Uniform Medical Plan coverage limits

Updates effective 4/1/2025

The benefit coverage limits listed below apply to these UMP plans:

- Uniform Medical Plan (UMP) Classic (PEBB)
- UMP Select (PEBB)
- UMP Consumer-Directed Health Plan (UMP CDHP) (PEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (PEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (PEBB)

- UMP Achieve 1 (SEBB)
- UMP Achieve 2 (SEBB)
- UMP High Deductible Plan (SEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (SEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (SEBB)

Some services listed under these benefits have coverage limits. These limits are either determined by a Health Technology Clinical Committee (HTCC) decision or a Regence BlueShield medical policy. **The table below does not include every limit or exclusion under this benefit. For more details, refer to your plan's Certificate of Coverage.**

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.

NOTE: This document includes links to external webpages and documentation. To search inside this document, use CTRL+F for PCs or Command+F for Macs, and type in your search term.

Medical Policies Document 1:	Medical Policies Document 2:
Guidelines	Substance Use Disorder Mental Health
Inpatient Admissions	DME
Radiology Sleep Physical Medicine	Surgery
Lab Maternity Medicine	Transplants
Genetic Testing	

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

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)
- Durable medical equipment (DME) (PDF)
- Hospital Admit and Discharge Notification Form (PDF)
- NICU/PICU Notification of Admission Form (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)
    - Pre-authorization is only required for UMP members age 18 and older; please see the Applied Behavioral Analysis (ABA) Therapy section below
- Applied Behavioral Analysis (ABA) Concurrent Request Form (PDF)
    - Pre-authorization is only required for UMP members age 18 and older; please see the Applied Behavioral Analysis (ABA) Therapy section below
- 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

Professional services and DME		1 (800) 423-6884	1 (844) 679-7763
		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	
Concurrent review notification for: • Skilled nursing facilities (SNF) • Inpatient hospital continued stay • Inpatient rehabilitation (IPR) • Long-term acute care hospitalizations (LTACH)		1 (800) 423-6884	1 (855) 848-8220
Admission or discharge notifications for inpatient hospital			1 (800) 453-4341
Admission or discharge notifications for SNF/IPRL/LTACH		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
Acute inpatient medical and behavioral health hospital stays require concurrent review.			

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 Must notify within 24 hours for newborn intensive care unit (NICU) or pediatric	72 hours

	intensive care unit (PICU) admission. Exception: Maternity notifications are required on day 6.	
*Note that additional timeframes for review are after receipt of the requested documentation or after the timeframe for submission of the requested information has expired - whichever comes first.		

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
- ECMO for UMP is subject to HTCC Decision for initiation. Regence Medical Policy is used for continued use criteria not addressed in the HTCC.
- 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'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.

- **Inpatient: Psychiatric, eating disorder, ASAM 3.7 in a hospital setting, or ASAM 4.0**
    - Pre-authorization requests should be submitted as soon as possible and are accepted if they are within 3 business days of admission.
    - Timely concurrent review will be required if additional days are requested after an initial pre-authorization is issued. Concurrent review records are due on the last covered date of a pre-authorization. Failure to follow concurrent review requirements may result in an administrative denial, claim non-payment and provider and facility write-off. Members may not be balance billed.
- **Residential levels of care (LOC)**
    - Includes chemical dependency (ASAM 3.7and ASAM 3.5) residential, mental health residential and eating disorder residential requests.
        - Pre-authorization requests must be received within 3 business days of admission.
        - Initial notification of admission of ASAM 3.7 or ASAM 3.7 LOC can be submitted prior to sending a pre-authorization request if clinical records are not available at time of admission.
- **Partial hospitalization & intensive outpatient treatment**
    - Includes mental health, eating disorder and chemical dependency (ASAM 2.5, ASAM 2.1)
        - Request for pre-authorization is required within 7 calendar days of start date.
- **Transcranial magnetic stimulation (TMS) & applied behavior analysis (ABA)**
    - Request for pre-authorization is required within 7 calendar days of start date.
    - ABA services only require pre-authorization for members over the age of 18.

Behavioral health criteria:

- The American Society of Addiction Medicine (ASAM) guide (PDF)
- Level of Care Utilization System (LOCUS) guide (PDF)
- Child and Adolescent Level of Care/Service Intensity Utilization System (CALOCUS-CASII) guide (PDF)
- Early Childhood Service Intensity Instrument (ECSII) guide (PDF)
- Health Technology Clinical Committee (HTCC) Final Findings and Decision for TMS

- Regence medical policies for review of ABA and TMS (for members under the age of 18):
    - Applied Behavior Analysis for the Treatment of Autism Spectrum Disorders (PDF)
    - Applied Behavior Analysis Initial Assessment for the Treatment of Autism Spectrum Disorders (PDF)
    - Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders (PDF)

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

Cardiovascular

Carelon Cardiovascular

We partner with Carelon to administer our cardiovascular program.

- Login to Carelon's Provider Portal
- Phone 1 (877) 291-0509
- View workarounds for Carelon system outages
- **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: C1721, C1722, C1764, C1777, C1785, C1786, C1882, C1895, C1896, C1899, C2619, C2620, C2621, E0616, G0448, K0606, 0823T, 0825T, 0913T, 33206, 33207, 33208, 33212, 33213, 33214, 33221, 33227, 33228, 33229, 33230, 33231, 33240, 33249, 33270, 33271, 33274, 33285, 37220, 37221, 37224, 37225, 37226, 37227, 37228, 37229, 37230, 37231, 92920, 92924, 92928, 92933, 92937, 92943, 93228, 93229, 93454, 93455,

93456, 93457, 93458, 93459, 93460, 93461, 93650, 93653, 93654, 93656, 93880, 93882, 93922, 93923, 93924, 93925, 93926, 93930, 93931, 93978, 93979

- **Effective May 1, 2025, Pre-authorization will be required for codes: C7513, C7514, C7515, C7530, 36901, 36902, 36903, 36904, 36905, 36906, 37241, 37242, 37243, 37244, 93580, 93600, 93602, 93603, 93610, 93612, 93618, 93619, 93620, 93624, 93642, 93644**
- **Effective July 1, 2025, Pre-authorization will be required for codes: C7557, C7558**
- Retrospective review is not allowed for cardiac rhythm monitors (93228 and 33285). Retrospective review is allowed for cardiac ablation and wearable and cardioverter defibrillators if records are received within 10 business days of the date of service.
- Procedures performed in an inpatient setting or on an emergent basis **do not** require pre-authorization from Carelon. Inpatient stays are subject to review by Regence for determining the appropriate length of stay.

