 31 28 49	*Adults:* o80% at 1 y; 47% at 3 y; 29% at 5 y o63% at 1 y; 56% at 3 y; 47% at 5 y *Children:* o81% at 1 y; 74% at 3 y; 57% at 5 y o42% at 1 y; 42% at 3 y; 42% at 5 y	NR
Abu-Elmagdl (2009)[48]	oIsolated IT oCombined liver IT oMultivisceral graft	31 7 9	All transplantations combined: o69% at 1 y o47% at 5 y	NR

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Mazariegos (2008)[49]	o Isolated IT o Combined liver IT o Multivisceral graft	1 3 10	All transplantations combined: o 71% at last follow-up	100%

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

Survival Outcomes

The published literature consists of case series, mainly reported by single centers in the United States and Europe. Tables 3 and 4 summarize the characteristics and results of the case series, respectively. Many case series have included isolated small bowel transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off TPN. Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multivisceral transplants (see Table 4).

Several investigators have reported higher survival rates in transplants conducted more recently than those conducted earlier.[44, 48, 50] Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex procedure.

Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

Table 3. Summary of Key Case Series Characteristics for Transplantations

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
				Treatment	n	
Raghu (2019)[51]	International	2,080	2.5 (1.1-6.3)	• Isolated IT • Combined liver IT • Multivisceral graft	725 966 389	5 y
Elsabbagh (2019)[52]	United States	174	19 (0.42–66)	• Isolated IT • Combined liver IT • Multivisceral graft • Modified multivisceral	98 44 28 4	8.1 (3-13.2) y
Lacaille (2017)[47]	France	110	5.3 (0.4-19)	• Isolated IT • Combined liver IT • Multivisceral graft	45 60 5	Of 55 alive: • 17 at <5 y • 17 at 5-10 y • 21 at ≥10 y
Garcia Aroz (2017)[53]	United States	10	1.5 (0.7-13)	• Isolated IT • Combined liver IT	7 3	6/7 alive at follow-up ≥10 y
Dore (2016)[54]	United States	30	0.2 (0.1-18)	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	28 (4-175) mo

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
				Treatment	n	
Rutter (2016)[55]	United Kingdom	60	1.8 (0-8)	• Isolated IT • Multivisceral graft • Modified multivisceral	16 35 9	21.3 (0-95) mo
Lauro (2014)[56]	Italy	46	34 (NR)	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	51.3 mo
Varkey (2013)[57]	Sweden	20	Adults: • 44 (20-67) Children: • 6 (0.5-13)	• Isolated IT • Combined liver IT • Multivisceral graft	4 1 15	NR
Mangus (2013)[50]	United States	100	Adults: • 48 (NR to 66) Children: • 1 (0.6 to NR)	• Multivisceral graft • Modified multivisceral	84 16	25 mo

IT: intestinal transplantation; NR: not reported.
[a] Living donors.

Table 4. Summary of Key Case Series Results for Transplantations

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Raghu (2019)[51]	• Isolated IT • Combined liver IT • Multivisceral graft	725 966 389	All transplantations combined: • Patient survival: 72.7% at 1 y, 57.2 at 5 y • Graft survival: 66.1% at 1 y, 47.8% at 5y	NR
Elsabbagh (2019)[52]	• Isolated IT • Combined liver IT • Multivisceral graft • Modified multivisceral	98 44 28 4	All transplantations combined: • 69.5% at 3 y • 66% at 5 y • 63% at 10 y	NR
Lacaille (2017)[47]	• Isolated IT • Combined liver IT • Multivisceral graft	60 45 5	• 59% at 10 y; 54% at 18 y • 48% at 10 y • NR	All treatments combined: • 73% at last follow-up
Garcia Aroz (2017)[53]a	• Isolated IT • Combined liver IT	7 3	All transplantations combined: • 70%	All treatments combined: • 100% at last follow-up
Dore (2016)[54]	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	• 83% at 9 y • 33% at 10 y • 67% at 2.5 y	All treatments combined: • 71% in 31 d • 62% at last follow-up
Rutter (2016)[55]	• Isolated IT • Multivisceral graft • Modified multivisceral	16 35 9	• 92% at 1 y; 37% at 5 y • 71% at 1 y; 33% at 5 y • 85% at 1 y; 65% at 5 y	NR

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Lauro (2014)[56]	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	All transplantations combined: • 77% at 1 y • 58% at 3 y • 53% at 5 y • 37% at 10 y	NR
Varkey (2013)[57]	• Isolated IT • Combined liver IT • Multivisceral graft	4 1 15	All transplantations combined: • 78% at 1 y • 50% at 5 y	NR
Mangus (2013)[50]	• Multivisceral graft • Modified multivisceral	84 16	All transplantations combined: • 72% at 1 y • 57% at 5 y	NR

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.
[a] Living donors.

HIV POSITIVE TRANSPLANT RECIPIENTS

This subgroup of recipients has long been controversial due to the long term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Although HIV positive transplant recipients may be a research interest of some transplant centers, the minimal data regarding long term outcomes in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

The Organ Procurement and Transplantation Network (OPTN) considers HIV+ organ candidates to be acceptable recipients "if permitted by the transplant hospital. Care of HIV test positive organ candidate and recipients should not deviate from general medical practice."[58]

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

In 2022, The American Gastroenterological Association published a clinical practice update on the management of short bowel syndrome (SBS) that includes best practice advice on referral for intestinal transplantation.[59] The update is focused on adult patients. In general, early referral for transplant is recommended to avoid the need for simultaneous liver transplant, which leads to increased mortality risk while on the waiting list. Referral for intestinal transplant is recommended for:

- People with SBS-IF and onset of TPN failure. Patients with SBS-IF who have high morbidity or low acceptance of TPN should be considered for referral to transplant individually.

Transplant referral is also suggested for certain patients who do not meet criteria for TPN failure:

- Post-operative referral for patients with large abdominal desmoid tumors.
- Patients with severe dysmotility syndromes who have no prospect of weaning from TPN.

XIV INTERNATIONAL SMALL BOWEL TRANSPLANT SYMPOSIUM WORKING GROUP CRITERIA FOR PLACEMENT ON A WAITLIST FOR INTESTINAL TRANSPLANTATION

In 2020, Kaufman published an update of the 2001 American Society of Transplantation Indications.[5] The new guidance was developed by a multidisciplinary team of providers and is based on practice advances since 2001 that have led to improved management of SBS both with and without small bowel transplant.

Criteria for placement on a waitlist for intestinal transplantation:

- Evidence of advanced or progressive intestinal failure-associated liver disease
    - Hyperbilirubinemia >75 µmol/L[b] (4.5 mg/dL) despite intravenous lipid modification strategies that persists for >2 months.
    - Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 month in the absence of a confounding infectious event(s).
- Thrombosis of:
    - 3 out of 4 discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) or
    - Occlusion of a brachiocephalic vein in children (in adults, this criterion should be evaluated in a case-by-case basis).
- Live-threatening morbidity in the setting of indefinite parenteral nutrition dependence of either anatomical or functional cause, as suggested by:
    - In children, 2 admissions to an intensive care unit (after initial recovery from the event resulting in intestinal failure) because of cardiorespiratory failure (mechanical ventilation or inotrope infusion) due to sepsis or other complication of intestinal failure
    - In adults, on a case-by-case basis.
- Invasive intra-abdominal desmoids in adolescents and adults
- Acute diffuse intestinal infarction with hepatic failure
- Failure of first intestinal transplant

SUMMARY

There is enough research to show that small bowel transplant from a living donor does not improve health outcomes in certain patient populations except when a cadaveric intestine is not available. Therefore, small bowel transplant from a living donor is considered not medically necessary in all other situations except when a cadaveric intestine is not available and is indicated.

There is enough research to show that small bowel transplants can improve health outcomes in certain patients with intestinal failure with serious complications from total parenteral nutrition (TPN). Therefore, isolated small bowel transplant may be considered medically necessary in patients that meet the policy criteria.

There is enough research to show that small bowel transplant does not improve health outcomes in patients with intestinal failure who are able to tolerate TPN. Therefore, small bowel transplant may be considered not medically necessary for these patients.

There is enough research to show that small bowel retransplant improves health outcomes in patients that have had a failed small bowel transplant. Therefore, for patients with failed small bowel transplant, retransplant may be considered medically necessary.

There is enough research to show that small bowel transplant from a living donor does not improve health outcomes in certain patient populations except when a cadaveric intestine is not available. Therefore, small bowel transplant from a living donor is considered not medically necessary in all other situations except when a cadaveric intestine is not available and is indicated.

There is enough research to show that small bowel/liver and multivisceral transplant and retransplant can improve survival in certain patients. Therefore, these procedures may be considered medically necessary for patients with intestinal failure who have been managed with long-term total parenteral nutrition and who have developed evidence of impending end-stage liver failure. Transplants or retransplants are considered not medically necessary when the policy criteria are not met.

REFERENCES

1. O'Keefe SJ, Buchman AL, Fishbein TM, et al. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol.* 2006;4(1):6-10. PMID: 16431298
2. Organ Procurement and Transplantation Network (OPTN). National Data. [cited 1/5/2024]. 'Available from:' https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
3. Matarese LE, Costa G, Bond G, et al. Therapeutic efficacy of intestinal and multivisceral transplantation: survival and nutrition outcome. *Nutr Clin Pract.* 2007;22(5):474-81. PMID: 17906271
4. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. *Adv Surg.* 2008;42:129-50. PMID: 18953814

5. Kaufman SS, Avitzur Y, Beath SV, et al. New Insights Into the Indications for Intestinal Transplantation: Consensus in the Year 2019. *Transplantation.* 2020;104(5):937-46. PMID: 31815899
6. International Intestinal Transplant Registry: 2019 Report. [cited 2/2/2024]. 'Available from:' https://graphics.tts.org/ITR_2019_ReportSlides.pdf.
7. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal transplant registry report: global activity and trends. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2015;15(1):210-9. PMID: 25438622
8. TEC Assessment 1995. "Transplants Involving the Small Bowel." BlueCross BlueShield Association Technology Evaluation Center, Vol. 10, Tab 27.
9. TEC Assessment 1999. "Small Bowel Transplants in Adults and Multivisceral Transplants in Adults and Children." BlueCross BlueShield Association Technology Evaluation Center, Vol. 14, Tab 9.
10. Sudan D. Long-term outcomes and quality of life after intestine transplantation. *Curr Opin Organ Transplant.* 2010;15(3):357-60. PMID: 20445450
11. Gruessner RW, Sharp HL. Living-related intestinal transplantation: first report of a standardized surgical technique. *Transplantation.* 1997;64(11):1605-7. PMID: 9415566
12. Jaffe BM, Beck R, Flint L, et al. Living-related small bowel transplantation in adults: a report of two patients. *Transplant Proc.* 1997;29(3):1851-2. PMID: 9142299
13. Fujimoto Y, Uemoto S, Inomata Y, et al. Living-related small bowel transplant: management of rejection and infection. *Transplant Proc.* 1998;30(1):149. PMID: 9474986
14. Tesi R, Beck R, Lambiase L, et al. Living-related small-bowel transplantation: donor evaluation and outcome. *Transplant Proc.* 1997;29(1-2):686-7. PMID: 9123480
15. Cicalese L, Baum C, Brown M, et al. Segmental small bowel transplant from adult living-related donors. *Transplant Proc.* 2001;33(1-2):1553. PMID: 11267417
16. Wu GS, Wang WZ, Song WL, et al. The living-related small bowel transplant: the first case in China. *Transplant Proc.* 2000;32(6):1218. PMID: 10995917
17. Cicalese L, Sileri P, Coady N, et al. Proposed protocol to reduce bacterial infectious complications in living related small bowel transplant recipients. *Transplant Proc.* 2002;34(3):950. PMID: 12034255
18. Wada M, Ishii T, Kato T, et al. Living-related small bowel transplantation: two cases experiences. *Transplant Proc.* 2005;37(2):1381-2. PMID: 15848727
19. Ueno T, Wada M, Hoshino K, et al. Impact of intestinal transplantation for intestinal failure in Japan. *Transplant Proc.* 2014;46(6):2122-4. PMID: 25131121
20. Gangemi A, Benedetti E. Living donor small bowel transplantation: literature review 2003-2006. *Pediatr Transplant.* 2006;10(8):875-8. PMID:
21. Benedetti E, Holterman M, Asolati M, et al. Living related segmental bowel transplantation: from experimental to standardized procedure. *Ann Surg.* 2006;244(5):694-9. PMID: 17060761
22. Chang YC, Young RR, Mavis AM, et al. Epstein-Barr Virus DNAemia and post-transplant lymphoproliferative disorder in pediatric solid organ transplant recipients. *PLoS One.* 2022;17(10):e0269766. PMID: 36256635
23. Santarsieri A, Rudge JF, Amin I, et al. Incidence and outcomes of post-transplant lymphoproliferative disease after 5365 solid-organ transplants over a 20-year period at two UK transplant centres. *Br J Haematol.* 2022;197(3):310-19. PMID: 35235680

24. Clouse JW, Kubal CA, Fridell JA, et al. Post-intestine transplant graft-vs-host disease associated with inclusion of a liver graft and with a high mortality risk. *Clinical transplantation.* 2019;33(1):e13409. PMID: 30222903
25. Spence AB, Natarajan M, Fogleman S, et al. Intra-abdominal infections among adult intestinal and multivisceral transplant recipients in the 2-year post-operative period. *Transpl Infect Dis.* 2020;22(1):e13219. PMID: 31778012
26. Raveh Y, Rodriguez Y, Pretto E, et al. Thrombotic and hemorrhagic complications during visceral transplantation: risk factors, and association with intraoperative disseminated intravascular coagulation-like thromboelastographic qualities: a single-center retrospective study. *Transplant international : official journal of the European Society for Organ Transplantation.* 2018;31(10):1125-34. PMID: 29786890
27. Danziger-Isakov L, Steinbach WJ, Paulsen G, et al. A Multicenter Consortium to Define the Epidemiology and Outcomes of Pediatric Solid Organ Transplant Recipients With Inpatient Respiratory Virus Infection. *Journal of the Pediatric Infectious Diseases Society.* 2018. PMID: 29538674
28. Vo HD, Florescu DF, Brown CR, et al. Invasive pneumococcal infections in pediatric liver-small bowel-pancreas transplant recipients. *Pediatr Transplant.* 2018. PMID: 29441651
29. Nagai S, Mangus RS, Anderson E, et al. Cytomegalovirus Infection After Intestinal/Multivisceral Transplantation: A Single-Center Experience With 210 Cases. *Transplantation.* 2016;100(2):451-60. PMID: 26247555
30. Timpone JG, Yimen M, Cox S, et al. Resistant cytomegalovirus in intestinal and multivisceral transplant recipients. *Transpl Infect Dis.* 2016;18(2):202-9. PMID: 26853894
31. Wu GS, Cruz RJ, Jr., Cai JC. Acute antibody-mediated rejection after intestinal transplantation. *World journal of transplantation.* 2016;6(4):719-28. PMID: 28058223
32. Limketkai BN, Orandi BJ, Luo X, et al. Mortality and Rates of Graft Rejection or Failure Following Intestinal Transplantation in Patients With vs Without Crohn's Disease. *Clin Gastroenterol Hepatol.* 2016;14(11):1574-81. PMID: 27374004
33. Cromvik J, Varkey J, Herlenius G, et al. Graft-versus-host Disease After Intestinal or Multivisceral Transplantation: A Scandinavian Single-center Experience. *Transplant Proc.* 2016;48(1):185-90. PMID: 26915866
34. Varkey J, Simren M, Jalanko H, et al. Fifteen years' experience of intestinal and multivisceral transplantation in the Nordic countries. *Scandinavian journal of gastroenterology.* 2015;50(3):278-90. PMID: 25592555
35. Calvo Pulido J, Jimenez Romero C, Morales Ruiz E, et al. Renal failure associated with intestinal transplantation: our experience in Spain. *Transplant Proc.* 2014;46(6):2140-2. PMID: 25131125
36. Boyer O, Noto C, De Serre NP, et al. Renal function and histology in children after small bowel transplantation. *Pediatr Transplant.* 2013;17(1):65-72. PMID: 22882667
37. Florescu DF, Qiu F, Langnas AN, et al. Bloodstream infections during the first year after pediatric small bowel transplantation. *The Pediatric infectious disease journal.* 2012;31(7):700-4. PMID: 22466325
38. Florescu DF, Langnas AN, Grant W, et al. Incidence, risk factors, and outcomes associated with cytomegalovirus disease in small bowel transplant recipients. *Pediatr Transplant.* 2012;16(3):294-301. PMID: 22212495
39. Florescu DF, Islam KM, Grant W, et al. Incidence and outcome of fungal infections in pediatric small bowel transplant recipients. *Transpl Infect Dis.* 2010;12(6):497-504. PMID: 20626710