HTCC decisions administered by Carelon:

- Cardiac Stents
  - UMP is subject to HTCC Decision (PDF): 92928, 92933, 92937, 92943
- Catheter Ablation for Supraventricular Tachyarrhythmias (SVTA)
  - UMP is subject to HTCC Decision (PDF): 93653, 93656

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 pre-authorization 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 pre-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, 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, 0461U
- UMP is subject to HTCC Decision (PDF) for codes 81225, 81418, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U and 0461U.
- Codes 81225, 81418, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 0461U and 0533U 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, 0471U

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, 0045U, 0047U, 0067U, 0009U, 0262U, 0497U
- 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, 0478U, 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, 81434, 81437, 81440, 81441, 81443, 81450, 81451, 81455, 81456, 81460, 81465, 81470, 81471, 0461U
- UMP is subject to HTCC Decision (PDF) for code 81225 and 0461U
- Codes 81225 and 0461U 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 Red Blood Cell Antigen 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
- UMP is subject to HTCC Decision (PDF) for 0094U, 0212U, 0213U, 0265U, 0266U, 0267U, 0335U, 0336U, 0425U, 0426U, 0532U, 81425, 81426, 81427

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, 0469U

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, 0473U, 0498U, 0499U, 0523U, 0538U, 0543U, 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, 0485U, 0487U, 0530U, 0539U, 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, G0552, G0553, G0554

Digital Therapeutic Products for Attention Deficit Hyperactivity Disorder (PDF)

- 98978, A9291, G0552, G0553, G0554

Digital Therapeutic Products for Chronic Low Back Pain (PDF)

- 98978, A9291, E1905, G0552, G0553, G0554

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

- A9291, G0552, G0553, G0554

Digital Therapeutic Products for Substance Use Disorders (PDF)

- 98978, A9291

Digital Therapeutic Products for Amblyopia (PDF)

- A9292

Electromagnetic Navigation Bronchoscopy

- **Effective July 1, 2025: Pre-authorization will be required for codes: 31626, 31627, C7509, C7510, C7511, C9751**

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
- Acute/sudden sensorineural hearing loss is a covered condition for this HTCC and is no longer applicable as an exclusion.
    - Note, chronic sensorineural hearing loss remains an exclusion under this HTCC.
- 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 pre-authorization requirements.
- Review the codes requiring pre-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)

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

- UMP is subject to HTCC Decision (PDF) for codes 90867, 90868, 90869, 0889T, 0890T, 0891T, 0892T
    - 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)

- 11920, 11921, 15769, 15771, 15772, 15773, 15774, 15775, 15776, 15825, 15828, 15829, 17380, 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, 55970, 55980, 56625, 56800, 56805, 57106, 57110, 57291, 57292, 57295, 57296, 57335, 57426, 58353, 58356, 58563, C1813, C2622, L8600

- Codes 55970 and 55980 are non-specific. The specific procedure code(s) must be requested in place of these non-specific codes.
- 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

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 Radiology

We partner with Carelon to administer our Radiology Program.

- Login to Carelon's ProviderPortal
- Phone 1 (877) 291-0509
- View workarounds for Carelon system outages
- **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, 70450, 70460, 70470, 70480, 70481, 70482, 70486, 70487, 70488, 70490, 70491, 70492, 70496, 70498, 70540, 70542, 70543, 70544, 70545, 70546, 70547, 70548, 70549, 70551, 70552, 70553, 70554, 70550, 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, 75557, 75561, 75559, 75563, 75572, 75573, 75574, 75580, 75635, 76391, 77046, 77047, 77048, 77049, 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, 78608, 78609, 78610, 78630, 78635, 78645, 78650, 78660, 78700, 78701, 78707, 78708, 78709, 78725, 78740, 78761, 78800, 78801, 78802, 78803, 78804, 78811, 78812, 78813, 78814, 78815, 78816, 78830, 78831, 78832, 93303, 93304, 93306, 93307, 93308, 93312, 93313, 93314, 93315, 93316, 93317, 93350, 93351, 0042T, 0648T, 0649T

- Procedures performed in an inpatient setting or an emergent basis **do not** require pre-authorization from Carelon. Inpatient stays are subject to review by Regence for determining the appropriate length of stay.
- 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

Carelon Sleep Medicine

We partner with Carelon to administer our Sleep Medicine program.

- Login to Carelon's Provider Portal
- Phone 1 (877) 291-0509
- View workarounds for Carelon system outages
- **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. Also refer to the Surgery section for additional information about pre-

authorization requirements related to surgery for Sleep Apnea Diagnosis and Treatment.
- 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.
- Procedures performed in an inpatient setting or on an emergent basis **do not** require pre-authorization from Carelon. Inpatient stays are subject to review by Regence for determining the appropriate length of stay.
- 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

Anterior Abdominal Wall (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 K42.9, K43.2 and K43.9 for ventral hernia repair

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, 43645, 43772, 43773, 43774, 43775, 43820, 43843, 43845, 43846, 43847, 43887, 43888, C9784, C9785, S2083
- **Note**: Intragastric ballons will not be a covered benefit and the following codes will not be covered: 43290, 43291, 0813T
- Bariatric surgery and HTCC guidelines apply, in order to establish eligibility for surgery and medical necessity.

Benign Prostatic Hyperplasia Surgical Treatments (PDF)

- 0421T, 53854, C2596

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

Extracranial Carotid Angioplasty and Stenting (PDF)

- C7563
- UMP is subject to HTCC Decision (PDF): 37215, 37216, 37217, 37246, 37247, C7532

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 (PDF)
- 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

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

- 33340

Lumbar Fusion for Degenerative Disc Disease (PDF)

- 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: For indications or populations not addressed in the HTCC, the Regence Medical Policy will apply. This includes but is not limited to the following: 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, and Transurethral Ultrasound Ablation (TULSA) (PDF)

- 55880, 61715

Microwave Tumor Ablation (PDF)

- 32998, 50592

Negative Pressure Wound Therapy for Home Use (NPWT)

- 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
- **Note**: Medical necessity for negative pressure wound therapy devices must be established prior to requesting pre-authorization for clinical care and supplies related to the device.