40. Suzuki M, Mujtaba MA, Sharfuddin AA, et al. Risk factors for native kidney dysfunction in patients with abdominal multivisceral/small bowel transplantation. *Clinical transplantation.* 2012;26(4):E351-8. PMID: 22694120
41. Wu G, Selvaggi G, Nishida S, et al. Graft-versus-host disease after intestinal and multivisceral transplantation. *Transplantation.* 2011;91(2):219-24. PMID: 21076376
42. Duchateau NM, Canovai E, Vianna RM, et al. Combined liver-intestinal and multivisceral transplantation for neuroendocrine tumors extending beyond the liver: A systematic literature review. *Transplant Rev (Orlando).* 2022;36(1):100678. PMID: 35090785
43. Cruz RJ, Jr., Costa G, Bond GJ, et al. Modified multivisceral transplantation with spleen-preserving pancreaticoduodenectomy for patients with familial adenomatous polyposis "Gardner's Syndrome". *Transplantation.* 2011;91(12):1417-23. PMID: 21512435
44. Desai CS, Khan KM, Gruessner AC, et al. Intestinal retransplantation: analysis of Organ Procurement and Transplantation Network database. *Transplantation.* 2012;93(1):120-5. PMID: 22113492
45. Ekser B, Kubal CA, Fridell JA, et al. Comparable outcomes in intestinal retransplantation: Single-center cohort study. *Clinical transplantation.* 2018;32(7):e13290. PMID: 29782661
46. Kubal CA, Pennington C, Fridell J, et al. Challenges with Intestine and Multivisceral Re-Transplantation: Importance of Timing of Re-Transplantation and Optimal Immunosuppression. *Annals of transplantation.* 2018;23:98-104. PMID: 29402878
47. Lacaille F, Irtan S, Dupic L, et al. Twenty-eight years of intestinal transplantation in Paris: experience of the oldest European center. *Transplant international : official journal of the European Society for Organ Transplantation.* 2017;30(2):178-86. PMID: 27889929
48. Abu-Elmagd KM, Costa G, Bond GJ, et al. Five Hundred Intestinal and Multivisceral Transplantations at a Single Center: Major Advances With New Challenges. *Ann Surg.* 2009. PMID: 19730240
49. Mazariegos GV, Soltys K, Bond G, et al. Pediatric intestinal retransplantation: techniques, management, and outcomes. *Transplantation.* 2008;86:1777-82. PMID: 19104421
50. Mangus RS, Tector AJ, Kubal CA, et al. Multivisceral transplantation: expanding indications and improving outcomes. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(1):179-86; discussion p 86-7. PMID: 23070622
51. Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. *Pediatr Transplant.* 2019;23(8):e13580. PMID: 31531934
52. Elsabbagh AM, Hawksworth J, Khan KM, et al. Long-term survival in visceral transplant recipients in the new era: A single-center experience. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2019. PMID: 30672105
53. Garcia Aroz S, Tzvetanov I, Hetterman EA, et al. Long-term outcomes of living-related small intestinal transplantation in children: A single-center experience. *Pediatr Transplant.* 2017;21(4). PMID: 28295952
54. Dore M, Junco PT, Andres AM, et al. Surgical rehabilitation techniques in children with poor prognosis short bowel syndrome. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie.* 2016;26(1):112-6. PMID: 26535775

55. Rutter CS, Amin I, Russell NK, et al. Adult Intestinal and Multivisceral Transplantation: Experience From a Single Center in the United Kingdom. *Transplant Proc.* 2016;48(2):468-72. PMID: 27109980
56. Lauro A, Zanfi C, Dazzi A, et al. Disease-related intestinal transplant in adults: results from a single center. *Transplant Proc.* 2014;46(1):245-8. PMID: 24507060
57. Varkey J, Simren M, Bosaeus I, et al. Survival of patients evaluated for intestinal and multivisceral transplantation - the Scandinavian experience. *Scandinavian journal of gastroenterology.* 2013;48(6):702-11. PMID: 23544434
58. Organ Procurement and Transplantation Network (OPTN) Policies. 12/13/2023 [cited 1/5/2024]. 'Available from:' https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf.
59. Iyer K, DiBaise JK, Rubio-Tapia A. AGA Clinical Practice Update on Management of Short Bowel Syndrome: Expert Review. *Clin Gastroenterol Hepatol.* 2022;20(10):2185-94.e2. PMID: 35700884

CODES

Codes	Number	Description
CPT	43999	Unlisted procedure, stomach
	44132	Donor enterectomy (including cold preservation), open; from cadaver donor
	44133	Donor enterectomy (including cold preservation), open partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
	44799	Unlisted procedure, small intestine
	47133	Donor hepatectomy, (including cold preservation) from cadaver donor
	47135	Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	;total left lobectomy (segments II, III and IV)
	47142	;total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	;with trisegment split of whole liver graft into 2 partial liver grafts (ie, left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
	47145	;with lobe split of whole liver graft into 2 partial liver grafts (ie, left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each

Codes	Number	Description
	47399	Unlisted procedure, liver
	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
	48999	Unlisted procedure, pancreas
HCPCS	S2053	Transplantation of small intestine, and liver allografts
	S2054	Transplantation of multivisceral organs
	S2055	Harvesting of donor multivisceral organs, with preparation and maintenance of allografts; from cadaver donor
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre and posttransplant care in the global definition

Date of Origin: *January 1996*

Regence

Medical Policy Manual Transplant, Policy No. 13

Islet Transplantation

Effective: July 1, 2023

Next Review: March 2024
Last Review: May 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Islet cells are responsible for producing insulin, which is necessary for the regulation of blood glucose levels. Following islet transplantation, it is proposed that the beta cells in the transplanted islets will begin to make and release insulin.

MEDICAL POLICY CRITERIA

I. Autologous pancreas islet cell transplantation may be considered **medically necessary** as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

II. Autologous pancreas islet cell transplantation for all other indications is considered **investigational**.

III. Allogeneic and xeno islet cell transplantation for any diagnosis are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Pancreas Transplant, Transplant, Policy No. 6

BACKGROUND

CHRONIC PANCREATITIS

Although the incidence of chronic pancreatitis is rising, it is still a relatively rare condition, affecting an estimated seven to eight new people out of every 100,000 people each year.[1] Some patients with chronic pancreatitis may experience intractable pain that can only be relieved with a total or near-total pancreatectomy. However, the pain relief must be balanced against the certainty that the patient will be rendered an insulin-dependent diabetic. Autologous islet cell transplantation, also called islet autotransplantation (IAT), has been investigated as a technique to prevent this serious morbidity.

TYPE 1 DIABETES

Glucose control is a challenge for individuals with type 1 diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease.[2]

ISLET TRANSPLANTATION

In autologous islet transplantation during the pancreatectomy procedure, islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient's liver. Once implanted, the beta cells in these islets begin to make and release insulin.

Allogeneic islet cell transplantation is normally conducted as a stand-alone procedure among patients with type 1 diabetes. Islet cells, harvested from a deceased donor's pancreas, are processed and injected into the recipient's portal vein.

Allogeneic islet cell transplantation potentially offers an alternative to whole-organ pancreas transplantation to treat type 1 diabetes, restore normoglycemia and ultimately reduce or eliminate the long-term complications of diabetes, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. However, a limitation of islet cell transplantation is that two or more donor organs are usually required for successful transplantation, and only pancreases rejected for whole-organ transplant are typically used for islet transplantation. Due to limited islet cell supply, allogeneic islet cell transplantation is recommended only for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management. In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen was developed in Edmonton, Canada and is known as the "Edmonton protocol."

While most of the published research to date involves the transplantation of allogeneic human islet cells, there is also interest in xenotransplantation, using porcine islet cells.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Allogeneic islet cells are included in these regulations.

EVIDENCE SUMMARY

AUTOLOGOUS ISLET CELL TRANSPLANT AS AN ADJUNCT TO PANCREATECTOMY

Autologous islet cell transplantation as an adjunct to pancreatectomy or near total pancreatectomy among patients with chronic pancreatitis has been investigated since 1977. Since then, the experience has grown slowly with incremental improvements in the islet cell isolation process. The focus of this section is on systematic reviews.

Systematic Reviews

Zhang (2020) published a systematic review and meta-analysis of 17 studies that reported clinical outcomes following total pancreatectomy with islet transplant in patients with chronic pancreatitis.[3] Most studies were single-center, small case series from the United States. The median age was 53 years. Insulin independence was 33.29% (95% CI 27.77 to 39.05; I^2=32.3%) at one year (eight studies). Mortality at 30 days was 1.32% (95% CI 0.68 to 2.16; I^2=0.0%) and mortality at one year was 2.54% (95% CI 1.32 to 4.16; I^2=17.6%).

Kempeneers (2019) published a systematic review of studies examining pain, endocrine function, or quality of life outcomes in patients with chronic pancreatitis undergoing total pancreatectomy with islet transplantation.[4] A total of 15 studies met the inclusion criteria. All included studies were retrospective and observational. The median age was 41 years. Pooled insulin free rate was 30% (95% confidence interval [CI] 20% to 43%) at one year (four studies). The pooled mortality rate was 2% (95% CI 1% to 4%) at 30 days (11 studies) and 4% at one year (six studies). At one year, 63% (95% CI 46% to 77%, I^2=89%) of patients were opioid free (six studies, 657 patients). An analysis revealed a high risk for publication bias among the included studies, which could have led to an overestimation of the true affect.

In 2015, Wu published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis.[5] Studies could use any type of design but needed to include at least five patients or have a median follow-up of at least six months. Twelve studies with a total of 677 patients met the review's inclusion criteria. The mean age of the patients was 38 years and mean duration of pancreatitis was 6.6 years. A meta-analysis of the insulin independence rate at one year (five studies, 362 patients) was 28.4% (95% CI 15.7% to 46.0%). At two years, the pooled insulin independence rate (three studies, 297 patients) was 19.7% (95% CI 5.1% to 52.6%). The pooled 30-day mortality rate (11 studies) was 2.1% (95% CI 1.2% to 3.8%). Long-term mortality data were not pooled.

In 2012, Bramis searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation.[6] Case series were included if they included more than five individuals and reported outcomes for

consecutive patients. A total of 72 full-text articles were reviewed, and five studies were found to meet inclusion criteria. The postoperative insulin independence rate in the five studies ranged from 10% (mean follow-up of eight years) to 46% (mean follow-up of five years). In the study with the longest follow-up, the insulin independence rate was 28% at ten years. Two studies reported postoperative morphine use with a decrease in morphine use of 116 mg and 55 mg, respectively.

A 2011 systematic review by Dong included studies regardless of design or sample size.[7] After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, two studies of partial pancreatectomy, and two studies that included both types of surgery. Sample sizes in individual studies ranged from three to 173 patients. Thirteen studies included patients with chronic pancreatitis, and two included patients with benign pancreatic tumors. The pooled 30-day mortality was 5% (95% CI 2 to 10%), and the cumulative mortality at one year (reported by ten studies) was 4.9% (95% CI 2.6 to 7.3%) In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100-person years (95% CI 1.53 to 7.62). The pooled rate of insulin independence at one year (five studies) was 27% (95% CI 21 to 33%) and at two years (three studies) was 21% (95% CI 16 to 27%).

ALLOGENEIC ISLET CELL TRANSPLANT FOR TYPE 1 DIABETES

Islet cell transplantation has also been investigated as a treatment for type 1 diabetes, particularly in patients with poor glucose control despite insulin therapy.

The principal outcomes associated with treatment of type 1 diabetes are improvement in overall mortality rate, and reductions in rates of diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease normally associated with type 1 diabetes. In order to understand the impact of islet cell transplantation for treatment of type 1 diabetes on these outcomes, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as insulin treatment, are needed. Further, an understanding of any adverse treatment effects, particularly those associated with life-long immunosuppressant therapy, must be carefully weighed against any benefits associated with islet transplantation to understand the net treatment effect of this therapy.

Systematic Reviews

In 2020, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a systematic review islet transplantation for type 1 diabetes.[8] Search dates were limited to January 1, 2014 to February 25, 2020. One systematic review, one RCT, and five non-randomized study met inclusion criteria. The one RCT (Lablanche 2018) is described in detail below. The reviewers concluded that the literature suggests that islet cell transplantation may lead to improved glycemic control and quality of life and additionally may reduce secondary complications of diabetes. There were many limitations noted, including the minimal availability of randomized studies, poor descriptions of the comparators, and lack of long-term follow-up and the authors noted that the results of these studies should be interpreted with caution given these numerous methodological limitations. Additionally, there was a trend of decreased insulin independence over time in three nonrandomized studies with long term follow-ups of 2, 5, and 10 years, which may indicate that the effectiveness of islet cell transplantation decreases over time.

In 2015 Health Quality Ontario published a systematic review on islet transplantation for type 1

diabetes, and included one health technology assessment, 11 observational, nonrandomized clinical studies, one registry report, and four guidelines.[9] There was a large degree of heterogeneity in patient populations, study design, and outcome measurement in the included studies. The reviewers reported that islet transplantation can improve blood sugar control and quality of life, and may reduce diabetic complications; however, the results were inconsistent between studies. Compared with insulin therapy, there were more adverse events with islet transplantation. The studies that were included that assessed health-related quality of life, secondary complications of diabetes, glycemic control, and adverse events were all ranked as low to very low quality, with two studies having high risk of bias. Therefore, uncertainty of the effectiveness of islet transplantation in type 1 diabetics still remains.

Randomized Controlled Trials

An open-label randomized controlled trial (RCT) was published by Lablanche in 2018 evaluating patients who had type 1 diabetes with severe hypoglycemia or in kidney transplant patients following transplantation.[10] A total of 50 patients with severe hypoglycemia, hypoglycemia unawareness, or kidney grafts with poor glycemic control received immediate islet transplantation (n=25) or intensive insulin therapy followed by delayed islet transplantation (n=22). Median follow-up was six months for both groups. The primary end point was a composite score (β score) which has not been validated and which reflected fasting glucose, HbA1c level, C-peptide, and insulin independence. The proportion of patients with a modified β-score of 6 or higher at six months was 64% of patients in the immediate transplantation group and 0% in the control group ($p<0.001$). Of note, few patients in the insulin group used continuous glucose monitoring or other technologies to monitor for hypoglycemia. At six months, insulin independence was achieved in 44% of patients in the immediate transplantation group (n= 25; $p=0.0004$). After the entire cohort received islet transplantation, the one-year insulin independence rate was 59% (n=46; $p<0.0001$). Negative effects reported at 12 months included bleeding complications in 7% of patients and a decrease in median glomerular filtration rate from 90.5 mL/min to 71.8 mL/min in islet transplant patients who had not previously received a kidney graft and from 63.0 mL/min to 57.0 mL/min in islet transplant patients who had previously received a kidney graft. Trial limitations included possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability.

Froud randomized 16 type 1 diabetes mellitus patients to evaluate cultured islet transplantation with or without tumor necrosis factor (TNF-alpha) blockade using Infliximab just prior to islet infusion.[11] Insulin independence was achieved in 14 patients after one to two infusions, and was maintained in 11 patients after one year, and in six patients at 33 +/- 6-months without additional infusions. The authors reported no identifiable clinical benefit with the use of Infliximab, but concluded cultured human islet allografts produced results comparable to freshly transplanted islets including normalization of HBA1c. Further research in larger studies is needed to explore different immunosuppressive regimens.

Nonrandomized Studies

Two prospective, Phase 3, single-arm, open-label, multicenter trials of purified human pancreatic islet cell transplant have been conducted in North America under the guidance of the National Institutes of Health-sponsored Clinical Islet Transplantation (CIT) Consortium.[12, 13] Hering (2016) studied 48 patients with type 1 diabetes, hypoglycemic unawareness, and a history of experiencing severe hypoglycemic events (Protocol CIT07).[13] The primary outcome

(HbA1c level ≤7% and freedom from severe hypoglycemia after one year) was achieved in 87.5% and 71% of patients at one and two years. Median HbA1c level decreased from 7.2% at baseline to 5.6% at one and two years (both p<0.001). Only two patients experienced severe hypoglycemia in the first year posttransplant. Insulin independence was achieved in 52.1% of patients at one year, and median insulin use decreased from 0.49 units/kg/day at baseline to 0 units/kg/day at one year (p<0.0003). Glomerular filtration rate decreased posttransplant (p<0.0008 vs. baseline) due to adverse effects of immunosuppression. Twenty-two serious adverse events during the first year were attributed to the procedure or subsequent immunosuppression.

Markmann (2021) reported results of a Phase 3 trial of human islet-after-kidney transplantation for type 1 diabetes. A total of 24 patients received purified human pancreatic islets. The primary endpoint of freedom from severe hypoglycemic events and HbA1c ≤ 6.5% or reduced by ≥ 1 percentage point at one-year posttransplant was achieved in 62.5% of patients. Median HbA_{1c} was significantly reduced versus baseline at one, two, and three years post-transplant (8.1%, 6.0%, 6.3%, and 6.3%, respectively; p<0.001). Severe hypoglycemia was eliminated in 79.2% of patients at one year, 75% at two years, and 62.5% at three years. Median insulin requirements decreased from 0.5 units/kg/day at baseline to 0 units/kg/day at one, two, and three years (p<0.001, p<0.001, and p=0.002, respectively). Kidney function remained stable throughout follow-up. Thirteen serious adverse events were considered related or possibly related to islet transplant or immunosuppression.