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, 60660, 60661

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 (PDF) for codes 0786T, 0787T, 0788T, 0789T

Sacroiliac Joint Fusion (PDF)

- UMP is subject to HTCC Decision (PDF): 27278, 27279, 27280, C1737
- 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
- Spinal cord stimulation for the treatment of complex regional pain syndrome is not a covered benefit, per HTCC Decision (PDF) 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:
    - G56.40, G56.41, G56.42, G56.43, G57.70, G57.71, G57.72, G57.73, G90.50, G90.511, G90.512, G90.513, G90.519, G90.521, G90.522, G90.523, G90.529, G90.59
- **Note**: Spinal cord stimulation for the treatment of the following is not a covered benefit:
    - Life expectancy less than one (1) year
    - Hemoglobin A1C (HbA1C) >10 (for PDN)
    - Body mass index (BMI)>45
    - Maximum daily morphine milligram equivalent (MME) ≥120
    - Concurrent, untreated, substance use disorder (including alcohol, prescription or illicit drugs) per American Society of Addiction Medicine (ASAM) guidelines
    - Active, substantial chronic pain in other regions that have required treatment in the past year
    - Related or pending worker's compensation claim (for FBSS and NSRBP)
    - Pending or existing litigation for the condition being treated with SCS
- 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**:
    - 62292 for Therapeutic Medial Branch Nerve Block, Intradiscal and Facet Spinal Injections are not a covered benefit, reference the HTCC Decision (PDF) :

- 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 decisions Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy (PDF) and Stereotactic body radiation therapy (SBRT) (PDF): 32701, 61796, 61797, 61798, 61799, 61800, 63620, 63621, 77301, 77338, 77371, 77372, 77373, 77432, 77435, G0339, G0340, G0563
- The HTCC Decision (PDF) is specific to the treatment of cancer of stereotactic radiation surgery and SBRT for cancers of spine/paraspinal structures, and CNS tumors.
- **Notes**:
  - HTCC Decision (PDF) applies for osteosarcoma of the spine
  - Stereotactic radiation surgery is not covered for conditions other than Central Nervous System (CNS) and Metastatic tumors
- HTCC Decision (PDF) 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, renal cancers, as well as primary bone, head and neck, adrenal, melanoma, Merkel cell, breast, ovarian, and cervical cancers.
- Regence medical policies apply for any condition not mentioned specific to the HTCC determinations above:
  - Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites (PDF) (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 Site of Care - Hospital Outpatient

- Pre-authorization is required on codes 10060, 10061, 10080, 10081, 10120, 10121, 10140, 10160, 10180, 11000, 11010, 11012, 11042, 11044, 11200, 11310, 11402, 11403, 11404, 11406, 11420, 11421, 11422, 11423, 11424, 11426, 11440, 11441, 11442, 11443, 11444, 11446, 11450, 11451, 11462, 11463, 11470, 11471, 11601, 11602, 11603, 11604, 11606, 11620, 11621, 11622, 11623, 11624, 11626, 11640, 11641, 11642, 11643, 11644, 11646, 11730, 11750, 11755, 11760, 11765, 11770, 11772, 11900, 12001, 12002, 12011, 12020, 12031, 12032, 12034, 12035, 12037, 12041, 12042, 12051, 13120, 13121, 13131, 13132, 13151, 13152, 13160, 14020, 14040, 14060, 15120, 15220, 15240, 15760, 15851, 17000, 17110, 17111, 17311, 17313, 19020, 19101, 19110, 19112, 19120, 19125, 20200, 20205, 20220, 20225, 20240, 20520, 20525, 20670, 20680, 20693, 20694, 20912, 21011, 21012, 21013, 21014, 21029, 21030, 21031, 21040, 21046, 21048, 21315, 21320, 21325, 21330, 21335, 21336, 21337, 21356, 21550, 21552, 21554, 21555, 21556, 21557, 21920, 21930, 21931, 21932, 22900, 22901, 22902, 22903, 23030, 23071, 23075, 23140, 23150, 23415, 23450, 23460, 23465, 23515, 23550, 23615, 23630, 23655, 23665, 24000, 24006, 24065, 24066, 24071, 24073, 24075, 24076, 24101, 24105, 24110, 24120, 24130, 24147, 24200, 24201, 24305, 24340, 24341, 24342, 24343, 24345, 24346, 24357, 24358, 24359, 24366, 24505, 24516, 24530, 24538, 24545, 24546, 24575, 24579, 24586, 24605, 24620, 24635, 24655, 24665, 24666, 24685, 25000, 25071, 25073, 25075, 25076, 25085, 25107, 25109, 25111, 25112, 25118, 25120, 25130, 25210, 25215, 25240, 25260, 25270, 25280, 25290, 25295, 25310, 25320, 25350, 25360, 25390, 25447, 25505, 25515, 25545, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25628, 25645, 25652, 25825, 26011, 26020, 26055, 26070, 26080, 26105, 26110, 26111, 26113, 26115, 26121, 26123, 26145, 26160, 26180, 26200, 26210, 26236, 26320, 26340, 26350, 26356, 26357, 26370, 26410, 26418, 26426, 26432, 26433, 26440, 26445, 26480, 26500, 26516, 26520, 26525, 26530, 26540, 26541, 26542, 26608, 26615, 26650, 26665, 26676, 26725, 26727, 26735, 26746, 26756, 26765, 26785, 26841, 26850, 26860, 26862, 26951, 26952, 27006, 27043, 27045, 27047, 27048, 27062, 27310, 27323, 27324, 27327, 27328, 27329, 27335, 27337, 27339, 27340, 27345, 27347, 27424, 27605, 27606, 27612, 27613, 27614, 27618, 27620, 27625, 27626, 27632, 27634, 27638, 27640, 27650, 27652, 27654, 27659, 27675, 27676, 27680, 27685, 27687, 27690, 27691, 27695, 27696, 27698, 27705, 27720, 27752, 27762, 27766, 27769, 27781, 27784, 27786, 27788, 27792, 27810, 27814, 27818, 27822, 27823, 27840, 28002, 28005,