Lemos (2021) reported 20-year results for a retrospective series of 49 patients with type 1 diabetes, hypoglycemic unawareness, and severe hypoglycemia who underwent islet allotransplant.[14] Median follow-up time after transplant was 13.8 years. Median duration of graft function while on immunosuppression was 4.4 years (interquartile range, 1.3 to 12.2 years). Kaplan-Meier survival analysis showed cumulative survival of >80% at 20 years; two patients died during follow-up, one from myocardial infarction and one from suspected hypoglycemia.

In 2015 Caiazzo assessed procedure-related complications on long-term outcome of islet transplantation in 26 patients with type 1 diabetes.[15] Each patient had two to three intraportal islet infusions, performed surgically or under ultrasound guidance, within a three-month time frame. Complications included: bowel obstruction, biliary peritonitis and a major hepatic hematoma. The investigators reported no deaths or patient dropouts. Early complications occurred in nine of 68 procedures. Procedure-related complications negatively impacted graft function (p = 0.009) and was an independent negative predictor of long-term graft survival (p=0.033) in multivariate analysis. The investigators concluded that even nonsevere complications occurring during islet transplantation, despite islet preparation method or transplantation method, significantly impair primary graft function and graft survival.

Moassesfar (2016) compared safety and efficacy of islet cell transplantation to pancreas transplantation at a center in the U.S.[16] Sequential patients with type 1 diabetes had either an islet cell transplant (n=10) or a pancreas transplant (n=15). After one year, 90% of patients in the islet group and 93% of patients in the pancreas group were insulin independent. At three years, the proportion with insulin independence dropped to 70 % and 64%, respectively. The authors concluded that islet cell transplantation can produce similar outcome to pancreatic transplantation.

In 2013, Rickels reported on 12 patients with type 1 diabetes and severe hypoglycemia who had islet transplantation.[17] Mean glycosylated hemoglobin decreased from 7.0%±0.3% before the procedure to 5.6%±0.1% after six to seven months ($p<0.01$). All of the insulin sensitivity measures were significantly less than normal before islet transplantation and not significantly different from normal after transplantation. Adverse events were not discussed.

In 2013, O'Connell reported on 17 patients who underwent islet transplantation for type 1 diabetes and severe hypoglycemia.[18] The primary end point was the proportion of patients who had had an HbA1c less than 7% and no severe hypoglycemic events two months after the initial transplant. (Patients could have one or two infusions.) Fourteen of the 17 (82%) patients achieved the primary end point. Nine (53%) patients attained insulin independence for a median of 26 months. At the time of data analysis for this publication, six patients remained insulin independent. Most adverse events were related to immunosuppression. Seven of the 17 (41%) patients developed mild lymphopenia and one developed Clostridium difficile colitis; these all responded to treatment. Eight patients developed anemia shortly after transplant and one required a blood transfusion. Procedure-related complications included one partial portal vein thrombosis and three postoperative bleeds; two of the bleeds required transfusion. Patients were followed for different amounts of time; long-term follow-up data were not available for a consistent length of time.

In 2012, Vantyghem reported on 23 patients with type 1 diabetes who underwent islet transplantation; 14 had islet-only transplants and nine had islet after kidney transplants.[19] Median HbA1c was 8.3% at baseline and 6.7% at three years. Ten of the 23 patients (43%) were insulin independent three years after islet transplantation. Findings were not reported separately for the islet-only transplant recipients.

In 2011 Thompson reported on a prospective cross-over study of intensive medical therapy (pre-transplant) versus islet cell transplantation among 32 patients with type 1 diabetes.[20] Following enrollment in the study, median follow-up was 47 months pre-transplant and 66 months post-transplant. Although improvements in HbA1c, retinopathy progression, and renal function were seen in the transplant group, small sample size and lack of treatment randomization limit interpretation of these findings. The authors also noted that their finding of reduced microvascular complications after islet transplantation may be due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil (MMF).

In 2006, Shapiro reported on 36 patients with type 1 diabetes mellitus that had undergone islet transplantation.[21] While short-term results were promising, insulin independence was generally not sustainable; only five patients were insulin-independent at two years. In a landmark study known as the Edmonton Protocol, seven consecutive patients achieved insulin independence following islet cell transplants from two to four donors on a glucocorticoid-free immunosuppressive regimen.[22] However, five-year outcomes from the first patients transplanted under the Edmonton protocol reported less than a 10% rate of insulin independence at five years, despite persistent graft survival as measured by C-peptide positivity (~80%).[23] The authors noted that problems with glycemic lability and hypoglycemia, the primary indications for transplant, were corrected; however, no clear advantages for chronic complications of diabetes (e.g., peripheral neuropathy) were evident. Chronic complications related to standard immunosuppressive therapy led to the need to alter the protocol in 23% of patients, thus leading the authors to conclude that "safer immunosuppression associated with fewer side effects is needed." Complications and side

effects related to both immunosuppression and the procedure itself are also reported to be more common than originally thought.[24] The experience of the transplant center itself has a demonstrated effect on patient outcomes, with the more experienced centers reporting higher success rates.

Long-term results from the Edmonton Protocol were published by Brennan (2016), who reported that all seven of the original subjects continued to have some islet function more than ten years after the transplantation.[25] One of the patients achieved insulin independence for eight years, but had graft failure 10.9 years after the first transplant. Of the other six subjects, three received an additional islet transplant, five were receiving insulin, and two were insulin-independent (with one taking liraglutide). None of the subjects had lymphoma, severe hypoglycemia, or opportunistic infections during follow-up.

Several other small case series have focused on identifying alternatives to current transplant techniques, studying encapsulated islet transplantation without immunosuppression,[26] optimizing single versus multiple-donor transplantations,[27] and comparing whole pancreas transplant to islet cell transplantation.[28, 29] Recent research also addresses islet-after-kidney transplantation.[30] However, results from these studies should be interpreted with caution as the small sample sizes (n≤ 66), lack of randomized treatment allocation and/or appropriate comparison groups do not allow for ruling out chance as an explanation of findings.

Current non-randomized studies of allogeneic islet cell transplantation appear to suggest an initial benefit (such as a decline in HbA1c levels, for example) associated with the transplant. However, as a 2010 review of this therapy notes:[31]

> "[O]ne cannot be certain of the claim that partially failed islet transplantation leads to the use of less insulin and less hypoglycemia on a cause-effect basis. It could just as easily be that patients who enter transplant programs come under close clinical scrutiny by interested diabetologists who begin managing them more skillfully."

Additional randomized controlled trials are needed to determine the strength and magnitude of potential benefits associated with this therapy and to isolate such the impact of such benefits from standard medical care.

REGISTRY DATA

LaBlanche (2021) reported 10-year outcomes from the Swiss-French GRAIL Network of 44 patients who received islet transplant for type 1 diabetes between 2003 and 2010.[32] Thirty one patients were still being followed at 10 years; six patients died between years 1 and 10 posttransplant. Median HbA1c levels were 7.2% (range, 6.2% to 8.0%) after 10 years compared to 8.0% pretransplant ($p<0.001$). One patient was insulin independent at 10 years and 73.9% were free of severe hypoglycemia. Insulin requirements were significantly lower posttransplant (0.3 units/kg/day vs. 0.5 units/kg/day; $p<.001$). Islet graft survival was 51.9% at 10 years.

Bretzel reported in 2007 data collected from the International Islet Transplant Registry from 1999-2004.[33] Data were available for 458 human islet cell transplantations. At 1-year post transplant, patient survival was 97%, islet grafts were functioning in 82% of the cases, and insulin independence was achieved in 43% of the cases.

Founded in 2001 by the National Institute of Diabetes, Digestive and Kidney Diseases, the Collaborative Islet Transplant Registry (CITR) has been collecting information on allogeneic

islet transplantation in North America, Europe, and Australia. The most recent peer-reviewed publication of CITR data was published in 2012.[34] The update focused on changes in outcomes over time in 677 patients, all of whom received a transplant as of December 31, 2010 (n=575 islet-only; n=102 kidney+islet). Unfortunately, outcomes presented in this report were limited by considerable levels of missing data which increased with longer follow-up. The missing data were reported to be a mixture of unavailable medical records and data still pending entry into the registry.

The authors reported improved insulin independence at three years post-transplant, from 27% in the early era (1999 to 2002, n=214) to 37% in the mid era (2003–2006, n = 255) and 44% in the most recent era (2007 to 2010, n=208; p=0.006 for years-by-era; p=0.01 for era alone). However, not all recipients in the latter era had reached the three-year milestone at the time of this updated report. The need for islet reinfusion for loss of function of first graft by one-year decreased significantly from 60 to 65% in 1999 to 2006 to 48% in 2007 to 2010 (p<0.01). There was also a modest decrease in clinically reportable adverse events in the 2007 to 2010 era, from 50 to 53% in 1999 to 2006 to 38% in 2007 to 2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999-2003 and 3.1% in 2007 to 2010. The authors did not report findings separately from the subset of patients who underwent islet-only transplants.

The Institute for Clinical and Experimental Medicine (IKEM), based in the Czech Republic, published results from a retrospective analysis of a registry of all patients receiving one or more allogeneic or autologous islet transplants from 2005 to 2010 (n=15 and n=5, respectively).[35] Although islet function was documented in 11 of 15 and three of five patients, respectively, after 12 months (as indicated by C-peptide levels), only one patient receiving an allogeneic transplant was able to achieve independence from insulin beyond 12 months. The authors conclude that islet transplant may be best suited for high-risk recipients, as “routine clinical application is still hampered by the limited availability of usable organ transplants and viability of transplanted islets.”

Results from the above registry reports should be interpreted with caution as these registries are not reflective of the complete North American experience with islet transplants; not all transplant centers participated in each regional endeavor, nor is data complete for all those who do participate. Therefore, there may be inherent bias in the data. The focus on intermediate outcomes instead of long-term health outcomes, also limits interpretation of these findings.

XENOTRANSPLANTATION

Although there is research interest in porcine islets as an alternative and potentially unlimited source of islet cells, current data from human clinical trials is limited to three case series.

Matsumoto (2016) transplanted two doses of encapsulated neonatal porcine islets (approximately 5000IEQ/kg and 10,000IEQ/kg) twice in two groups of four patients each with type 1 diabetes.[36] The two transplants were performed three months apart. One patient had a serious adverse event potentially related to the treatment, paralytic ileus, which was resolved with medication. While both groups had decreases in HbA1c, for the high dose group this difference remained significant at 600 days after the first transplant.

In 2011, Wang published results from a small clinical trial on the safety and feasibility of neonatal porcine islets (NPIs) in 22 patients in China.[37] However, only six of the 22 patients

were subsequently followed for more than two months, limiting conclusions about the long-term use of NPIs.

Also in 2011, Esquivel-Pérez published a report on 23 patients not on immunosuppression, transplanted with a porcine cell-filled device.[38] Following an average of 5.7 years post-transplantation, the researchers reported that the patients with the lowest levels of antibodies were significantly more likely to report higher insulin dose reductions. However, not all patients were able to attain low levels of antibodies, for reasons not clearly known. Therefore, this report provides evidence for transplantation protocols but does not address the clinical utility of xenotransplantation.

Current literature has not directly addressed problems related to xenograft rejection and xeno-zoonosis (transmission of animal disease to humans).

PRACTICE GUIDELINE SUMMARY

In 2021, the American Diabetes Association (ADA) updated their position statement on comprehensive care for patients with type 1 diabetes. The statement includes a recommendation with a C rating stating that “Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes.” In addition, it states:

> “Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, patients receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management.”

SUMMARY

There is enough research to show that autologous islet cell transplantation is relatively safe and can reduce the chance of developing diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. Therefore, autologous islet cell transplantation may be considered medically necessary as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

There is not enough research to show that autologous islet cell transplantation can improve health outcomes for people with any other conditions. Therefore, autologous pancreatic islet cell transplantation for all other indications is considered investigational.

Although there is research interest in porcine islets (xeno islet cells) as a source of islet cells and allogeneic transplantation, there is not enough research to show that xenotransplantation or allogeneic transplantation is safe and effective, and there are no clinical guidelines based on research that recommend xenotransplantation or allogeneic transplantation. Therefore, xeno islet cell transplantation and allogeneic islet transplantation for any diagnosis are considered investigational.

REFERENCES

1. Jupp J, Fine D, Johnson CD. The epidemiology and socioeconomic impact of chronic pancreatitis. *Best Pract Res Clin Gastroenterol.* 2010;24(3):219-31. PMID: 20510824
2. National Institute of Diabetes and Digestive and Kidney Diseases. Pancreatic Islet Transplantation. . [cited 5/9/2023]. 'Available from:' https://www.niddk.nih.gov/health-information/diabetes/overview/insulin-medicines-treatments/pancreatic-islet-transplantation.
3. Zhang YJ, Duan DD, Yuan H. Efficacy and safety of islet autotransplantation after total pancreatectomy in chronic pancreatitis: A systematic review and meta-analysis including 17 studies. *Clin Res Hepatol Gastroenterol.* 2020;44(4):598-608. PMID: 31523018
4. Kempeneers MA, Scholten L, Verkade CR, et al. Efficacy of total pancreatectomy with islet autotransplantation on opioid and insulin requirement in painful chronic pancreatitis: A systematic review and meta-analysis. *Surgery.* 2019;166(3):263-70. PMID: 31085044
5. Wu Q, Zhang M, Qin Y, et al. Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients [Review]. *Endocrine journal.* 2015;62(3):227-34. PMID: 25735805
6. Bramis K, Gordon-Weeks AN, Friend PJ, et al. Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *The British journal of surgery.* 2012;99(6):761-6. PMID: 22434330
7. Dong M, Parsaik AK, Erwin PJ, et al. Systematic review and meta-analysis: islet autotransplantation after pancreatectomy for minimizing diabetes. *Clinical endocrinology.* 2011;75(6):771-9. PMID: 21605156
8. Freige C, McCormack S, Ford C. CADTH Rapid Response Reports. Islet Cell Transplantation for Patients with Unstable or Uncontrollable Diabetes Mellitus: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright © 2020 Canadian Agency for Drugs and Technologies in Health., 2020.
9. Pancreas Islet Transplantation for Patients With Type 1 Diabetes Mellitus: A Clinical Evidence Review. *Ontario health technology assessment series.* 2015;15(16):1-84. PMID: 26644812
10. Lablanche S, Vantyghem MC, Kessler L, et al. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. *The lancet Diabetes & endocrinology.* 2018;6(7):527-37. PMID: 29776895
11. Froud T, Ricordi C, Baidal DA, et al. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. *Am J Transplant.* 2005;5(8):2037-46. PMID: 15996257
12. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. *Am J Transplant.* 2021;21(4):1477-92. PMID: 32627352
13. Hering BJ, Clarke WR, Bridges ND, et al. Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia. *Diabetes care.* 2016;39(7):1230-40. PMID: 27208344

14. Lemos JRN, Baidal DA, Ricordi C, et al. Survival After Islet Transplantation in Subjects With Type 1 Diabetes: Twenty-Year Follow-Up. *Diabetes care.* 2021;44(4):e67-e68. PMID: 33579716
15. Caiazzo R, Vantyghem MC, Raverdi V, et al. Impact of Procedure-Related Complications on Long-term Islet Transplantation Outcome. *Transplantation.* 2015;99(5):979-84. PMID: 25393157
16. Moassesfar S, Masharani U, Frassetto LA, et al. A Comparative Analysis of the Safety, Efficacy, and Cost of Islet Versus Pancreas Transplantation in Nonuremic Patients With Type 1 Diabetes. *Am J Transplant.* 2016;16(2):518-26. PMID: 26595767
17. Rickels MR, Kong SM, Fuller C, et al. Improvement in insulin sensitivity after human islet transplantation for type 1 diabetes. *J Clin Endocrinol Metab.* 2013;98:E1780-5. PMID: 24085506
18. O'Connell PJ, Holmes-Walker DJ, Goodman D, et al. Multicenter Australian trial of islet transplantation: improving accessibility and outcomes. *Am J Transplant.* 2013;13(7):1850-8. PMID: 23668890
19. Vantyghem MC, Raverdy V, Balavoine AS, et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function (beta-score greater than 7) Is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia (beta-score greater than 3). *J Clin Endocrinol Metab.* 2012;97:E2078-83. PMID: 22996144
20. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation.* 2011;91(3):373-8. PMID: 21258272
21. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med.* 2006;355(13):1318-30. PMID: 17005949
22. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med.* 2000;343(4):230-8. PMID: 10911004
23. Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. *Diabetes.* 2005;54(7):2060-9. PMID: 15983207
24. Gaglia JL, Shapiro AM, Weir GC. Islet transplantation: progress and challenge. *Arch Med Res.* 2005;36(3):273-80. PMID: 15925017
25. Brennan DC, Kopetskie HA, Sayre PH, et al. Long-Term Follow-Up of the Edmonton Protocol of Islet Transplantation in the United States. *Am J Transplant.* 2016;16(2):509-17. PMID: 26433206
26. Basta G, Montanucci P, Luca G, et al. Long-term metabolic and immunological follow-up of nonimmunosuppressed patients with type 1 diabetes treated with microencapsulated islet allografts: four cases. *Diabetes care.* 2011;34(11):2406-9. PMID: 21926290
27. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA.* 2005;293(7):830-5. PMID: 15713772
28. Maffi P, Scavini M, Socci C, et al. Risks and benefits of transplantation in the cure of type 1 diabetes: whole pancreas versus islet transplantation. A single center study. *Rev Diabet Stud.* 2011;8(1):44-50. PMID: 21720672
29. Frank A, Deng S, Huang X, et al. Transplantation for type I diabetes: comparison of vascularized whole-organ pancreas with isolated pancreatic islets. *Ann Surg.* 2004;240(4):631-40; discussion 40-3. PMID: 15383791