28008, 28010, 28011, 28022, 28035, 28039, 28041, 28043, 28045, 28047, 28060, 28062, 28080, 28086, 28090, 28092, 28100, 28103, 28104, 28110, 28112, 28113, 28116, 28118, 28119, 28120, 28122, 28124, 28126, 28160, 28190, 28192, 28200, 28208, 28230, 28232, 28234, 28238, 28250, 28270, 28272, 28285, 28288, 28289, 28291, 28292, 28295, 28296, 28297, 28298, 28299, 28300, 28304, 28306, 28308, 28310, 28313, 28315, 28322, 28415, 28445, 28465, 28475, 28476, 28485, 28505, 28515, 28525, 28555, 28585, 28615, 28645, 28666, 28715, 28725, 28740, 28750, 28755, 28810, 28820, 28825, 29834, 29835, 29837, 29838, 29844, 29846, 29848, 29900, 29901, 30000, 30020, 30100, 30110, 30115, 30117, 30118, 30130, 30140, 30220, 30310, 30520, 30580, 30630, 30801, 30802, 30901, 30903, 30930, 31020, 31030, 31032, 31200, 31205, 31525, 31238, 31526, 31528, 31529, 31530, 31535, 31536, 31540, 31541, 31545, 31570, 31571, 31574, 31575, 31576, 31578, 31591, 31611, 31622, 31623, 31624, 31625, 31628, 31652, 31820, 32408, 32555, 32557, 36010, 36215, 36246, 36556, 36569, 36571, 36581, 36582, 36589, 36590, 37607, 38221, 38222, 38500, 38505, 38510, 38520, 38525, 38740, 38760, 40490, 40510, 40520, 40525, 40530, 40808, 40810, 40812, 40814, 40816, 41010, 41100, 41105, 41108, 41110, 41112, 41113, 41116, 42100, 42104, 42106, 42330, 42335, 42405, 42408, 42410, 42415, 42420, 42425, 42440, 42450, 42500, 42650, 42800, 42804, 42808, 42810, 42821, 42826, 42831, 42870, 43191, 43195, 43197, 43211, 43212, 43213, 43214, 43215, 43216, 43217, 43220, 43226, 43227, 43229, 43231, 43232, 43233, 43240, 43241, 43243, 43244, 43245, 43246, 43247, 43248, 43249, 43250, 43251, 43253, 43254, 43260, 43261, 43266, 43270, 43450, 43453, 44340, 44360, 44361, 44364, 44369, 44376, 44377, 44380, 44381, 44382, 44385, 44386, 44388, 44389, 44391, 44392, 44394, 44408, 45100, 45171, 45172, 45190, 45305, 45330, 45331, 45332, 45333, 45334, 45335, 45337, 45338, 45340, 45341, 45342, 45346, 45347, 45349, 45350, 45378, 45379, 45380, 45381, 45382, 45384, 45385, 45386, 45388, 45389, 45390, 45391, 45392, 45393, 45398, 45505, 45541, 45560, 45905, 45910, 45915, 45990, 46020, 46030, 46040, 46045, 46050, 46060, 46080, 46083, 46200, 46220, 46221, 46230, 46250, 46255, 46257, 46258, 46260, 46261, 46262, 46270, 46275, 46280, 46285, 46288, 46320, 46606, 46607, 46610, 46612, 46615, 46700, 46750, 46910, 46917, 46922, 46924, 46930, 46940, 46945, 46946, 47000, 49082, 49083, 49422, 49500, 49505, 49507, 49520, 49521, 49525, 49550, 49553, 49650, 49651, 49900, 50435, 50575, 50590, 50688, 51040, 51102, 51600, 51610, 51702, 51710, 51715, 51720, 51726, 51728, 51729, 52000, 52001, 52005, 52007, 52204, 52214, 52224, 52234, 52235, 52240, 52260, 52265, 52275, 52276, 52281, 52282, 52283, 52285, 52287, 52300, 52310, 52315, 52317, 52318, 52320, 52325, 52327, 52330, 52332, 52341, 52344, 52351, 52352, 52353, 52354, 52356, 52450, 52500, 52601, 52630, 52640, 53020, 53200, 53230, 53260, 53265, 53270, 53440, 53445, 53450, 53500, 53605, 53665, 54001, 54055, 54057, 54060, 54065, 54100, 54110, 54150, 54161, 54162, 54163, 54164, 54300, 54450, 54512, 54530, 54600, 54620, 54640, 54700, 54830, 54840, 54860, 55000, 55040, 55041, 55060, 55100, 55110, 55120, 55250, 55400, 55500, 55520, 55540, 55700, 56405, 56420, 56440, 56441, 56442, 56501, 56515, 56605, 56620, 56700, 56740, 56810, 56821, 57000, 57061, 57065, 57100, 57130, 57135, 57210, 57240, 57250, 57260, 57268, 57282, 57283, 57287, 57300, 57400, 57410, 57415, 57420, 57421, 57425, 57452, 57454, 57456, 57461, 57500, 57505, 57510, 57513, 57520, 57522, 57530, 57700, 57720,

57800, 58100, 58120, 58263, 58558, 58560, 58561, 58565, 58662, 58670, 58671, 58700, 58925, 59200, 62270, 63661, 63663, 64600, 64647, 64702, 64718, 64719, 64721, 64774, 64776, 64782, 64784, 64788, 64795, 64831, 64835, 65275, 65400, 65420, 65426, 65435, 65436, 65710, 65730, 65750, 65755, 65756, 65772, 65778, 65779, 65780, 65800, 65815, 65820, 65850, 65855, 65865, 65875, 65920, 66020, 66170, 66172, 66179, 66180, 66183, 66184, 66185, 66250, 66682, 66710, 66711, 66761, 66762, 66821, 66825, 66840, 66850, 66852, 66982, 66983, 66984, 66985, 66986, 66987, 66988, 67005, 67010, 67015, 67025, 67028, 67031, 67036, 67039, 67040, 67041, 67042, 67043, 67101, 67105, 67107, 67108, 67110, 67113, 67120, 67121, 67141, 67145, 67210, 67218, 67220, 67221, 67228, 67311, 67312, 67314, 67316, 67318, 67345, 67400, 67412, 67414, 67420, 67445, 67550, 67560, 67700, 67800, 67801, 67805, 67808, 67810, 67825, 67840, 67875, 67935, 67961, 67966, 67971, 67973, 67975, 68100, 68110, 68115, 68135, 68320, 68440, 68530, 68700, 68720, 68750, 68761, 68801, 68811, 68815, 69000, 69100, 69110, 69140, 69145, 69205, 69222, 69310, 69320, 69440, 69450, 69502, 69505, 69550, 69602, 69610, 69620, 69631, 69632, 69633, 69635, 69636, 69641, 69642, 69643, 69644, 69645, 69646, 69650, 69660, 69661, 69662, 69666, 69801, 69805, 69806, G0104, G0105, G0106, G0120, G0121, G0122

- **NOTE**: Pre-authorization is not required when procedures performed in an ambulatory surgery center, physician office, or emergency facility for urgent services or when the member is age 17 or younger
- If faxing a pre-authorization for these services, submit the Surgical Site of Care Additional Information Form (PDF) with the Medical Services (PDF) pre-authorization request form.

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

Transcatheter Heart Valve Procedures for Mitral or Tricuspid Valve Disorders excluding Transcatheter Edge-to-Edge Repair (TEER) (PDF)

- 0483T, 0484T

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.

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 Availity Essentials 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

Transplants and ventricular assist devices

Transplants - Cell

- 38205, 38206, 38232, 38240, 38241, 38242, 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.
- **Effective July 1, 2025: HCPCS codes A0431, A0436, S9961 will be reviewed post-service**

Clinical Edits by Code List
Complete List
Applies to Uniform Medical Plan (UMP)