30. Borot S, Niclauss N, Wojtusciszyn A, et al. Impact of the number of infusions on 2-year results of islet-after-kidney transplantation in the GRAGIL network. *Transplantation.* 2011;92(9):1031-8. PMID: 21926944
31. Robertson RP. Islet transplantation a decade later and strategies for filling a half-full glass. *Diabetes.* 2010;59(6):1285-91. PMID: 20508222
32. Lablanche S, Borot S, Wojtusciszyn A, et al. Ten-year outcomes of islet transplantation in patients with type 1 diabetes: Data from the Swiss-French GRAGIL network. *Am J Transplant.* 2021;21(11):3725-33. PMID: 33961335
33. Bretzel RG, Jahr H, Eckhard M, et al. Islet cell transplantation today. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie.* 2007;392(3):239-53. PMID: 17393180
34. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes care.* 2012;35(7):1436-45. PMID: 22723582
35. Girman P, Saudek F. The IKEM pancreas and islet transplant program as part of healthcare for type 1 diabetes patients: retrospective analysis of outcome from 1983 to 2010. *Rev Diabet Stud.* 2011;8(1):35-43. PMID: 21720671
36. Matsumoto S, Abalovich A, Wechsler C, et al. Clinical Benefit of Islet Xenotransplantation for the Treatment of Type 1 Diabetes. *EBioMedicine.* 2016;12:255-62. PMID: 27592597
37. Wang W, Mo Z, Ye B, et al. A clinical trial of xenotransplantation of neonatal pig islets for diabetic patients. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2011;36(12):1134-40. PMID: 22246351
38. Esquivel-Perez R, Rodriguez-Ventura AL, Dorantes LM, et al. Correlation between insulin requirements and anti-galactose antibodies in patients with type 1 diabetes transplanted with neonatal pig islets. *Clin Exp Immunol.* 2011;165(1):104-9. PMID: 21501149

CODES

Codes	Number	Description
CPT	0584T	Percutaneous islet cell transplant, includes portal vein catheterization and Infusion
	0585T	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
	0586T	Laparoscopy for islet cell transplant, open approach
	48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islets
	48999	Unlisted procedure, pancreas
HCPCS	G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
	G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
	G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion
	S2102	Islet cell tissue transplant from pancreas; allogeneic

Date of Origin: *January 1996*

Regence

Medical Policy Manual Utilization Management, Policy No. 13

Air Ambulance Transport

Effective: April 1, 2024

Next Review: February 2025
Last Review: February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Air ambulance transportation is provided by helicopters (rotary wing) or fixed wing aircraft that are specially designed, equipped, and staffed for transporting sick and injured patients.

MEDICAL POLICY CRITERIA

Note: This policy only applies to member contracts that are subject to review for air ambulance services, as specified by their group plan. Please check the preauthorization website for the member contract to confirm requirements.

I. Air ambulance transport may be considered **medically necessary** when all of the following criteria (A. – C.) are met:

   A. Urgent and rapid ambulance transport is essential to stabilize or preserve the patient's life.

   B. One of the following criteria is met:

      1. Transport cannot be safely provided by ground ambulance due to great distances, prolonged transport time, or other obstacles that would endanger the patient's health or threaten survival; or

      2. The point of pick up is inaccessible by ground ambulance.

C. Transport is to the nearest acute care facility equipped to provide the appropriate treatment for the patient's condition.

II. Air ambulance transport is considered **not medically necessary** for circumstances not meeting the Criteria in I.A. – C. and above, including but not limited to the following:

A. Transport from a facility providing a higher level of care to a facility providing an equivalent or lower level of care, including to an inpatient rehabilitation facility, long term acute care facility, or skilled nursing facility;

B. Transport for personal or convenience purposes, such as return to home;

C. Transport beyond the nearest facility equipped to provide the most appropriate care for the patient's condition.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Documentation that the member's medical condition required immediate and rapid ambulance transportation that could not have been provided by ground ambulance.
- Location of transport pick-up.
- Location of transport drop-off.
- Level of care of facility which the member is being transferred to.
- Level of care of facility which the member is being transferred from.
- All additional documentation supporting the need for air ambulance services (i.e., accessibility of the point of pick-up, distances, obstacles, etc.).

CROSS REFERENCES

None

CODES

Codes	Number	Description
CPT	None	
HCPCS	A0140	Nonemergency transportation and air travel (private or commercial) intra- or interstate
	A0430	Ambulance service, conventional air services, transport, one way (fixed wing)
	A0431	Ambulance service, conventional air services, transport, one way (rotary wing)
	A0435	Fixed wing air mileage, per statute mile
	A0436	Rotary wing air mileage, per statute mile
	S9960	Ambulance service, conventional air services, nonemergency transport, one way (fixed wing)
	S9961	Ambulance service, conventional air service, nonemergency transport, one way (rotary wing)

Date of Origin: *March 2013*

Regence

Medical Policy Manual Utilization Management, Policy No. 19

Surgical Site of Service – Hospital Outpatient

Effective: March 1, 2024

Next Review: July 2024
Last Review: November 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

An ambulatory surgery center (ASC) is a health care facility which offers same-day surgery services outside the hospital setting. An ASC is a surgical facility that does not have inpatient beds, and the entity may or may not be sponsored by a hospital. An individual's health status is considered when determining the appropriateness for the site of service among other factors including facility and geographic availability, specialty requirements, and physician privileges.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address procedures performed in an ambulatory surgery center (ASC), physician office, or emergency facility for urgent services.
- This policy addresses prior authorization for site of service only. The procedure may require prior authorization separately (see applicable Medical Policy).
- For coverage of a procedure in a hospital outpatient department, in addition to meeting the criteria in this medical policy, the type of service being performed must be considered medically necessary per prior authorization review requirements

and the applicable medical policy OR the health plan does not require prior authorization for the service being performed.

I. The use of a hospital outpatient department instead of an ambulatory surgery center (ASC) or physician office for surgical services may be considered **medically necessary** when one or more of the following Criteria is met:

A. There is no qualifying ASC within 25 miles that can provide the necessary care for the patient due to one of the following:

1. There is no geographically accessible ASC that has the necessary equipment for the procedure; or
2. There is no geographically accessible ASC available at which the individual's physician has privileges; or
3. An ASC's specific guideline regarding the individual's weight or health conditions prevents the use of an ASC;

B. The procedure requires discontinuing medications (e.g. antiarrhythmics, antiseizure medication), which necessitate preoperative or postoperative inpatient monitoring or treatment;

C. The individual is using substances or medications (e.g. cocaine, amphetamines, monoamine oxidase inhibitor, alcohol) that may interact with the anticipated anesthetic regimen or lead to withdrawal syndrome;

D. History of a significant hemodynamic instability during a prior surgical procedure and is considered a risk for future procedures;

E. Age 17 years and younger;

F. The service being performed is in conjunction with an additional service that requires the use of a hospital outpatient department and they are being performed in the same operative session;

G. American Society of Anesthesiologists (ASA) Physical Status (PS) Classification III or higher (see Policy Guidelines);

H. Body mass index (BMI) is over 40;

I. Bleeding disorder requiring replacement factor or special infusion products to correct a coagulation defect;

J. Complex anticoagulation management anticipated;

K. Transfusion anticipated;

L. Sickle cell disease;

M. Clinical documentation that cardiovascular risk is increased by any of the following factors:

1. Symptomatic cardiac arrhythmia despite medication
2. Coronary artery disease (CAD)
3. Drug eluting stents (DES) placed within one year or bare metal stents (BMS) or plain angioplasty within 90 days

4. History of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within past three months
5. History of myocardial infarction (MI) within past three months
6. Implantable cardioverter-defibrillator (ICD)
7. Implanted pacemaker
8. Mechanical cardiovascular support (e.g., left ventricular assist device [LVAD] or total artificial heart)
9. Peripheral vascular disease (PVD)
10. Ongoing evidence of myocardial ischemia
11. Hypertension, severe (>180/110) or resistant (not responsive to three antihypertensive medications)
12. Uncompensated chronic heart failure (CHF) (NYHA class III or IV)
13. Valvular heart disease and/or cardiomyopathy, moderate or severe;

N. Prolonged surgery (> 3 hours);

O. Advanced liver disease (Model for End-Stage Liver Disease [MELD] Score > 8);

P. Diabetes, when uncontrolled (HgbA1c >8%) or with recurrent diabetic ketoacidosis (DKA) or severe hypoglycemia;

Q. End stage renal disease (ESRD), Stage 4 or 5 chronic kidney disease;

R. Incompletely treated skin or wound infection;

S. Pregnancy;

T. Pulmonary risk is increased by any of the following factors:
1. Abnormal airway
2. Prior difficult intubation
3. Active respiratory infection
4. Chronic obstructive pulmonary disease (COPD) (FEV1 < 50%)
5. Medical conditions that are commonly connected with difficult airway (e.g., Pierre-Robin, Treacher-Collins, Goldenhar's Syndrome, and Epidermolysis Bullosa)
6. Poorly controlled asthma (FEV1 < 80% despite medical management)
7. Moderate to severe obstructive sleep apnea:
   a. Moderate = Apnea hypopnea index (AHI) or respiratory disturbance index (RDI) $\geq$15 and $\leq$30;
   b. Severe = AHI or RDI >30/hr;
8. Dependent on a ventilator or continuous supplemental oxygen;

U. Personal history or family history of complication of anesthesia such as malignant hyperthermia;

V. History of any of the following gastrointestinal conditions that would increase risk for aspiration:

1. Documented history of achalasia

2. Documented history of delayed gastric emptying disorder or gastroparesis;

W. History of any of the following neurological diagnoses that would increase risk:

1. Active multiple sclerosis

2. Myasthenia gravis

3. Severe motor disorder (e.g. severe Parkinson's, or other severe neurological dysfunction)

4. A condition is present that will require the use of restraints;

X. History of total joint infection;

Y. Individual is awaiting major organ transplant;

Z. Risk of procedure-specific complication;

AA. Provider documents a requirement for overnight recovery based on a unique circumstance for the individual.

II. The use of a hospital outpatient department for surgical services instead of an ambulatory surgery center or physician office is considered **not medically necessary** when Criteria I. is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Site of service medical necessity reviews will be conducted for surgical procedures on the Codes list provided in this policy only when performed in an outpatient hospital setting.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) PHYSICAL STATUS CLASSIFICATION SYSTEM[1]

ASA PS Classification	Definition	Adult Examples, including but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis,

ASA PS Classification	Definition	Adult Examples, including but not limited to:
		premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

*The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- American Society of Anesthesiologists (ASA) score, as applicable
- Clinical documentation for specific policy criteria (refer to the Policy Criteria) that qualifies the individual for the site of service requested
- For specific services requiring prior authorization in addition to the site of service, submission of the applicable medical policy clinical documentation required for review.
- The best way to ensure criteria are met is to submit the Surgical Site of Service Additional Information form if faxing a pre-authorization request for these services.

CROSS REFERENCES

1. Medicine Policy Section, Medical Policy Manual Index
2. Radiology Policy Section, Medical Policy Manual Index
3. Surgery Policy Section, Medical Policy Manual Index

BACKGROUND

An ambulatory surgery center (ASC) is a health care facility which offers same-day surgery services outside the hospital setting. An ASC is a surgical facility that does not have inpatient beds, and the entity may or may not be sponsored by a hospital.

An individual's health status is considered when determining the appropriateness for the site of service among other factors including facility and geographic availability, specialty requirements, and physician privileges. The American Society of Anesthesiologist (ASA) physical status classification system (see Appendix I), and/or significant comorbidities may be

taken into account.[1] The ASA risk scoring system is regarded by hospitals, legal firms, accrediting bodies, and other healthcare groups as a preoperative health grading system for individuals undergoing a surgical procedure. For example, individuals with ASA I-II status might be appropriate candidates for ASC care, though ASA III and above may not. Significant comorbidities may include but are not limited to significant cardiorespiratory condition (e.g., recent myocardial infarction, cardiac arrhythmia, and myocardial ischemia), moderate-to-severe obstructive sleep apnea, pregnancy, and poorly controlled asthma.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF ANESTHESIOLOGISTS

The American Society of Anesthesiologists (ASA) maintains a Physical Status Classification System with definitions and ASA-approved examples (reproduced in Appendix I).[1] This system is intended to be used in conjunction with other factors to aid in predicting perioperative risks. The system was originally proposed in 1942, and the current version was published in 2014 with the inclusion of examples, and was most recently updated in 2020.

SUMMARY

The use of a hospital outpatient department instead of an ambulatory surgical center (ASC) for surgical services may be considered medically necessary when the procedure is of a level of complexity such that it may not be performed in a less intensive setting, the service being performed is medically necessary, and the surgical site of service policy criteria are met.

The use of a hospital outpatient department instead of an ambulatory surgical center (ASC) for surgical services is not medically necessary when the policy criteria are not met including when the procedure can be safely performed in a less intensive setting, the specific service requires prior authorization and does not meet applicable policy criteria, or the surgical site of service policy criteria are not met.

REFERENCES

1. American Society of Anesthesiologists (ASA) Physical Status Classification System. Last amended: December 13, 2020. [cited 08/16/2023]. 'Available from:' https://www.asahq.org/standards-and-practice-parameters/statement-on-asa-physical-status-classification-system.

CODES

NOTE: Site of service medical necessity reviews will be conducted for surgical procedures on the Codes list below only when performed in an outpatient hospital setting.

Codes	Number	Description
CPT	10060	Incision and drainage of abscess (eg, carbuncle, suppurative hidradenitis, cutaneous or subcutaneous abscess, cyst, furuncle, or paronychia); simple or single

Codes	Number	Description
	10061	Incision and drainage of abscess (eg, carbuncle, suppurative hidradenitis, cutaneous or subcutaneous abscess, cyst, furuncle, or paronychia); complicated or multiple
	10080	Incision and drainage of pilonidal cyst; simple
	10081	Incision and drainage of pilonidal cyst; complicated
	10120	Incision and removal of foreign body, subcutaneous tissues; simple
	10121	Incision and removal of foreign body, subcutaneous tissues; complicated
	10140	Incision and drainage of hematoma, seroma or fluid collection
	10160	Puncture aspiration of abscess, hematoma, bulla, or cyst
	10180	Incision and drainage, complex, postoperative wound infection
	11000	Debridement of extensive eczematous or infected skin; up to 10% of body surface
	11010	Debridement including removal of foreign material at the site of an open fracture and/or an open dislocation (eg, excisional debridement); skin and subcutaneous tissues
	11012	Debridement including removal of foreign material at the site of an open fracture and/or an open dislocation (eg, excisional debridement); skin, subcutaneous tissue, muscle fascia, muscle, and bone
	11042	Debridement, subcutaneous tissue (includes epidermis and dermis, if performed); first 20 sq cm or less
	11044	Debridement, Debridement, bone (includes epidermis, dermis, subcutaneous tissue, muscle and/or fascia, if performed); first 20 sq cm or less
	11200	Removal of skin tags, multiple fibrocutaneous tags, any area; up to and including 15 lesions
	11310	Shaving of epidermal or dermal lesion, single lesion, face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 0.5 cm or less
	11402	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), trunk, arms or legs; excised diameter 1.1 to 2.0 cm
	11403	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), trunk, arms or legs; excised diameter 2.1 to 3.0 cm
	11404	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), trunk, arms or legs; excised diameter 3.1 to 4.0 cm
	11406	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), trunk, arms or legs; excised diameter over 4.0 cm
	11420	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 0.5 cm or less
	11421	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 0.6 to 1.0 cm
	11422	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 1.1 to 2.0 cm
	11423	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 2.1 to 3.0 cm
	11424	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter 3.1 to 4.0 cm
	11426	Excision, benign lesion including margins, except skin tag (unless listed elsewhere), scalp, neck, hands, feet, genitalia; excised diameter over 4.0 cm
	11440	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 0.5 cm or less
	11441	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 0.6 to 1.0 cm

Codes	Number	Description
	11442	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 1.1 to 2.0 cm
	11443	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 2.1 to 3.0 cm
	11444	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter 3.1 to 4.0 cm
	11446	Excision, other benign lesion including margins, except skin tag (unless listed elsewhere), face, ears, eyelids, nose, lips, mucous membrane; excised diameter over 4.0 cm
	11450	Excision of skin and subcutaneous tissue for hidradenitis, axillary; with simple or intermediate repair
	11451	Excision of skin and subcutaneous tissue for hidradenitis, axillary; with complex repair
	11462	Excision of skin and subcutaneous tissue for hidradenitis, inguinal; with simple or intermediate repair
	11463	Excision of skin and subcutaneous tissue for hidradenitis, inguinal; with complex repair
	11470	Excision of skin and subcutaneous tissue for hidradenitis, perianal, perineal, or umbilical; with simple or intermediate repair
	11471	Excision of skin and subcutaneous tissue for hidradenitis, perianal, perineal, or umbilical; with complex repair
	11601	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 0.6 to 1.0 cm
	11602	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 1.1 to 2.0 cm
	11603	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 2.1 to 3.0 cm
	11604	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 3.1 to 4.0 cm
	11606	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter over 4.0 cm
	11620	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 0.5 cm or less
	11621	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 0.6 to 1.0 cm
	11622	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 1.1 to 2.0 cm
	11623	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 2.1 to 3.0 cm
	11624	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 3.1 to 4.0 cm
	11626	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter over 4.0 cm
	11640	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 0.5 cm or less
	11641	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 0.6 to 1.0 cm
	11642	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 1.1 to 2.0 cm

Codes	Number	Description
	11643	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 2.1 to 3.0 cm
	11644	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 3.1 to 4.0 cm
	11646	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter over 4.0 cm
	11730	Avulsion of nail plate, partial or complete, simple; single
	11750	Excision of nail and nail matrix, partial or complete (eg, ingrown or deformed nail), for permanent removal;
	11755	Biopsy of nail unit (eg, plate, bed, matrix, hyponychium, proximal and lateral nail folds) (separate procedure)
	11760	Repair of nail bed
	11765	Wedge excision of skin of nail fold (eg, for ingrown toenail)
	11770	Excision of pilonidal cyst or sinus; simple
	11772	Excision of pilonidal cyst or sinus; complicated
	11900	Injection, intralesional; up to and including 7 lesions
	12001	Simple repair of superficial wounds of scalp, neck, axillae, external genitalia, trunk and/or extremities (including hands and feet); 2.5 cm or less
	12002	Simple repair of superficial wounds of scalp, neck, axillae, external genitalia, trunk and/or extremities (including hands and feet); 2.6 cm to 7.5 cm
	12011	Simple repair of superficial wounds of face, ears, eyelids, nose, lips and/or mucous membranes; 2.5 cm or less
	12020	Treatment of superficial wound dehiscence; simple closure
	12031	Repair, intermediate, wounds of scalp, axillae, trunk and/or extremities (excluding hands and feet); 2.5 cm or less
	12032	Repair, intermediate, wounds of scalp, axillae, trunk and/or extremities (excluding hands and feet); 2.6 cm to 7.5 cm
	12034	Repair, intermediate, wounds of scalp, axillae, trunk and/or extremities (excluding hands and feet); 7.6 cm to 12.5 cm
	12035	Repair, intermediate, wounds of scalp, axillae, trunk and/or extremities (excluding hands and feet); 12.6 cm to 20.0 cm
	12037	Repair, intermediate, wounds of scalp, axillae, trunk and/or extremities (excluding hands and feet); over 30.0 cm
	12041	Repair, intermediate, wounds of neck, hands, feet and/or external genitalia; 2.5 cm or less
	12042	Repair, intermediate, wounds of neck, hands, feet and/or external genitalia; 2.6 cm to 7.5 cm
	12051	Repair, intermediate, wounds of face, ears, eyelids, nose, lips and/or mucous membranes; 2.5 cm or less
	13120	Repair, complex, scalp, arms, and/or legs; 1.1 cm to 2.5 cm
	13121	Repair, complex, scalp, arms, and/or legs; 2.6 cm to 7.5 cm
	13131	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 1.1 cm to 2.5 cm
	13132	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 2.6 cm to 7.5 cm
	13151	Repair, complex, eyelids, nose, ears and/or lips; 1.1 cm to 2.5 cm
	13152	Repair, complex, eyelids, nose, ears and/or lips; 2.6 cm to 7.5 cm
	13160	Secondary closure of surgical wound or dehiscence, extensive or complicated
	14020	Adjacent tissue transfer or rearrangement, scalp, arms and/or legs; defect 10 sq cm or less
	14040	Adjacent tissue transfer or rearrangement, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; defect 10 sq cm or less

Codes	Number	Description
	14060	Adjacent tissue transfer or rearrangement, eyelids, nose, ears and/or lips; defect 10 sq cm or less
	15120	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
	15220	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
	15240	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
	15760	Graft; composite (eg, full thickness of external ear or nasal ala), including primary closure, donor area
	~~15850~~	~~Removal of sutures under anesthesia (other than local), same surgeon~~ (Deleted 1/1/2023)
	15851	Removal of sutures or staples requiring anesthesia (ie, general anesthesia, moderate sedation)
	17000	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (eg, actinic keratoses); first lesion
	17110	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions
	17111	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; 15 or more lesions
	17311	Mohs micrographic technique, including removal of all gross tumor, surgical excision of tissue specimens, mapping, color coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (eg, hematoxylin and eosin, toluidine blue), head, neck, hands, feet, genitalia, or any location with surgery directly involving muscle, cartilage, bone, tendon, major nerves, or vessels; first stage, up to 5 tissue blocks
	17313	Mohs micrographic technique, including removal of all gross tumor, surgical excision of tissue specimens, mapping, color coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (eg, hematoxylin and eosin, toluidine blue), of the trunk, arms, or legs; first stage, up to 5 tissue blocks
	19020	Mastotomy with exploration or drainage of abscess, deep
	19101	Biopsy of breast; open, incisional
	19110	Nipple exploration, with or without excision of a solitary lactiferous duct or a papilloma lactiferous duct
	19112	Excision of lactiferous duct fistula
	19120	Excision of cyst, fibroadenoma, or other benign or malignant tumor, aberrant breast tissue, duct lesion, nipple or areolar lesion (except 19300), open, male or female, 1 or more lesions
	19125	Excision of breast lesion identified by preoperative placement of radiological marker, open; single lesion
	20200	Biopsy, muscle; superficial
	20205	Biopsy, muscle; deep
	20220	Biopsy, bone, trocar, or needle; superficial (eg, ilium, sternum, spinous process, ribs)
	20225	Biopsy, bone, trocar, or needle; deep (eg, vertebral body, femur)

Codes	Number	Description
	20240	Biopsy, bone, open; superficial (eg, sternum, spinous process, rib, patella,
	20526	Injection, therapeutic (eg, local anesthetic, corticosteroid), carpal tunnel
		Arthrocentesis, aspiration and/or injection, small joint or bursa (eg, fingers, toes); without ultrasound guidance
	20604	Arthrocentesis, aspiration and/or injection, small joint or bursa (eg, fingers, toes); with ultrasound guidance, with permanent recording and reporting
	20605	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); without ultrasound guidance
	20606	Arthrocentesis, aspiration and/or injection, intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa); with ultrasound guidance, with permanent recording and reporting
	20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance
	20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance, with permanent recording and reporting
	20912	Cartilage graft; nasal septum
	21011	Excision, tumor, soft tissue of face or scalp, subcutaneous; less than 2 cm
	21012	Excision, tumor, soft tissue of face or scalp, subcutaneous; 2 cm or greater
	21013	Excision, tumor, soft tissue of face and scalp, subfascial (eg, subgaleal, intramuscular); less than 2 cm
	21014	Excision, tumor, soft tissue of face and scalp, subfascial (eg, subgaleal, intramuscular); 2 cm or greater
	21029	Removal by contouring of benign tumor of facial bone (eg, fibrous dysplasia)
	21030	Excision of benign tumor or cyst of maxilla or zygoma by enucleation and curettage
	21031	Excision of torus mandibularis
	21040	Excision of benign tumor or cyst of mandible, by enucleation and/or curettage
	21046	Excision of benign tumor or cyst of mandible; requiring intra-oral osteotomy (eg, locally aggressive or destructive lesion[s])
	21048	Excision of benign tumor or cyst of maxilla; requiring intra-oral osteotomy (eg, locally aggressive or destructive lesion[s])
	21315	Closed treatment of nasal bone fracture with manipulation; without stabilization
	21320	Closed treatment of nasal bone fracture with manipulation; with stabilization
	21325	Open treatment of nasal fracture; uncomplicated
	21330	Open treatment of nasal fracture; complicated, with internal and/or external skeletal fixation
	21335	Open treatment of nasal fracture; with concomitant open treatment of fractured septum
	21336	Open treatment of nasal septal fracture, with or without stabilization
	21337	Closed treatment of nasal septal fracture, with or without stabilization
	21356	Open treatment of depressed zygomatic arch fracture (eg, Gillies approach)
	21550	Biopsy, soft tissue of neck or thorax
	21552	Excision, tumor, soft tissue of neck or anterior thorax, subcutaneous; 3 cm or greater
	21554	Excision, tumor, soft tissue of neck or anterior thorax, subfascial (eg, intramuscular); 5 cm or greater
	21555	Excision, tumor, soft tissue of neck or anterior thorax, subcutaneous; less than 3 cm

Codes	Number	Description
	21556	Excision, tumor, soft tissue of neck or anterior thorax, subfascial (eg, intramuscular); less than 5 cm
	21557	Radical resection of tumor (eg, sarcoma), soft tissue of neck or anterior thorax; less than 5 cm
	21920	Biopsy, soft tissue of back or flank; superficial
	21930	Excision, tumor, soft tissue of back or flank, subcutaneous; less than 3 cm
	21931	Excision, tumor, soft tissue of back or flank, subcutaneous; 3 cm or greater
	21932	Excision, tumor, soft tissue of back or flank, subfascial (eg, intramuscular); less than 5 cm
	22900	Excision, tumor, soft tissue of abdominal wall, subfascial (eg, intramuscular); less than 5 cm
	22901	Excision, tumor, soft tissue of abdominal wall, subfascial (eg, intramuscular); 5 cm or greater
	22902	Excision, tumor, soft tissue of abdominal wall, subcutaneous; less than 3 cm
	22903	Excision, tumor, soft tissue of abdominal wall, subcutaneous; 3 cm or greater
	23030	Incision and drainage, shoulder area; deep abscess or hematoma
	23071	Excision, tumor, soft tissue of shoulder area, subcutaneous; 3 cm or greater
	23075	Excision, tumor, soft tissue of shoulder area, subcutaneous; less than 3 cm
	23140	Excision or curettage of bone cyst or benign tumor of clavicle or scapula;
	23150	Excision or curettage of bone cyst or benign tumor of proximal humerus;
	24000	Arthrotomy, elbow, including exploration, drainage, or removal of foreign body
	24006	Arthrotomy of the elbow, with capsular excision for capsular release (separate procedure)
	24065	Biopsy, soft tissue of upper arm or elbow area; superficial
	24066	Biopsy, soft tissue of upper arm or elbow area; deep (subfascial or intramuscular)
	24071	Excision, tumor, soft tissue of upper arm or elbow area, subcutaneous; 3 cm or greater
	24073	Excision, tumor, soft tissue of upper arm or elbow area, subfascial (eg, intramuscular); 5 cm or greater
	24075	Excision, tumor, soft tissue of upper arm or elbow area, subcutaneous; less than 3 cm
	24076	Excision, tumor, soft tissue of upper arm or elbow area, subfascial (eg, intramuscular); less than 5 cm
	24101	Arthrotomy, elbow; with joint exploration, with or without biopsy, with or without removal of loose or foreign body
	24110	Excision or curettage of bone cyst or benign tumor, humerus;
	24120	Excision or curettage of bone cyst or benign tumor of head or neck of radius or olecranon process;
	24130	Excision, radial head
	24147	Partial excision (craterization, saucerization, or diaphysectomy) bone (eg, osteomyelitis), olecranon process
	24200	Removal of foreign body, upper arm or elbow area; subcutaneous
	24201	Removal of foreign body, upper arm or elbow area; deep (subfascial or intramuscular)
	24366	Arthroplasty, radial head; with implant
	25071	Excision, tumor, soft tissue of forearm and/or wrist area, subcutaneous; 3 cm or greater
	25073	Excision, tumor, soft tissue of forearm and/or wrist area, subfascial (eg, intramuscular); 3 cm or greater
	25075	Excision, tumor, soft tissue of forearm and/or wrist area, subcutaneous; less than 3 cm

Codes	Number	Description
	25076	Excision, tumor, soft tissue of forearm and/or wrist area, subfascial (eg, intramuscular); less than 3 cm
	25085	Capsulotomy, wrist (eg, contracture)
	25109	Excision of tendon, forearm and/or wrist, flexor or extensor, each
	25120	Excision or curettage of bone cyst or benign tumor of radius or ulna (excluding head or neck of radius and olecranon process);
	25130	Excision or curettage of bone cyst or benign tumor of carpal bones;
	25350	Osteotomy, radius; distal third
	26070	Arthrotomy, with exploration, drainage, or removal of loose or foreign body; carpometacarpal joint
	26105	Arthrotomy with biopsy; metacarpophalangeal joint, each
	26110	Arthrotomy with biopsy; interphalangeal joint, each
	26111	Excision, tumor or vascular malformation, soft tissue of hand or finger, subcutaneous; 1.5 cm or greater
	26113	Excision, tumor, soft tissue, or vascular malformation, of hand or finger, subfascial (eg, intramuscular); 1.5 cm or greater
	26115	Excision, tumor or vascular malformation, soft tissue of hand or finger, subcutaneous; less than 1.5 cm
	26180	Excision of tendon, finger, flexor or extensor, each tendon
	26200	Excision or curettage of bone cyst or benign tumor of metacarpal;
	26210	Excision or curettage of bone cyst or benign tumor of proximal, middle, or distal phalanx of finger;
	26357	Repair or advancement, flexor tendon, in zone 2 digital flexor tendon sheath (eg, no man's land); secondary, without free graft, each tendon
	26432	Closed treatment of distal extensor tendon insertion, with or without percutaneous pinning (eg, mallet finger)
	26433	Repair of extensor tendon, distal insertion, primary or secondary; without graft (eg, mallet finger)
	26500	Reconstruction of tendon pulley, each tendon; with local tissues (separate procedure)
	26530	Arthroplasty, metacarpophalangeal joint; each joint
	26542	Reconstruction, collateral ligament, metacarpophalangeal joint, single; with local tissue (eg, adductor advancement)
	26841	Arthrodesis, carpometacarpal joint, thumb, with or without internal fixation;
	26862	Arthrodesis, interphalangeal joint, with or without internal fixation; with autograft (includes obtaining graft)
	27006	Tenotomy, abductors and/or extensor(s) of hip, open (separate procedure)
	27043	Excision, tumor, soft tissue of pelvis and hip area, subcutaneous; 3 cm or greater
	27045	Excision, tumor, soft tissue of pelvis and hip area, subfascial (eg, intramuscular); 5 cm or greater
	27047	Excision, tumor, soft tissue of pelvis and hip area, subcutaneous; less than 3 cm
	27048	Excision, tumor, soft tissue of pelvis and hip area, subfascial (eg, intramuscular); less than 5 cm
	27062	Excision; trochanteric bursa or calcification
	27093	Injection procedure for hip arthrography; without anesthesia
	27095	Injection procedure for hip arthrography; with anesthesia
	27310	Arthrotomy, knee, with exploration, drainage, or removal of foreign body (eg, infection)
	27323	Biopsy, soft tissue of thigh or knee area; superficial
	27324	Biopsy, soft tissue of thigh or knee area; deep (subfascial or intramuscular)

Codes	Number	Description
	27327	Excision, tumor, soft tissue of thigh or knee area, subcutaneous; less than 3 cm
	27328	Excision, tumor, soft tissue of thigh or knee area, subfascial (eg, intramuscular); less than 5 cm
	27329	Radical resection of tumor (eg, sarcoma), soft tissue of thigh or knee area; less than 5 cm
	27337	Excision, tumor, soft tissue of thigh or knee area, subcutaneous; 3 cm or greater
	27339	Excision, tumor, soft tissue of thigh or knee area, subfascial (eg, intramuscular); 5 cm or greater
	27340	Excision, prepatellar bursa
	27345	Excision of synovial cyst of popliteal space (eg, Baker's cyst)
	27347	Excision of lesion of meniscus or capsule (eg, cyst, ganglion), knee
	27613	Biopsy, soft tissue of leg or ankle area; superficial
	27614	Biopsy, soft tissue of leg or ankle area; deep (subfascial or intramuscular)
	27618	Excision, tumor, soft tissue of leg or ankle area, subcutaneous; less than 3 cm
	27632	Excision, tumor, soft tissue of leg or ankle area, subcutaneous; 3 cm or greater
	27634	Excision, tumor, soft tissue of leg or ankle area, subfascial (eg, intramuscular); 5 cm or greater
	27638	Excision or curettage of bone cyst or benign tumor, tibia or fibula; with allograft
	27640	Partial excision (craterization, saucerization, or diaphysectomy), bone (eg, osteomyelitis); tibia
	27720	Repair of nonunion or malunion, tibia; without graft, (eg, compression technique)
	28011	Tenotomy, percutaneous, toe; multiple tendons
	28039	Excision, tumor, soft tissue of foot or toe, subcutaneous; 1.5 cm or greater
	28041	Excision, tumor, soft tissue of foot or toe, subfascial (eg, intramuscular); 1.5 cm or greater
	28043	Excision, tumor, soft tissue of foot or toe, subcutaneous; less than 1.5 cm
	28045	Excision, tumor, soft tissue of foot or toe, subfascial (eg, intramuscular); less than 1.5 cm
	28047	Radical resection of tumor (eg, sarcoma), soft tissue of foot or toe; 3 cm or greater
	28100	Excision or curettage of bone cyst or benign tumor, talus or calcaneus;
	28103	Excision or curettage of bone cyst or benign tumor, talus or calcaneus; with allograft
	28104	Excision or curettage of bone cyst or benign tumor, tarsal or metatarsal, except talus or calcaneus;
	28126	Resection, partial or complete, phalangeal base, each toe
	28666	Percutaneous skeletal fixation of interphalangeal joint dislocation, with manipulation
	29835	Arthroscopy, elbow, surgical; synovectomy, partial
	29900	Arthroscopy, metacarpophalangeal joint, diagnostic, includes synovial biopsy
	29901	Arthroscopy, metacarpophalangeal joint, surgical; with debridement
	30000	Drainage abscess or hematoma, nasal, internal approach
	30020	Drainage abscess or hematoma, nasal septum
	30100	Biopsy, intranasal
	30110	Excision, nasal polyp(s), simple
	30115	Excision, nasal polyp(s), extensive
	30117	Excision or destruction (eg, laser), intranasal lesion; internal approach
	30118	Excision or destruction (eg, laser), intranasal lesion; external approach (lateral rhinotomy)
	30130	Excision inferior turbinate, partial or complete, any method