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0001F	Heart Failure Composite	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0002M	ASH FibroSURE LapCorp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0002U	measure of subst in urine to predict polyps large intestine	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0003M	NASH FibroSURE LapCorp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0003U	Oncology ovarian 5 proteins ser alg scor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0005F	Osteoarthritis Composite	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0005U	Test detect genes assoc with prostate cancer in urine	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0006M	Oncology mRNA express tumor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0007M	Oncology PCR express tumor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0008U	Hpylori detection abx resistance, DNA	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0010U	Infectious disease strain type whole gen seq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0011M	Onc prstate cancer mrna 12 gen alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0011U	Rx monitoring LCMS/MS oral fluid	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0012F	Cap Bacterial Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0012M	ONC mRNA 5 gene risk urothelial carcinoma	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0013M	ONC mRNA gene recurrent urothelial carcinoma	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0014F	Comprehensive Preoperative Assessment Performed Fo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0014M	Liver ds alys 3 bmrk srm alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0015F	Melanoma Follow Up Completed (includes Assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0015M	Adrnl cortcl tum bchm asy 25	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0016M	Onc bladder mrna 209 gen alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0018M	Trnsplj Rnl Meas Cd154+Cll	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0019M	Cv Ds Plasma Alys Prtn Bmrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0019U	Oncology RNA tissue predictive algorithm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0021U	Oncology prostate detection 8 autoanitbodies	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0024U	Glyca nuc mr spectrsc quan	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0029U	Rx metab advrs trgt seq alys	HTCC Decision	Possible HTCC decision denial
0030U	Rx metab warf trgt seq alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0031U	Cyp1a2 gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0032U	Comt gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0033U	Htr2a htr2c genes	HTCC Decision	Possible HTCC decision denial
0036U	XOME TUM & NML SPEC SEQ ALYS	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0038U	Vitamin D serum microsample quan	Medical Necessity	Review for medical necessity
0041U	Borrelia burgdoferi antibody 5 protein IgM	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0042U	Borrelia burgdoferi antibody 12 protein IgG	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0050U	Targeted genomic sequence DNA 194 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0052U	Lipoprotein blood w/5 major classes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0054T	Bone Surgery Using Computer	HTCC Decision	Possible HTCC decision denial
0055T	Bone Surgery Using Computer	HTCC Decision	Possible HTCC decision denial
0055U	Cardiology heart transplant 96 DNA sequence	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0060U	Twin zygosity genomic seq analysis chromosome 2	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0061U	Transcutaneous meas bmrk SFDI M-S Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0062U	Autoimmue SLE IgG & IgM analysis 80 biomakers	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0063U	Neurology autism 32 amines algorithm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0068U	Candida species panel amplified probe	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0069U	Oncology colorectal microRNA miR-31-3p	HTCC Benefit Denial	Not a covered benefit per HTCC
0071T	U/s Leiomyomata Ablate <200	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0072T	U/s Leiomyomata Ablate >200	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0075T	Perq Stent/chest Vert Art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0076T	S&i Stent/chest Vert Art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0080U	Onc lung 5 clin rsk factr alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0082U	Rx test def 90+ RX/sbsts ur	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
0083U	Onc rspse chemo cntrst tomog	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0087U	Crd hrt trnspl mrna 1283 gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0088U	Trnsplj kdn algrft rej 1494	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0089U	Onc mlnma prame & linc00518	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0090U	Onc cutan mlnma mrna 23 gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0091U	Onc clrct scr whl bld alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0092U	Onc lng 3 prtn bmrk plsm alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0100T	Prosth Retina Receive&gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.

The presence of codes on this list does not necessarily indicate coverage under the member's benefit contract.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0101T	Extracorp Shockwv Tx,hi Enrg	HTCC Benefit Denial	Not a covered benefit per HTCC
0101U	Hered colon ca do 15 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0102T	Extracorp Shockwv Tx,anesth	HTCC Benefit Denial	Not a covered benefit per HTCC
0102U	Hered brst ca rltd do 17 gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0103U	Hered ova ca pnl 24 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0106T	Touch Quant Sensory Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0107T	Vibrate Quant Sensory Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0108T	Cool Quant Sensory Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0108U	Gi barrett esoph 9 prtn bmrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0109T	Heat Quant Sensory Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0110T	Nos Quant Sensory Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0113U	Onc prst8 pca3&tmprss2- erg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0115U	Respir iadna 18 viral&2 bact	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0116U	Rx mntr nzm ia 35+oral flu	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0117U	Pain mgmt 11 endogenous anal	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0118U	Trnsplj don-drv cll-fr dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0129U	Hered brst ca rltd do panel	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0130U	Hered colon ca do mrna pnl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0131U	Hered brst ca rltd do pnl 13	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0132U	Hered ova ca rltd do pnl 17	Investigational Denial	Always considered investigational; investigational services are denied member liability.

The presence of codes on this list does not necessarily indicate coverage under the member's benefit contract.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0133U	Hered prst8 ca rltd do 11	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0134U	Hered pan ca mrna pnl 18 gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0135U	Hered gyn ca mrna pnl 12 gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0153U	Onc breast mrna 101 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0163U	Onc clrct scr 3 prtn alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0164T	Remove Lumb Artif Disc Addl	HTCC Benefit Denial	Not a covered benefit per HTCC
0165T	Revise Lumb Artif Disc Addl	HTCC Benefit Denial	Not a covered benefit per HTCC
0166U	Liver ds 10 biochem asy srm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0170U	Neuro asd rna next gen seq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0171U	Trgt gen seq alys pnl dna 23	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0173U	Psyc gen alys panel 14 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0174T	Cad Cxr With Interp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0174U	Onc solid tumor 30 prtn trgt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0175T	Cad Cxr Remote	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0175U	Psyc gen alys panel 15 genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0179U	Onc nonsm cll lng ca alys 23	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0198T	Ocular Blood Flow Measure	Investigational Denial	Always considered investigational; investigational services are denied member liability.
01999	Unlisted Anesth Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
0200T	Percutaneous sacral augmentation unilateral injec.	HTCC Benefit Denial	Not a covered benefit per HTCC
0201T	Percutaneous sacral augmentation bilateral injec	HTCC Benefit Denial	Not a covered benefit per HTCC

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0202T	Post vertebral arthorplasty 1 lumbar	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0202U	Nfct ds 22 trgt sars-cov-2	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0205U	Oph amd alys 3 gene variants	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0206U	Neuro alzheimer cell aggregj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0207T	Clear eyelid gland w/heat	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0207U	Neuro alzheimer quan imaging	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0213T	Us facet jt inj cerv/t 1 lev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0214T	Us facet jt inj cerv/t 2 lev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0215T	Us facet jt inj cerv/t 3 lev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0216T	Us facet jt inj ls 1 level	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0216U	Neuro inh ataxia dna 12 com	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0217T	Us facet jt inj ls 2 level	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0217U	Neuro inh ataxia dna 51 gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0218T	Us facet jt inj ls 3 level	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0219T	Fuse spine facet jt cerv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0220T	Fuse spine facet jt thor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0221T	Fuse spine facet jt lumbar	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0222T	Fuse spine facet jt add seg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0223U	Infection disease (bacterial or viral respiratory tract infection)	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0225U	Nfct DS DNA & RNA 21 SARSCOV2	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0226U	Svnt SAR COV2 elisa plsm srm	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
0228U	Onc prst8 ma molec prfl alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0229U	Bcat1 promoter mthyltn alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0232T	Inj plasma IMG guide harvest and prep	HTCC Benefit Denial	Not a covered benefit per HTCC
0234T	Trluml prph athrc rnl art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0235T	Trluml prph athrc visc art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0236T	Trluml prph athrc abdl aorta	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0237T	Trluml prph athrc brchcphlc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0238T	Trluml prph athrc iliac art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0243U	Ob pe biochem assay pgf alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0247U	Ob prtrm brth ibp4 shbg meas	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0248U	Onc Brn Sphrd Cll 12 Rx Pnl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0249U	Onc Brst Alys 32 Phsprtn Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0252U	Ftl Aneuploidy Str Alys Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0254U	Reprdtve Med Alys 24 Chrmsm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0258U	Ai Psor Mrna 50-100 Gen Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0261U	Onc Clrct Ca Img Alys W/Ai	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0263T	IM B1 MRW cell therapy complete	HTCC Benefit Denial	Not a covered benefit per HTCC
0263U	Neuro Asd Meas 16 C Metblt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0264T	IM B1 MRW cell therapy excluding harvest	HTCC Benefit Denial	Not a covered benefit per HTCC