Codes	Number	Description
	30140	Submucous resection inferior turbinate, partial or complete, any method
	30220	Insertion, nasal septal prosthesis (button)
	30310	Removal foreign body, intranasal; office type procedure
	30520	Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft
	30580	Removal foreign body, intranasal; requiring general anesthesia
	30630	Repair fistula; oromaxillary (combine with 31030 if antrotomy is included)
	30801	Repair nasal septal perforations
	30802	Ablation, soft tissue of inferior turbinates, unilateral or bilateral, any method (eg, electrocautery, radiofrequency ablation, or tissue volume reduction); intramural (ie, submucosal)
	30901	Ablation, soft tissue of inferior turbinates, unilateral or bilateral, any method (eg, electrocautery, radiofrequency ablation, or tissue volume reduction); superficial
	30903	Control nasal hemorrhage, anterior, simple (limited cautery and/or packing) any method
	30930	Control nasal hemorrhage, anterior, complex (extensive cautery and/or packing) any method
	31020	Fracture nasal inferior turbinate(s), therapeutic
	31030	Sinusotomy, maxillary (antrotomy); intranasal
	31032	Sinusotomy, maxillary (antrotomy); radical (Caldwell-Luc) without removal of antrochoanal polyps
	31200	Ethmoidectomy; intranasal, anterior
	31205	Ethmoidectomy; extranasal, total
	31238	Sinusotomy, maxillary (antrotomy); radical (Caldwell-Luc) with removal of antrochoanal polyps
	31525	Laryngoscopy direct, with or without tracheoscopy; diagnostic, except newborn
	31526	Nasal/sinus endoscopy, surgical; with control of nasal hemorrhage
	31528	Laryngoscopy direct, with or without tracheoscopy; diagnostic, with operating microscope or telescope
	31529	Laryngoscopy direct, with or without tracheoscopy; with dilation, initial
	31530	Laryngoscopy direct, with or without tracheoscopy; with dilation, subsequent
	31535	Laryngoscopy, direct, operative, with foreign body removal;
	31536	Laryngoscopy, direct, operative, with biopsy;
	31540	Laryngoscopy, direct, operative, with biopsy; with operating microscope or telescope
	31541	Laryngoscopy, direct, operative, with excision of tumor and/or stripping of vocal cords or epiglottis;
	31545	Laryngoscopy, direct, operative, with excision of tumor and/or stripping of vocal cords or epiglottis; with operating microscope or telescope
	31570	Laryngoscopy, direct, operative, with operating microscope or telescope, with submucosal removal of non-neoplastic lesion(s) of vocal cord; reconstruction with local tissue flap(s)
	31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
	31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral
	31575	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
	31576	Laryngoscopy, flexible; diagnostic
	31578	Laryngoscopy, flexible; with biopsy(ies)
	31591	Laryngoplasty, medialization, unilateral
	31611	Laryngoscopy, flexible; with removal of lesion(s), non-laser

Codes	Number	Description
	31622	Construction of tracheoesophageal fistula and subsequent insertion of an alaryngeal speech prosthesis (eg, voice button, Blom-Singer prosthesis)
	31623	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; diagnostic, with cell washing, when performed (separate procedure)
	31624	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with brushing or protected brushings
	31625	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial alveolar lavage
	31628	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial or endobronchial biopsy(s), single or multiple sites
	31652	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with transbronchial lung biopsy(s), single lobe
	31820	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), one or two mediastinal and/or hilar lymph node stations or structures
	32408	Core needle biopsy, lung or mediastinum, percutaneous, including imaging guidance, when performed
	32555	Thoracentesis, needle or catheter, aspiration of the pleural space; with imaging guidance
	32557	Pleural drainage, percutaneous, with insertion of indwelling catheter; with imaging guidance
	36010	Surgical closure tracheostomy or fistula; without plastic repair
	36215	Selective catheter placement, arterial system; each first order thoracic or brachiocephalic branch, within a vascular family
	36246	Selective catheter placement, arterial system; initial second order abdominal, pelvic, or lower extremity artery branch, within a vascular family
	36556	Insertion of non-tunneled centrally inserted central venous catheter; age 5 years or older
	36569	Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, without imaging guidance; age 5 years or older
	36571	Insertion of peripherally inserted central venous access device, with subcutaneous port; age 5 years or older
	36581	Replacement, complete, of a tunneled centrally inserted central venous catheter, without subcutaneous port or pump, through same venous access
	36582	Replacement, complete, of a tunneled centrally inserted central venous access device, with subcutaneous port, through same venous access
	36589	Removal of tunneled central venous catheter, without subcutaneous port or pump
	36590	Removal of tunneled central venous access device, with subcutaneous port or pump, central or peripheral insertion
	37607	Ligation or banding of angioaccess arteriovenous fistula
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38500	Biopsy or excision of lymph node(s); open, superficial
	38505	Biopsy or excision of lymph node(s); by needle, superficial (eg, cervical, inguinal, axillary)
	38510	Biopsy or excision of lymph node(s); open, deep cervical node(s)
	38520	Biopsy or excision of lymph node(s); open, deep cervical node(s) with excision scalene fat pad
	38525	Biopsy or excision of lymph node(s); open, deep axillary node(s)
	38740	Axillary lymphadenectomy; superficial

Codes	Number	Description
	38760	Inguinofemoral lymphadenectomy, superficial, including Cloquet's node (separate procedure)
	40490	Biopsy of lip
	40510	Excision of lip; transverse wedge excision with primary closure
	40520	Excision of lip; V-excision with primary direct linear closure
	40525	Excision of lip; full thickness, reconstruction with local flap (eg, Estlander or fan)
	40530	Resection of lip, more than one-fourth, without reconstruction
	40808	Biopsy, vestibule of mouth
	40810	Excision of lesion of mucosa and submucosa, vestibule of mouth; without repair
	40812	Excision of lesion of mucosa and submucosa, vestibule of mouth; with simple repair
	40814	Excision of lesion of mucosa and submucosa, vestibule of mouth; with complex repair
	40816	Excision of lesion of mucosa and submucosa, vestibule of mouth; complex, with excision of underlying muscle
	41010	Incision of lingual frenum (frenotomy)
	41100	Biopsy of tongue; anterior two-thirds
	41105	Biopsy of tongue; posterior one-third
	41108	Biopsy of floor of mouth
	41110	Excision of lesion of tongue without closure
	41112	Excision of lesion of tongue with closure; anterior two-thirds
	41113	Excision of lesion of tongue with closure; posterior one-third
	41116	Excision, lesion of floor of mouth
	42100	Biopsy of palate, uvula
	42104	Excision, lesion of palate, uvula; without closure
	42106	Excision, lesion of palate, uvula; with simple primary closure
	42330	Sialolithotomy; submandibular (submaxillary), sublingual or parotid, uncomplicated, intraoral
	42335	Sialolithotomy; submandibular (submaxillary), complicated, intraoral
	42405	Biopsy of salivary gland; incisional
	42408	Excision of sublingual salivary cyst (ranula)
	42410	Excision of parotid tumor or parotid gland; lateral lobe, without nerve dissection
	42415	Excision of parotid tumor or parotid gland; lateral lobe, with dissection and preservation of facial nerve
	42420	Excision of parotid tumor or parotid gland; total, with dissection and preservation of facial nerve
	42425	Excision of parotid tumor or parotid gland; total, en bloc removal with sacrifice of facial nerve
	42440	Excision of submandibular (submaxillary) gland
	42450	Excision of sublingual gland
	42500	Plastic repair of salivary duct, sialodochoplasty; primary or simple
	42650	Dilation salivary duct
	42800	Biopsy; oropharynx
	42804	Biopsy; nasopharynx, visible lesion, simple
	42808	Excision or destruction of lesion of pharynx, any method
	42810	Excision branchial cleft cyst or vestige, confined to skin and subcutaneous tissues
	42821	Tonsillectomy and adenoidectomy; age 12 or over
	42826	Tonsillectomy, primary or secondary; age 12 or over
	42831	Adenoidectomy, primary; age 12 or over
	42870	Excision or destruction lingual tonsil, any method (separate procedure)

Codes	Number	Description
	43191	Esophagoscopy, rigid, transoral; diagnostic, including collection of specimen(s) by brushing or washing when performed (separate procedure)
	43195	Esophagoscopy, rigid, transoral; with balloon dilation (less than 30 mm diameter)
	43197	Esophagoscopy, flexible, transnasal; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	43200	Esophagoscopy, flexible, transoral; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	43211	Esophagoscopy, flexible, transoral; with endoscopic mucosal resection
	43212	Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)
	43213	Esophagoscopy, flexible, transoral; with dilation of esophagus, by balloon or dilator, retrograde (includes fluoroscopic guidance, when performed)
	43214	Esophagoscopy, flexible, transoral; with dilation of esophagus with balloon (30 mm diameter or larger) (includes fluoroscopic guidance, when performed)
	43215	Esophagoscopy, flexible, transoral; with removal of foreign body(s)
	43216	Esophagoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
	43217	Esophagoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	43220	Esophagoscopy, flexible, transoral; with transendoscopic balloon dilation (less than 30 mm diameter)
	43226	Esophagoscopy, flexible, transoral; with insertion of guide wire followed by passage of dilator(s) over guide wire
	43227	Esophagoscopy, flexible, transoral; with control of bleeding, any method
	43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
	43231	Esophagoscopy, flexible, transoral; with endoscopic ultrasound examination
	43232	Esophagoscopy, flexible, transoral; with transendoscopic ultrasound-guided intramural or transmural fine needle aspiration/biopsy(s)
	43233	Esophagogastroduodenoscopy, flexible, transoral; with dilation of esophagus with balloon (30 mm diameter or larger) (includes fluoroscopic guidance, when performed)
	43235	Esophagogastroduodenoscopy, flexible, transoral; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	43237	Esophagogastroduodenoscopy, flexible, transoral; with endoscopic ultrasound examination limited to the esophagus, stomach or duodenum, and adjacent structures
	43238	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided intramural or transmural fine needle aspiration/biopsy(s), (includes endoscopic ultrasound examination limited to the esophagus, stomach or duodenum, and adjacent structures
	43239	Esophagogastroduodenoscopy, flexible, transoral; with biopsy, single or multiple
	43240	Esophagogastroduodenoscopy, flexible, transoral; with transmural drainage of pseudocyst (includes placement of transmural drainage catheter[s]/stent[s], when performed, and endoscopic ultrasound, when performed)
	43241	Esophagogastroduodenoscopy, flexible, transoral; with insertion of intraluminal tube or catheter

Codes	Number	Description
	43242	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided intramural or transmural fine needle aspiration/biopsy(s) (includes endoscopic ultrasound examination of the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis)
	43243	Esophagogastroduodenoscopy, flexible, transoral; with injection sclerosis of esophageal/gastric varices
	43244	Esophagogastroduodenoscopy, flexible, transoral; with band ligation of esophageal/gastric varices
	43245	Esophagogastroduodenoscopy, flexible, transoral; with dilation of gastric/duodenal stricture(s) (e.g., balloon, bougie)
	43246	Esophagogastroduodenoscopy, flexible, transoral; with directed placement of percutaneous gastrostomy tube
	43247	Esophagogastroduodenoscopy, flexible, transoral; with removal of foreign body(s)
	43248	Esophagogastroduodenoscopy, flexible, transoral; with insertion of guide wire followed by passage of dilator(s) through esophagus over guide wire
	43249	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic balloon dilation of esophagus (less than 30 mm diameter)
	43250	Esophagogastroduodenoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
	43251	Esophagogastroduodenoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	43253	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided transmural injection of diagnostic or therapeutic substance(s) (eg, anesthetic, neurolytic agent) or fiducial marker(s) (includes endoscopic ultrasound examination of the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis)
	43254	Esophagogastroduodenoscopy, flexible, transoral; with endoscopic mucosal resection
	43259	Esophagogastroduodenoscopy, flexible, transoral; with endoscopic ultrasound examination, including the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis
	43260	Endoscopic retrograde cholangiopancreatography (ERCP); diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	43261	Endoscopic retrograde cholangiopancreatography (ERCP); with biopsy, single or multiple
	43266	Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)
	43270	Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
	43450	Dilation of esophagus, by unguided sound or bougie, single or multiple passes
	43453	Dilation of esophagus, over guide wire
	44340	Revision of colostomy; simple (release of superficial scar) (separate procedure)
	44360	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)

Codes	Number	Description
	44361	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with biopsy, single or multiple
	44364	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	44369	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
	44376	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, including ileum; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
	44377	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, including ileum; with biopsy, single or multiple
	44380	Ileoscopy, through stoma; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	44381	Ileoscopy, through stoma; with transendoscopic balloon dilation
	44382	Ileoscopy, through stoma; with biopsy, single or multiple
	44385	Endoscopic evaluation of small intestinal pouch (eg, Kock pouch, ileal reservoir [S or J]); diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	44386	Endoscopic evaluation of small intestinal pouch (eg, Kock pouch, ileal reservoir [S or J]); with biopsy, single or multiple
	44388	Colonoscopy through stoma; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	44389	Colonoscopy through stoma; with biopsy, single or multiple
	44391	Colonoscopy through stoma; with control of bleeding, any method
	44392	Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
	44394	Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	44408	Colonoscopy through stoma; with decompression (for pathologic distention) (eg, volvulus, megacolon), including placement of decompression tube, when performed
	44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
	45100	Biopsy of anorectal wall, anal approach (eg, congenital megacolon)
	45171	Excision of rectal tumor, transanal approach; not including muscularis propria (ie, partial thickness)
	45172	Excision of rectal tumor, transanal approach; including muscularis propria (ie, full thickness)
	45190	Destruction of rectal tumor (eg, electrodesiccation, electrosurgery, laser ablation, laser resection, cryosurgery) transanal approach
	45305	Proctosigmoidoscopy, rigid; with biopsy, single or multiple
	45330	Sigmoidoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	45331	Sigmoidoscopy, flexible; with biopsy, single or multiple
	45332	Sigmoidoscopy, flexible; with removal of foreign body(s)
	45333	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
	45334	Sigmoidoscopy, flexible; with control of bleeding, any method
	45335	Sigmoidoscopy, flexible; with directed submucosal injection(s), any substance

Codes	Number	Description
	45337	Sigmoidoscopy, flexible; with decompression (for pathologic distention) (eg, volvulus, megacolon), including placement of decompression tube, when performed
	45338	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	45340	Sigmoidoscopy, flexible; with transendoscopic balloon dilation
	45341	Sigmoidoscopy, flexible; with endoscopic ultrasound examination
	45342	Sigmoidoscopy, flexible; with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s)
	45346	Sigmoidoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
	45347	Sigmoidoscopy, flexible; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)
	45349	Sigmoidoscopy, flexible; with endoscopic mucosal resection
	45350	Sigmoidoscopy, flexible; with band ligation(s) (eg, hemorrhoids)
	45378	Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	45379	Colonoscopy, flexible; with removal of foreign body(s)
	45380	Colonoscopy, flexible; with biopsy, single or multiple
	45381	Colonoscopy, flexible; with directed submucosal injection(s), any substance
	45382	Colonoscopy, flexible; with control of bleeding, any method
	45384	Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps
	45385	Colonoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
	45386	Colonoscopy, flexible; with transendoscopic balloon dilation
	45388	Colonoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
	45389	Colonoscopy, flexible; with endoscopic stent placement (includes pre- and post-dilation and guide wire passage, when performed)
	45390	Colonoscopy, flexible; with endoscopic mucosal resection
	45391	Colonoscopy, flexible; with endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures
	45392	Colonoscopy, flexible; with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s), includes endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures
	45393	Colonoscopy, flexible; with decompression (for pathologic distention) (eg, volvulus, megacolon), including placement of decompression tube, when performed
	45398	Colonoscopy, flexible; with band ligation(s) (e.g., hemorrhoids)
	45505	Proctoplasty; for prolapse of mucous membrane
	45541	Proctopexy (eg, for prolapse); perineal approach
	45560	Repair of rectocele (separate procedure)
	45905	Dilation of anal sphincter (separate procedure) under anesthesia other than local
	45910	Dilation of rectal stricture (separate procedure) under anesthesia other than local
	45915	Removal of fecal impaction or foreign body (separate procedure) under anesthesia

Codes	Number	Description
	45990	Anorectal exam, surgical, requiring anesthesia (general, spinal, or epidural), diagnostic
	46020	Placement of seton
	46030	Removal of anal seton, other marker
	46040	Incision and drainage of ischiorectal and/or perirectal abscess (separate procedure)
	46045	Incision and drainage of intramural, intramuscular, or submucosal abscess, transanal, under anesthesia
	46050	Incision and drainage, perianal abscess, superficial
	46060	Incision and drainage of ischiorectal or intramural abscess, with fistulectomy or fistulotomy, submuscular, with or without placement of seton
	46080	Sphincterotomy, anal, division of sphincter (separate procedure)
	46083	Incision of thrombosed hemorrhoid, external
	46200	Fissurectomy, including sphincterotomy, when performed
	46220	Excision of single external papilla or tag, anus
	46221	Hemorrhoidectomy, internal, by rubber band ligation(s)
	46230	Excision of multiple external papillae or tags, anus
	46250	Hemorrhoidectomy, external, 2 or more columns/groups
	46255	Hemorrhoidectomy, internal and external, single column/group;
	46257	Hemorrhoidectomy, internal and external, single column/group; with fissurectomy
	46258	Hemorrhoidectomy, internal and external, single column/group; with fistulectomy, including fissurectomy, when performed
	46260	Hemorrhoidectomy, internal and external, 2 or more columns/groups;
	46261	Hemorrhoidectomy, internal and external, 2 or more columns/groups; with fissurectomy
	46262	Hemorrhoidectomy, internal and external, 2 or more columns/groups; with fistulectomy, including fissurectomy, when performed
	46270	Surgical treatment of anal fistula (fistulectomy/fistulotomy); subcutaneous
	46275	Surgical treatment of anal fistula (fistulectomy/fistulotomy); intersphincteric
	46280	Surgical treatment of anal fistula (fistulectomy/fistulotomy); transsphincteric, suprasphincteric, extrasphincteric or multiple, including placement of seton, when performed
	46285	Surgical treatment of anal fistula (fistulectomy/fistulotomy); second stage
	46288	Closure of anal fistula with rectal advancement flap
	46320	Excision of thrombosed hemorrhoid, external
	46505	Chemodenervation of internal anal sphincter
	46606	Anoscopy; with biopsy, single or multiple
	46607	Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple
	46610	Anoscopy; with removal of single tumor, polyp, or other lesion by hot biopsy forceps or bipolar cautery
	46612	Anoscopy; with removal of multiple tumors, polyps, or other lesions by hot biopsy forceps, bipolar cautery or snare technique
	46615	Anoscopy; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
	46700	Anoplasty, plastic operation for stricture; adult
	46750	Sphincteroplasty, anal, for incontinence or prolapse; adult
	46910	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; electrodesiccation
	46917	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; laser surgery

Codes	Number	Description
	46922	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; surgical excision
	46924	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	46930	Destruction of internal hemorrhoid(s) by thermal energy (eg, infrared coagulation, cautery, radiofrequency)
	46940	Curettage or cautery of anal fissure, including dilation of anal sphincter (separate procedure); initial
	46945	Hemorrhoidectomy, internal, by ligation other than rubber band; single hemorrhoid column/group, without imaging guidance
	46946	Hemorrhoidectomy, internal, by ligation other than rubber band; 2 or more hemorrhoid columns/groups, without imaging guidance
	47000	Biopsy of liver, needle; percutaneous
	49082	Abdominal paracentesis (diagnostic or therapeutic); without imaging guidance
	49083	Abdominal paracentesis (diagnostic or therapeutic); with imaging guidance
	49422	Removal of tunneled intraperitoneal catheter
	49500	Repair initial inguinal hernia, age 6 months to younger than 5 years, with or without hydrocelectomy; reducible
	49505	Repair initial inguinal hernia, age 5 years or older; reducible
	49507	Repair initial inguinal hernia, age 5 years or older; incarcerated or strangulated
	49520	Repair recurrent inguinal hernia, any age; reducible
	49521	Repair recurrent inguinal hernia, any age; incarcerated or strangulated
	49525	Repair inguinal hernia, sliding, any age
	49550	Repair initial femoral hernia, any age; reducible
	49553	Repair initial femoral hernia, any age; incarcerated or strangulated
	49650	Laparoscopy, surgical; repair initial inguinal hernia
	49651	Laparoscopy, surgical; repair recurrent inguinal hernia
	49900	Suture, secondary, of abdominal wall for evisceration or dehiscence
	50430	Injection procedure for antegrade nephrostogram and/or ureterogram, complete diagnostic procedure including imaging guidance (eg, ultrasound and fluoroscopy) and all associated radiological supervision and interpretation; new access
	50435	Exchange nephrostomy catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation
	50575	Renal endoscopy through nephrotomy or pyelotomy, with or without irrigation, instillation, or ureteropyelography, exclusive of radiologic service; with endopyelotomy (includes cystoscopy, ureteroscopy, dilation of ureter and ureteral pelvic junction, incision of ureteral pelvic junction and insertion of endopyelotomy stent)
	50590	Lithotripsy, extracorporeal shock wave
	50688	Change of ureterostomy tube or externally accessible ureteral stent via ileal conduit
	51040	Cystostomy, cystotomy with drainage
	51102	Aspiration of bladder; with insertion of suprapubic catheter
	51600	Injection procedure for cystography or voiding urethrocystography
	51610	Injection procedure for retrograde urethrocystography
	51702	Insertion of temporary indwelling bladder catheter; simple (eg, Foley)
	51710	Change of cystostomy tube; complicated

Codes	Number	Description
	51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
	51720	Bladder instillation of anticarcinogenic agent (including retention time)
	51726	Complex cystometrogram (ie, calibrated electronic equipment);
	51728	Complex cystometrogram (ie, calibrated electronic equipment); with voiding pressure studies (ie, bladder voiding pressure), any technique
	51729	Complex cystometrogram (ie, calibrated electronic equipment); with voiding pressure studies (ie, bladder voiding pressure) and urethral pressure profile studies (ie, urethral closure pressure profile), any technique
	52000	Cystourethroscopy (separate procedure)
	52001	Cystourethroscopy with irrigation and evacuation of multiple obstructing clots
	52005	Cystourethroscopy, with ureteral catheterization, with or without irrigation, instillation, or ureteropyelography, exclusive of radiologic service;
	52007	Cystourethroscopy, with ureteral catheterization, with or without irrigation, instillation, or ureteropyelography, exclusive of radiologic service; with brush biopsy of ureter and/or renal pelvis
	52204	Cystourethroscopy, with biopsy(s)
	52214	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) of trigone, bladder neck, prostatic fossa, urethra, or periurethral glands
	52224	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) or treatment of MINOR (less than 0.5 cm) lesion(s) with or without biopsy
	52234	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of; SMALL bladder tumor(s) (0.5 up to 2.0 cm)
	52235	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of; MEDIUM bladder tumor(s) (2.0 to 5.0 cm)
	52240	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of; LARGE bladder tumor(s)
	52260	Cystourethroscopy, with dilation of bladder for interstitial cystitis; general or conduction (spinal) anesthesia
	52265	Cystourethroscopy, with dilation of bladder for interstitial cystitis; local anesthesia
	52275	Cystourethroscopy, with internal urethrotomy; male
	52276	Cystourethroscopy with direct vision internal urethrotomy
	52281	Cystourethroscopy, with calibration and/or dilation of urethral stricture or stenosis, with or without meatotomy, with or without injection procedure for cystography, male or female
	52282	Cystourethroscopy, with insertion of permanent urethral stent
	52283	Cystourethroscopy, with steroid injection into stricture
	52285	Cystourethroscopy for treatment of the female urethral syndrome with any or all of the following: urethral meatotomy, urethral dilation, internal urethrotomy, lysis of urethrovaginal septal fibrosis, lateral incisions of the bladder neck, and fulguration of polyp(s) of urethra, bladder neck, and/or trigone
	52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder
	52300	Cystourethroscopy; with resection or fulguration of orthotopic ureterocele(s), unilateral or bilateral
	52310	Cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder (separate procedure); simple
	52315	Cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder (separate procedure); complicated
	52317	Litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments; simple or small (less than 2.5 cm)

Codes	Number	Description
	52318	Litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments; complicated or large (over 2.5 cm)
	52320	Cystourethroscopy (including ureteral catheterization); with removal of ureteral calculus
	52325	Cystourethroscopy (including ureteral catheterization); with fragmentation of ureteral calculus (eg, ultrasonic or electro-hydraulic technique)
	52327	Cystourethroscopy (including ureteral catheterization); with subureteric injection of implant material
	52330	Cystourethroscopy (including ureteral catheterization); with manipulation, without removal of ureteral calculus
	52332	Cystourethroscopy, with insertion of indwelling ureteral stent (eg, Gibbons or double-J type)
	52341	Cystourethroscopy; with treatment of ureteral stricture (eg, balloon dilation, laser, electrocautery, and incision)
	52344	Cystourethroscopy with ureteroscopy; with treatment of ureteral stricture (eg, balloon dilation, laser, electrocautery, and incision)
	52351	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; diagnostic
	52352	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with removal or manipulation of calculus (ureteral catheterization is included)
	52353	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy (ureteral catheterization is included)
	52354	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with biopsy and/or fulguration of ureteral or renal pelvic lesion
	52356	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy including insertion of indwelling ureteral stent (eg, Gibbons or double-J type)
	52450	Transurethral incision of prostate
	52500	Transurethral resection of bladder neck (separate procedure)
	52601	Transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included)
	52630	Transurethral resection; residual or regrowth of obstructive prostate tissue including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included)
	52640	Transurethral resection; of postoperative bladder neck contracture
	53020	Meatotomy, cutting of meatus (separate procedure); except infant
	53200	Biopsy of urethra
	53230	Excision of urethral diverticulum (separate procedure); female
	53260	Excision or fulguration; urethral polyp(s), distal urethra
	53265	Excision or fulguration; urethral caruncle
	53270	Excision or fulguration; Skene's glands
	53440	Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)
	53445	Insertion of inflatable urethral/bladder neck sphincter, including placement of pump, reservoir, and cuff
	53450	Urethromeatoplasty, with mucosal advancement
	53500	Urethrolysis, transvaginal, secondary, open, including cystourethroscopy (eg, postsurgical obstruction, scarring)
	53605	Dilation of urethral stricture or vesical neck by passage of sound or urethral dilator, male, general or conduction (spinal) anesthesia
	53665	Dilation of female urethra, general or conduction (spinal) anesthesia
	54001	Slitting of prepuce, dorsal or lateral (separate procedure); except newborn

Codes	Number	Description
	54055	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; electrodesiccation
	54057	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; laser surgery
	54060	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; surgical excision
	54065	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	54100	Biopsy of penis; (separate procedure)
	54110	Excision of penile plaque (Peyronie disease);
	54150	Circumcision, using clamp or other device with regional dorsal penile or ring block
	54161	Circumcision, surgical excision other than clamp, device, or dorsal slit; older than 28 days of age
	54162	Lysis or excision of penile post-circumcision adhesions
	54163	Repair incomplete circumcision
	54164	Frenulotomy of penis
	54300	Plastic operation of penis for straightening of chordee (eg, hypospadias), with or without mobilization of urethra
	54450	Foreskin manipulation including lysis of preputial adhesions and stretching
	54512	Excision of extraparenchymal lesion of testis
	54530	Orchiectomy, radical, for tumor; inguinal approach
	54600	Reduction of torsion of testis, surgical, with or without fixation of contralateral testis
	54620	Fixation of contralateral testis (separate procedure)
	54640	Orchiopexy, inguinal or scrotal approach
	54700	Incision and drainage of epididymis, testis and/or scrotal space (eg, abscess or hematoma)
	54830	Excision of local lesion of epididymis
	54840	Excision of spermatocele, with or without epididymectomy
	54860	Epididymectomy; unilateral
	55000	Puncture aspiration of hydrocele, tunica vaginalis, with or without injection of medication
	55040	Excision of hydrocele; unilateral
	55041	Excision of hydrocele; bilateral
	55060	Repair of tunica vaginalis hydrocele (Bottle type)
	55100	Drainage of scrotal wall abscess
	55110	Scrotal exploration
	55120	Removal of foreign body in scrotum
	55250	Vasectomy, unilateral or bilateral (separate procedure), including postoperative semen examination(s)
	55400	Vasovasostomy, vasovasorrhaphy
	55500	Excision of hydrocele of spermatic cord, unilateral (separate procedure)
	55520	Excision of lesion of spermatic cord (separate procedure)
	55540	Excision of varicocele or ligation of spermatic veins for varicocele; with hernia repair
	55700	Biopsy, prostate; needle or punch, single or multiple, any approach
	56405	Incision and drainage of vulva or perineal abscess
	56420	Incision and drainage of Bartholin's gland abscess
	56440	Marsupialization of Bartholin's gland cyst
	56441	Lysis of labial adhesions

Codes	Number	Description
	56442	Hymenotomy, simple incision
	56501	Destruction of lesion(s), vulva; simple (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	56515	Destruction of lesion(s), vulva; extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	56605	Biopsy of vulva or perineum (separate procedure); 1 lesion
	56620	Vulvectomy simple; partial
	56700	Partial hymenectomy or revision of hymenal ring
	56740	Excision of Bartholin's gland or cyst
	56810	Perineoplasty, repair of perineum, nonobstetrical (separate procedure)
	56821	Colposcopy of the vulva; with biopsy(s)
	57000	Colpotomy; with exploration
	57061	Destruction of vaginal lesion(s); simple (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	57065	Destruction of vaginal lesion(s); extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
	57100	Biopsy of vaginal mucosa; simple (separate procedure)
	57130	Excision of vaginal septum
	57135	Excision of vaginal cyst or tumor
	57210	Colpoperineorrhaphy, suture of injury of vagina and/or perineum (nonobstetrical)
	57240	Anterior colporrhaphy, repair of cystocele with or without repair of urethrocele, including cystourethroscopy, when performed
	57250	Posterior colporrhaphy, repair of rectocele with or without perineorrhaphy
	57260	Combined anteroposterior colporrhaphy, including cystourethroscopy, when performed;
	57268	Repair of enterocele, vaginal approach (separate procedure)
	57282	Colpopexy, vaginal; extra-peritoneal approach (sacrospinous, iliococcygeus)
	57283	Colpopexy, vaginal; intra-peritoneal approach (uterosacral, levator myorrhaphy)
	57287	Removal or revision of sling for stress incontinence (eg, fascia or synthetic)
	57300	Closure of rectovaginal fistula; vaginal or transanal approach
	57400	Dilation of vagina under anesthesia (other than local)
	57410	Pelvic examination under anesthesia (other than local)
	57415	Removal of impacted vaginal foreign body (separate procedure) under anesthesia (other than local)
	57420	Colposcopy of the entire vagina, with cervix if present;
	57421	Colposcopy of the entire vagina, with cervix if present; with biopsy(s) of vagina/cervix
	57425	Laparoscopy, surgical, colpopexy (suspension of vaginal apex)
	57452	Colposcopy of the cervix including upper/adjacent vagina;
	57454	Colposcopy of the cervix including upper/adjacent vagina; with biopsy(s) of the cervix and endocervical curettage
	57456	Colposcopy of the cervix including upper/adjacent vagina; with endocervical curettage
	57461	Colposcopy of the cervix including upper/adjacent vagina; with loop electrode conization of the cervix
	57500	Biopsy of cervix, single or multiple, or local excision of lesion, with or without fulguration (separate procedure)
	57505	Endocervical curettage (not done as part of a dilation and curettage)
	57510	Cautery of cervix; electro or thermal
	57513	Cautery of cervix; laser ablation