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Code	Description	Edit Type	Comment
0265T	IM B1 MRW cell therapy harvest only	HTCC Benefit Denial	Not a covered benefit per HTCC
0266T	Implantation/Rpl carotid sinus device total	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0267T	Implantation/Rpl carotid sinus device lead	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0268T	Implantation/Rpl carotid sinus device generator	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0269T	Revision/Remvl carotid sinus device total	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0269U	Hem Aut Dm Cgen Trmbctpna 14	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0270T	Revision/Remvl carotid sinus device lead	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0270U	Hem Cgen Coagj Do 20 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0271T	Revision/Remvl carotid sinus device generator	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0272T	Interrogation carotid sinsus device	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0272U	Hem Genetic Bld Do 51 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0273T	Interrogation carotid sinus w/programming	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0273U	Hem Gen Hyprfibrnlysis 8 Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0274T	Perq lamot/lam crv/thrc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0274U	Hem Gen Pltlt Do 43 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0275T	Percutaneous laminotomy/laminectomy lumbar	HTCC Benefit Denial	Not a covered benefit per HTCC
0276U	Hem Inh Thrombocytopenia 23	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0277U	Hem Gen Pltlt Funcj Do 31	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0278T	Tempr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0278U	Hem Gen Thrombosis 12 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0285U	Onc Rsps Radj Cll Fr Dna Tox	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0288U	Onc Lung Mrna Quan Pcr 11&3	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0289U	Neuro Alzheimer Mrna 24 Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0290U	Pain Mgmt Mrna Gen Xprsn 36	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0291U	Psyc Mood Do Mrna 144 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0292U	Psyc Strs Do Mrna 72 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0293U	Psyc Suicidal Idea Mrna 54	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0294U	Lngvty&Mrtlty Rsk Mrna 18Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0295U	Onc Brst Dux Carc 7 Proteins	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0296U	Onc Orl&/Orop Ca 20 Mlc Feat	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0297U	Onc Pan Tum Whl Gen Seq Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0298U	Onc Pan Tum Whl Trns Seq Rna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0300U	Onc Pan Tum Whl Gen Seq&Opt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0306U	Onc Mrd Nxt-Gnrj Alys 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0307U	Onc Mrd Nxt-Gnrj Alys Sbsq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0308U	Crd Cad Alys 3 Prtn Plsm Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0309U	Crd Cv Ds Aly 4 Prtn Plm Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0310U	Ped Vsclts Kd Alys 3 Bmrks	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0312U	Ai Ds Sle Alys 8 Igg Autoant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0313U	Onc Pncrs Dna&Mrna Seq 74	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0314U	Onc Cutan Mlnma Mrna 35 Gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0315U	Onc Cutan Sq Cll Ca Mrna 40	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0316U	U B Brgdrferi Lyme Ds Ospa Evl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0317U	Onc Lung Ca 4-Prb Fish Assay	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0319U	Neph Rna Pretrnspl Perph Bld	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0320U	Neph Rna Psttrnspl Perph Bld	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0321U	Iadna Gu Pthgn 20Bct&Fng Org	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0322U	Neuro Asd Meas 14 Acyl Carn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0323U	Iadna Cns Pthgn Next Gen Seq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0328U	Drug Assay 120+ Rx&Metablt	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
0329T	Mntr IO pressure 24 hrs/> unilateral/bilateral	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0329U	Onc Neo Xome&Trns Seq Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0330T	Tear film imaging unilateral/bilateral w/I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0331T	Heart symp imaging planar	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0332T	Heart symp imaging planar spect	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0332U	Onc Pan Tum Gen Prflg 8 Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0333U	Onc Lvr Surveilanc Hcc Cfdna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0335T	Extraosseous joint stablj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0338T	Transcath renal symp denerv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0338U	Onc Sld Tum Crcg Tum Cl Slct	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0339T	Transcath renal symp denerv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0339U	Onc Prst8 Mrna Hoxc6 & Dlx1	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0340U	Onc Pan Ca Alys Mrd Plasma	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0341U	Ftl Aneup Dna Seq Cmpr Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0342T	Thxp apheresis w/ hdl delip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0342U	Onc Pncrtc Ca Mult Ia Eclia	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0343U	Onc Prst8 Xom Aly 442 Sncrna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0344U	Hep Nafld Semiq Evl 28 Lipid	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0345U	Psyc Genom Alys Pnl 15 Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0347T	In bone device for RSA	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0347U	Rx Metab/Pcx Dna 16 Gen Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0348T	RSA spine exam	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0348U	Rx Metab/Pcx Dna 25 Gen Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0349T	RSA upper extremity exam	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0349U	Rx Metab/Pcx Dna 27Gen Rx Ia	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0350T	RSA lower extremity exam	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0350U	Rx Metab/Pcx Dna 27 Gen Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0351T	Intraoperative optical breast/node specimen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0351U	Nfct Ds Bct/Viral Trail Ip10	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0352T	Optical breast/node I&R per spec	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0353T	Intraoperative optical breast cavity	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0354T	Optical breast surgical cavity I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0356U	Onc Orop 17 Dna Ddpcr Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0358T	BIA whole body	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0358U	Neuro Alys B-Amyl 1-42&1-40	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0359U	Onc Prst8 Ca Alys All Psa	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0360U	Onc Lung Elisa 7 Autoant Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0361U	Neurflmnt Lt Chn Dig Ia Quan	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0362U	Onc Pap Thyr Ca Rna 82&10	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0363U	Onc Urthl Mrna 5 Gen Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0365U	Onc Bldr 10 Prb Bldr Ca	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0366U	Onc Bldr 10 Prb Recr Bldr Ca	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0367U	Onc Bldr 10 Flwg Trurl Rescj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0368U	Onc Clrct Ca Mut&Mthyltn Mrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0370U	Iadna Surg Wnd Pthgn 34&21	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0371U	Iadna Gu Pthgn Semiq Dna16&1	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0372U	Nfct Ds Gu Pthgn Arg Detcj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0373U	Iadna Rsp Tr Nfct 17 8 13&16	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0374U	Iadna Gu Pthgn 21 Org&21Arg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0375U	Onc Ovrn Bchm Asy 7 Prtn Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0376U	Onc Prst8 Ca Img Alys 128	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0377U	Cv Ds Quan Advsrm/Plsm Lprtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0378T	Visual field assmnt rev/rprt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0379T	Vis field assmnt tech suppt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0384U	Neph Ckd Rsk Hi Stg Kdn Ds	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0385U	Neph Ckd Alg Rsk Dbtc Kdn Ds	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0387U	Onc Mlnma Ambra1&Amlo	