Codes	Number	Description
	57520	Conization of cervix, with or without fulguration, with or without dilation and curettage, with or without repair; cold knife or laser
	57522	Conization of cervix, with or without fulguration, with or without dilation and curettage, with or without repair; loop electrode excision
	57530	Trachelectomy (cervicectomy), amputation of cervix (separate procedure)
	57700	Cerclage of uterine cervix, nonobstetrical
	57720	Trachelorrhaphy, plastic repair of uterine cervix, vaginal approach
	57800	Dilation of cervical canal, instrumental (separate procedure)
	58100	Dilation and curettage, diagnostic and/or therapeutic (nonobstetrical)
	58120	Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C
	58263	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s), with repair of enterocele
	58558	Hysteroscopy, surgical; with division or resection of intrauterine septum (any method)
	58560	Hysteroscopy, surgical; with removal of leiomyomata
	58561	Hysteroscopy, surgical; with bilateral fallopian tube cannulation to induce occlusion by placement of permanent implants
	58565	Laparoscopy, surgical; with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method
	58662	Laparoscopy, surgical; with fulguration of oviducts (with or without transection)
	58670	Laparoscopy, surgical; with occlusion of oviducts by device (eg, band, clip, or Falope ring)
	58671	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)
	58700	Ovarian cystectomy, unilateral or bilateral
	58925	Insertion of cervical dilator (eg, laminaria, prostaglandin) (separate procedure)
	59200	Destruction by neurolytic agent, trigeminal nerve; supraorbital, infraorbital, mental, or inferior alveolar branch
	62270	Spinal puncture, lumbar, diagnostic;
	63661	Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
	63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
	64418	Injection(s), anesthetic agent(s) and/or steroid; suprascapular nerve
	64425	Injection(s), anesthetic agent(s) and/or steroid; ilioinguinal, iliohypogastric nerves
	64530	Injection, anesthetic agent; celiac plexus, with or without radiologic monitoring
	64600	Chemodenervation of trunk muscle(s); 6 or more muscles
	64610	Destruction by neurolytic agent, trigeminal nerve; second and third division branches at foramen ovale under radiologic monitoring
	64642	Chemodenervation of one extremity; 1-4 muscle(s)
	64644	Chemodenervation of one extremity; 5 or more muscles
	64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
	64647	Excision of neuroma; digital nerve, 1 or both, same digit
	64702	Neuroplasty; digital, 1 or both, same digit
	64718	Neuroplasty and/or transposition; ulnar nerve at elbow
	64719	Neuroplasty and/or transposition; ulnar nerve at wrist
	64721	Neuroplasty and/or transposition; median nerve at carpal tunnel
	64774	Excision of neuroma; cutaneous nerve, surgically identifiable
	64776	Excision of neuroma; hand or foot, except digital nerve
	64782	Excision of neuroma; major peripheral nerve, except sciatic
	64784	Excision of neurofibroma or neurolemmoma; cutaneous nerve

Codes	Number	Description
	64788	Suture of 1 nerve; median motor thenar
	64795	Biopsy of nerve
	64831	Suture of digital nerve, hand or foot; 1 nerve
	64835	Repair of laceration; cornea, nonperforating, with or without removal foreign body
	65275	Excision of lesion, cornea (keratectomy, lamellar, partial), except pterygium
	65400	Excision or transposition of pterygium; without graft
	65420	Excision or transposition of pterygium; with graft
	65426	Removal of corneal epithelium; with or without chemocauterization (abrasion, curettage)
	65435	Removal of corneal epithelium; with application of chelating agent (eg, EDTA)
	65436	Keratoplasty (corneal transplant); anterior lamellar
	65710	Keratoplasty (corneal transplant); penetrating (except in aphakia or pseudophakia)
	65730	Keratoplasty (corneal transplant); penetrating (in aphakia)
	65750	Keratoplasty (corneal transplant); penetrating (in pseudophakia)
	65755	Corneal relaxing incision for correction of surgically induced astigmatism
	65756	Keratoplasty (corneal transplant); endothelial
	65772	Corneal wedge resection for correction of surgically induced astigmatism
	65778	Placement of amniotic membrane on the ocular surface; without sutures
	65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
	65780	Ocular surface reconstruction; amniotic membrane transplantation, multiple layers
	65800	Paracentesis of anterior chamber of eye (separate procedure); with removal of aqueous
	65815	Paracentesis of anterior chamber of eye (separate procedure); with removal of blood, with or without irrigation and/or air injection
	65820	Goniotomy
	65850	Trabeculotomy ab externo
	65855	Trabeculoplasty by laser surgery
	65865	Severing adhesions of anterior segment of eye, incisional technique (with or without injection of air or liquid) (separate procedure); goniosynechiae
	65875	Severing adhesions of anterior segment of eye, incisional technique (with or without injection of air or liquid) (separate procedure); posterior synechiae
	65920	Removal of implanted material, anterior segment of eye
	66020	Injection, anterior chamber of eye (separate procedure); air or liquid
	66170	Fistulization of sclera for glaucoma; trabeculectomy ab externo in absence of previous surgery
	66172	Fistulization of sclera for glaucoma; trabeculectomy ab externo with scarring from previous ocular surgery or trauma (includes injection of antifibrotic agents)
	66179	Aqueous shunt to extraocular equatorial plate reservoir, external approach; without graft
	66180	Aqueous shunt to extraocular equatorial plate reservoir, external approach; with graft
	66183	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach
	66184	Revision of aqueous shunt to extraocular equatorial plate reservoir; without graft
	66185	Revision of aqueous shunt to extraocular equatorial plate reservoir; with graft
	66250	Revision or repair of operative wound of anterior segment, any type, early or late, major or minor procedure

Codes	Number	Description
	66682	Suture of iris, ciliary body (separate procedure) with retrieval of suture through small incision (eg, McCannel suture)
	66710	Ciliary body destruction; cyclophotocoagulation, transscleral
	66711	Ciliary body destruction; cyclophotocoagulation, endoscopic, without concomitant removal of crystalline lens
	66761	Iridotomy/iridectomy by laser surgery (eg, for glaucoma) (per session)
	66762	Iridoplasty by photocoagulation (1 or more sessions) (eg, for improvement of vision, for widening of anterior chamber angle)
	66821	Discission of secondary membranous cataract (opacified posterior lens capsule and/or anterior hyaloid); laser surgery (eg, YAG laser) (1 or more stages)
	66825	Repositioning of intraocular lens prosthesis, requiring an incision (separate procedure)
	66840	Removal of lens material; aspiration technique, 1 or more stages
	66850	Removal of lens material; phacofragmentation technique (mechanical or ultrasonic) (eg, phacoemulsification), with aspiration
	66852	Removal of lens material; pars plana approach, with or without vitrectomy
	66982	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (eg, iris expansion device, suture support for intraocular lens, or primary posterior capsulorrhexis) or performed on patients in the amblyogenic developmental stage; without endoscopic cyclophotocoagulation
	66983	Intracapsular cataract extraction with insertion of intraocular lens prosthesis (1 stage procedure)
	66984	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1 stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification); without endoscopic cyclophotocoagulation
	66985	Insertion of intraocular lens prosthesis (secondary implant), not associated with concurrent cataract removal
	66986	Exchange of intraocular lens
	66987	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (eg, iris expansion device, suture support for intraocular lens, or primary posterior capsulorrhexis) or performed on patients in the amblyogenic developmental stage; with endoscopic cyclophotocoagulation
	66988	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1 stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification); with endoscopic cyclophotocoagulation
	67005	Removal of vitreous, anterior approach (open sky technique or limbal incision); partial removal
	67010	Removal of vitreous, anterior approach (open sky technique or limbal incision); subtotal removal with mechanical vitrectomy
	67015	Aspiration or release of vitreous, subretinal or choroidal fluid, pars plana approach (posterior sclerotomy)
	67025	Injection of vitreous substitute, pars plana or limbal approach (fluid-gas exchange), with or without aspiration (separate procedure)
	67028	Intravitreal injection of a pharmacologic agent (separate procedure)
	67031	Severing of vitreous strands, vitreous face adhesions, sheets, membranes or opacities, laser surgery (1 or more stages)
	67036	Vitrectomy, mechanical, pars plana approach;

Codes	Number	Description
	67039	Vitrectomy, mechanical, pars plana approach; with focal endolaser photocoagulation
	67040	Vitrectomy, mechanical, pars plana approach; with endolaser panretinal photocoagulation
	67041	Vitrectomy, mechanical, pars plana approach; with removal of preretinal cellular membrane (eg, macular pucker)
	67042	Vitrectomy, mechanical, pars plana approach; with removal of internal limiting membrane of retina (eg, for repair of macular hole, diabetic macular edema), includes, if performed, intraocular tamponade (ie, air, gas or silicone oil)
	67043	Vitrectomy, mechanical, pars plana approach; with removal of subretinal membrane (eg, choroidal neovascularization), includes, if performed, intraocular tamponade (ie, air, gas or silicone oil) and laser photocoagulation
	67101	Repair of retinal detachment, including drainage of subretinal fluid when performed; cryotherapy
	67105	Repair of retinal detachment, including drainage of subretinal fluid when performed; photocoagulation
	67107	Repair of retinal detachment; scleral buckling (such as lamellar scleral dissection, imbrication or encircling procedure), including, when performed, implant, cryotherapy, photocoagulation, and drainage of subretinal fluid
	67108	Repair of retinal detachment; with vitrectomy, any method, including, when performed, air or gas tamponade, focal endolaser photocoagulation, cryotherapy, drainage of subretinal fluid, scleral buckling, and/or removal of lens by same technique
	67110	Repair of retinal detachment; by injection of air or other gas (eg, pneumatic retinopexy)
	67113	Repair of complex retinal detachment (eg, proliferative vitreoretinopathy, stage C-1 or greater, diabetic traction retinal detachment, retinopathy of prematurity, retinal tear of greater than 90 degrees), with vitrectomy and membrane peeling, including, when performed, air, gas, or silicone oil tamponade, cryotherapy, endolaser photocoagulation, drainage of subretinal fluid, scleral buckling, and/or removal of lens
	67120	Removal of implanted material, posterior segment; extraocular
	67121	Removal of implanted material, posterior segment; intraocular
	67141	Prophylaxis of retinal detachment (eg, retinal break, lattice degeneration) without drainage; cryotherapy, diathermy
	67145	Prophylaxis of retinal detachment (eg, retinal break, lattice degeneration) without drainage; photocoagulation
	67210	Destruction of localized lesion of retina (eg, macular edema, tumors), 1 or more sessions; photocoagulation
	67218	Destruction of localized lesion of retina (eg, macular edema, tumors), 1 or more sessions; radiation by implantation of source (includes removal of source)
	67220	Destruction of localized lesion of choroid (eg, choroidal neovascularization); photocoagulation (eg, laser), 1 or more sessions
	67221	Destruction of localized lesion of choroid (eg, choroidal neovascularization); photodynamic therapy (includes intravenous infusion)
	67228	Treatment of extensive or progressive retinopathy (eg, diabetic retinopathy), photocoagulation
	67311	Strabismus surgery, recession or resection procedure; 1 horizontal muscle
	67312	Strabismus surgery, recession or resection procedure; 2 horizontal muscles
	67314	Strabismus surgery, recession or resection procedure; 1 vertical muscle (excluding superior oblique)

Codes	Number	Description
	67316	Strabismus surgery, recession or resection procedure; 2 or more vertical muscles (excluding superior oblique)
	67318	Strabismus surgery, any procedure, superior oblique muscle
	67345	Chemodenervation of extraocular muscle
	67400	Orbitotomy without bone flap (frontal or transconjunctival approach); for exploration, with or without biopsy
	67412	Orbitotomy without bone flap (frontal or transconjunctival approach); with removal of lesion
	67414	Orbitotomy without bone flap (frontal or transconjunctival approach); with removal of bone for decompression
	67420	Orbitotomy with bone flap or window, lateral approach (eg, Kroenlein); with removal of lesion
	67445	Orbitotomy with bone flap or window, lateral approach (eg, Kroenlein); with removal of bone for decompression
	67550	Orbital implant (implant outside muscle cone); insertion
	67560	Orbital implant (implant outside muscle cone); removal or revision
	67700	Blepharotomy, drainage of abscess, eyelid
	67800	Excision of chalazion; single
	67801	Excision of chalazion; multiple, same lid
	67805	Excision of chalazion; multiple, different lids
	67808	Excision of chalazion; under general anesthesia and/or requiring hospitalization, single or multiple
	67810	Incisional biopsy of eyelid skin including lid margin
	67825	Correction of trichiasis; epilation by other than forceps (eg, by electrosurgery, cryotherapy, laser surgery)
	67840	Excision of lesion of eyelid (except chalazion) without closure or with simple direct closure
	67875	Temporary closure of eyelids by suture (eg, Frost suture)
	67935	Suture of recent wound, eyelid, involving lid margin, tarsus, and/or palpebral conjunctiva direct closure; full thickness
	67961	Excision and repair of eyelid, involving lid margin, tarsus, conjunctiva, canthus, or full thickness, may include preparation for skin graft or pedicle flap with adjacent tissue transfer or rearrangement; up to one-fourth of lid margin
	67966	Excision and repair of eyelid, involving lid margin, tarsus, conjunctiva, canthus, or full thickness, may include preparation for skin graft or pedicle flap with adjacent tissue transfer or rearrangement; over one-fourth of lid margin
	67971	Reconstruction of eyelid, full thickness by transfer of tarsoconjunctival flap from opposing eyelid; up to two-thirds of eyelid, 1 stage or first stage
	67973	Reconstruction of eyelid, full thickness by transfer of tarsoconjunctival flap from opposing eyelid; total eyelid, lower, 1 stage or first stage
	67975	Reconstruction of eyelid, full thickness by transfer of tarsoconjunctival flap from opposing eyelid; second stage
	68100	Biopsy of conjunctiva
	68110	Excision of lesion, conjunctiva; up to 1 cm
	68115	Excision of lesion, conjunctiva; over 1 cm
	68135	Destruction of lesion, conjunctiva
	68320	Conjunctivoplasty; with conjunctival graft or extensive rearrangement
	68440	Snip incision of lacrimal punctum
	68530	Removal of foreign body or dacryolith, lacrimal passages
	68700	Plastic repair of canaliculi
	68720	Dacryocystorhinostomy (fistulization of lacrimal sac to nasal cavity)

Codes	Number	Description
	68750	Conjunctivorhinostomy (fistulization of conjunctiva to nasal cavity); with insertion of tube or stent
	68761	Closure of the lacrimal punctum; by plug, each
	68801	Dilation of lacrimal punctum, with or without irrigation
	68811	Probing of nasolacrimal duct, with or without irrigation; requiring general anesthesia
	68815	Probing of nasolacrimal duct, with or without irrigation; with insertion of tube or stent
	69000	Drainage external ear, abscess or hematoma; simple
	69100	Biopsy external ear
	69110	Excision external ear; partial, simple repair
	69140	Excision exostosis(es), external auditory canal
	69145	Excision soft tissue lesion, external auditory canal
	69205	Removal foreign body from external auditory canal; with general anesthesia
	69222	Debridement, mastoidectomy cavity, complex (eg, with anesthesia or more than routine cleaning)
	69310	Reconstruction of external auditory canal (meatoplasty) (eg, for stenosis due to injury, infection) (separate procedure)
	69320	Reconstruction external auditory canal for congenital atresia, single stage
	69421	Myringotomy including aspiration and/or eustachian tube inflation requiring general anesthesia
	69424	Ventilating tube removal requiring general anesthesia
	69433	Tympanostomy (requiring insertion of ventilating tube), local or topical anesthesia
	69436	Tympanostomy (requiring insertion of ventilating tube), general anesthesia
	69440	Middle ear exploration through postauricular or ear canal incision
	69450	Tympanolysis, transcanal
	69502	Mastoidectomy; complete
	69505	Mastoidectomy; modified radical
	69550	Excision aural glomus tumor; transcanal
	69602	Revision mastoidectomy; resulting in modified radical mastoidectomy
	69610	Tympanic membrane repair, with or without site preparation of perforation for closure, with or without patch
	69620	Myringoplasty (surgery confined to drumhead and donor area)
	69631	Tympanoplasty without mastoidectomy (including canalplasty, atticotomy and/or middle ear surgery), initial or revision; without ossicular chain reconstruction
	69632	Tympanoplasty without mastoidectomy (including canalplasty, atticotomy and/or middle ear surgery), initial or revision; with ossicular chain reconstruction (eg, postfenestration)
	69633	Tympanoplasty without mastoidectomy (including canalplasty, atticotomy and/or middle ear surgery), initial or revision; with ossicular chain reconstruction and synthetic prosthesis (eg, partial ossicular replacement prosthesis [PORP], total ossicular replacement prosthesis [TORP])
	69635	Tympanoplasty with antrotomy or mastoidotomy (including canalplasty, atticotomy, middle ear surgery, and/or tympanic membrane repair); without ossicular chain reconstruction
	69636	Tympanoplasty with antrotomy or mastoidotomy (including canalplasty, atticotomy, middle ear surgery, and/or tympanic membrane repair); with ossicular chain reconstruction
	69641	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); without ossicular chain reconstruction

Codes	Number	Description
	69642	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); with ossicular chain reconstruction
	69643	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); with intact or reconstructed wall, without ossicular chain reconstruction
	69644	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); with intact or reconstructed canal wall, with ossicular chain reconstruction
	69645	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); radical or complete, without ossicular chain reconstruction
	69646	Tympanoplasty with mastoidectomy (including canalplasty, middle ear surgery, tympanic membrane repair); radical or complete, with ossicular chain reconstruction
	69650	Stapes mobilization
	69660	Stapedectomy or stapedotomy with reestablishment of ossicular continuity, with or without use of foreign material;
	69661	Stapedectomy or stapedotomy with reestablishment of ossicular continuity, with or without use of foreign material; with footplate drill out
	69662	Revision of stapedectomy or stapedotomy
	69666	Repair oval window fistula
	69801	Labyrinthotomy, with perfusion of vestibuloactive drug(s), transcanal
	69805	Endolymphatic sac operation; without shunt
	69806	Endolymphatic sac operation; with shunt
HCPCS	G0104	Colorectal cancer screening; flexible sigmoidoscopy
	G0105	Colorectal cancer screening; colonoscopy on individual at high risk
	G0106	Colorectal cancer screening; alternative to G0104, screening sigmoidoscopy, barium enema
	G0120	Colorectal cancer screening; alternative to G0105, screening colonoscopy, barium enema
	G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
	G0122	Colorectal cancer screening; barium enema

Date of Origin: *July 2022*