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0389U	Ped Fbrl Kd Ifi27&Mcemp1 Rna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0390U	Ob Pe Kdr Eng&Rbp4 Ia Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0392U	Rx Metab Genrx Ia 16 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0393U	Neu Prksn Msfl A-Syncln Prtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0395U	Onc Lng Multiomics Plsm Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0397T	Ercp w/optical endomicroscpy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0398U	Gi Baret Esph Dna Mthyln Aly	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0399U	Neuro Cere Folate Defncy Srm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0400U	Neuro Cere Folate Defncy Srm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0401U	Neuro Cere Folate Defncy Srm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0403U	Onc Prst8 Mrna 18 Gen Dre Ur	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0404U	Onc Brst Semiq Meas Thym Kn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0405U	Onc Pncrtc 59 Mthltn Blk Mrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0406U	Onc Lung Flow Cytmtry 5 Mrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0407U	Neph Dbtc Ckd Mult Eclia Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0408T	Insj/rplc cardiac modulj sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0409T	Insj/rplc cardiac modulj pls gn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0410T	Insj/rplc car modulj atr elt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0410U	Onc Pncrtc Dna Whl Gn Seq 5-	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0411T	Insj/rplc car modulj vnt elt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0411U	Psyc Genom Alys Pnl 15 Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0412T	Rmvl cardiac modulj pls gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0412U	Beta Amyloid Aβ42/40 Imprcip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0413T	Rmvl car modulj tranvns elt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0414T	Rmvl & rpl car modulj pls gn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0414U	Onc Lng Aug Alg Aly Whl Sld8	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0415T	Repos car modulj tranvns elt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0415U	Cv Ds Acs Bld Alg 5 Yr Score	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0416T	Reloc skin pocket pls gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0417T	Prgrmg eval cardiac modulj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0418T	Interro eval cardiac modulj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0418U	Onc Brst Aug Alg Aly Whl Sl8	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0419U	Nrpsyc Gen Seq Vrnt Aly 13	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0420U	Onc Urthl Mrna Xprsn 6 Snp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0421U	Onc Clrct Scr Sgl Amp 8 Rna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0422T	Tactile breast img uni/bi	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0422U	Onc Pan Solid Tum Alys Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0423U	Psyc Genomic Alys Pnl 26 Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0424U	Onc Prst8 Xom Alys 53 Sncrna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0429U	Hpv Orop Swab 14 Hirisk Typ	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0433U	Onc Prst8 5 Dna Reg Mrk Pcr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0434U	Rx Metab Advrs Vrnt Alys 25	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0435U	Onc Chemo Rx Cytox Csc 14 Rx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0436U	Onc Lng Plsm Alys 388 Prtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0437T	Implant synthetic reinforcement abdominal wall	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0437U	Psyc Anxiety Do Mrna 15 Bmrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0438U	Rx Metab Advrs Vrnt Alys 33	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0439U	Crd Chd Dna Alys 5 Snp 3 Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0440T	Ablation perc uxtr/peripheral nerve	HTCC Benefit Denial	Not a covered benefit per HTCC
0440U	Crd Chd Dna Alys 10 Snp 6Dna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0441T	Ablation perc lxtr/perphl nerve	HTCC Benefit Denial	Not a covered benefit per HTCC
0441U	Nfct Ds Bct Fngl/Viral Semiq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0442T	Ablation perc plex/trncl nerve	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0442U	Nfct Ds Respir Nfctj Mxa&Crp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0443T	R-T spectral analysis prostate tissue	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0443U	Neurflmnt Lt Chn Ultrsens Ia	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0444T	1st placement drug-eluting ocular insert	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0445T	Subsequent placement drug-eluting ocular insert	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0445U	Abeta42 & Ptau181 Eclia Csf	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0446T	Insj impltbl glucose sensor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0446U	Ai Ds Sle Alys 10 Cytokine	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0447T	Rmvl impltbl glucose sensor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0447U	Ai Ds Sle Alys 11 Cytokine	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0448T	Remvl insj impltbl gluc sens	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0449T	Insj aqueous drain dev 1st	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0449U	Car Scr Sev Inh Cond 5 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0450T	Insj aqueous drain dev each	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0450U	Onc Mm Lc-Ms/Ms Monoc P-Prtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0451U	Onc Mm Lc-Ms/Ms Pep Ion Quan	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0452U	Onc Bldr Mthyl Penk Lte-Qmsp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0453U	Onc Clrct Ca Cfdna Qpcr Asy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0458U	Onc Brst Ca S100 A8&A9 Elisa	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0459U	Abeta42 & Ttau Eclia Csf	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0460U	Onc Whl Bld/Bucc Rtpcr 24Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0461U	Onc Rxgenom Alys Rtpcr 24Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0461U	Onc Rxgenom Alys Rtpcr 24Gen	HTCC Benefit Denial	Not a covered benefit per HTCC
0462U	Melatonin Lvl Tst Slp Std7/9	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0464U	Onc Clrct Scr Qrtsa Dna Mrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0465U	Onc Urthl Carc Dna Qmsp 2Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0466U	Crd Cad Dna Gwas 564856 Snp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0467U	Onc Bldr Dna Ngs 60Gen&Aneup	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0468U	Hep Nash Mir34A5P A2M Ykl40	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0470U	Onc Orop Detcj Mrd 8 Dna Hpv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0472T	Progamming IO retinal +B6+B7	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0473T	Reprogamming IO retinal ELTRD RA	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0474U	Hered Pan Ca Gsap 88Gene Ngs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0475U	Hered Prst8 Ca Gsap 23 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0476U	Rx Metab Psyc 14Gen&Cyp2D6	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0476U	Rx Metab Psyc 14Gen&Cyp2D6	HTCC Benefit Denial	Not a covered benefit per HTCC
0477U	Rx Metab Psy 14&Cyp2D6 Gn-Rx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0477U	Rx Metab Psy 14&Cyp2D6 Gn-Rx	HTCC Benefit Denial	Not a covered benefit per HTCC
0479U	Tau Phosphorylated Ptau217	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0480U	Nfct Ds Csf Metag Ngs Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0481T	Njx autol wbc concentrate	HTCC Benefit Denial	Not a covered benefit per HTCC
0482U	Ob Pe Biochem Asy Sflt1&Plgf	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0485T	Oct mid ear i&r unilateral	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0486T	Oct mid ear i&r bilateral	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0486U	Onc Pan Sol Tum Ngs Cfctdna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0488U	U Ob Fetal Ag Nipt Cfdna Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0489T	Regn cell tx scldr hands	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0490T	Regn cell tx scldr h mlt inj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0490U	Onc Cutan/Uveal Mlnma Cd146	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0491U	Onc Sol Tum Ctc Slct Er Prtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0492U	Onc Sol Tum Ctc Slctn Pd-L1	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0493U	Trnspl Med Quan Dd-Cfdna Ngs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0494U	Rbc Ag Ftl Rhd Gene Alys Ngs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0495U	Onc Prst8 Alys Crcg Plsm Prt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0496U	Onc Clrct Cfdna 8/7 Genes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0500F	Initial Prenatal Care Visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0501F	Prenatal Flow Sheet	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0501U	Onc Clrc Bld Quan Meas Cfdna	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0502F	Subsequent Prenatal Care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0503F	Postpartum Care Visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0503U	Neuro Alz Ds Bamyl&Tau Prtn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0504U	Nfct Ds Uti Id 17 Path Orgs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0505F	Hemodialysis Plan Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0505T	Endovenous femoral arterial revsc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0506U	Gi Barretts Esophgl Cell 89	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0507F	Periton Dialysis Plan Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0507T	Near-infrared dual imaging meibomian glands I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0507U	Onc Ovr Dna Whole Gen W/5Hmc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0508U	Trnsplj Med Ddcfdna 40 Snps	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0509F	Urin Incon Plan Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0509U	Trnsplj Med Ddcfdna<12 Snps	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0510T	Rmvl sinus tarsi implant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0510U	Onc Pncrtc Ca Alg Alys 16Gen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0511T	Rmvl&rinsj sinus tarsi implt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0511U	Onc Sol Tum 3Dmicroenvir 36+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0512T	Esw integ wnd hlg 1st wnd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0512U	Onc Prst8 Alys Dgtz Img Msi	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0513F	Elevated Blood Pressure Plan Of Care Documented (c	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0513T	Esw integ wnd hlg ea addl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0513U	Onc Prst8 Alg Alys Msi&Hrd	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0514F	Plan Of Care For Elevated Hemoglobin Level Documen	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0515T	Insj wcs lv compl sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0516F	Anemia Plan Of Care Documented (esrd)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0516T	Insj wcs lv eltrd only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0516U	Rx Metab Rxgenomic Gnotyp 40	HTCC Benefit Denial	Not a covered benefit per HTCC
0517F	Glaucoma Plan Of Care Documented (ec)5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0517T	Insj wcs lv pg compnt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0518F	Falls Plan Of Care Documented (ger)5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0518T	Rmvl pg compnt wcs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0519F	Planned Chemotherapy Regimen, Including At A Minim	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0519T	Rmvl & rplcmt pg compnt wcs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0520F	Normal Tissue Dose Constraints Established Within	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0520T	Rmvl&rplcmt pg wcs new eltrd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0521F	Plan Of Care To Address Pain Documented (onc)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0521T	Interrog dev eval wcs ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0522T	Prgrmg dev eval wcs ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0524U	OB PE SFLT-1/PLGF IA SRM/PLS	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0525F	Initial Visit For Episode (bkp)2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0525T	Insj/rplcmt compl iims	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0525U	ONC SPHRD CELL CUL 11-RX PNL	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0526F	Subsequent Visit For Episode (bkp)2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0526T	Insj/rplcmt iims eltrd only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0526U	NEFRO RNL TRNSPL QUAN CXCL10	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0527T	Insj/rplcmt iims implt mntr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0528F	Rcmnd Flw-up 10 Yrs Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0528T	Prgrmg dev eval iims ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0528U	LRT IAD 18BCT/8VIR&7ARG RNA	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0529F	Intrvl 3+yrs Pts Clnscp Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0529T	Interrog dev eval iims ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0529U	HEM VTE SNP F2&F5 GEN LEIDEN	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0530T	Removal complete iims	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0531T	Removal iims electrode only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0532T	Removal iims implt mntr only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0533U	Rx Metab Advrs Gnotype 16Gens	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0534U	Onc Prst8 Mirna Snp 32 Vrnt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0535F	Dyspnea Mngmnt Plan Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0536U	Rbcag Ftl Rhd Pcr Alys Exon4	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0537U	Onc Clrct Ca Cfdna >2500 Dmr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0540F	Gluco Mngmnt Plan Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0540U	Trnsplj Med Quan Dd-Cfdna	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0541T	Myocardial imaging mcg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0541U	Cv Ds Hdl Rct Cec Lc-Ms/Ms 5	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0542T	Myocardial imaging mcg i&r	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0542U	Nefro Renal Trnspl Ur Nmr 84	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0543T	Ta mv rpr w/artif chord tend	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0544T	Tcat mv annulus rcnstj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0544U	Nefro Trnsp Mntr 48Vrnt Dpcr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0545F	Follow up care plan mdd docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0545T	Tcat tv annulus rcnstj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0547T	B1 matrl qual tst mcrind tib	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0549U	Onc Urthl Dna Mthyltd Rt Pcr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0550F	Cytopathology report non-gyn specimen	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0550U	Onc Prst8 Elisa Tot&Free Psa	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0551F	Cytopathology report non-routine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0551U	Tp Ptau217 Ult Dgt Prtn Detj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0554T	B1 str & fx rsk analysis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0555F	Symptom mgmnt plan care docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0555T	B1 str&fx rsk transmis data	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0556F	Plan care lipid control docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0556T	B1 str & fx rsk assessment	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0557F	Plan caremng angnl symptdocd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0557T	B1 str & fx rsk i&r	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0558T	Ct scan f/biomchn ct alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0559T	Antmc mdl 3d print 1st cmpnt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0560T	Antmc mdl 3d print ea addl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0561T	Antmc guide 3d print 1st gd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0562T	Antmc guide 3d print ea addl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0563T	Evac meibomian glnd heat bi	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0565T	Autol cell implt adps hrvg	HTCC Benefit Denial	Not a covered benefit per HTCC
0566T	Autol cell implt adps njx	HTCC Benefit Denial	Not a covered benefit per HTCC
0569T	Ttvr perq appr 1st prosth	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0570T	Ttvr perq ea addl prosth	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0571T	Insj/rplcmt icds ss eltrd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0572T	Insertion ss dfb electrode	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0573T	Removal ss dfb electrode	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0574T	Repos prev ss impl dfb eltrd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0575F	Hiv Rna Plan Care Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0575T	Prgrmg dev eval icds ss ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0576T	Interrog dev eval icds ss ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0577T	Ephys eval icds ss	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0578T	Rem interrog dev icds phys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0579T	Rem interrog dev icds tech	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0580F	Multidisciplinary care plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0580T	Rmvl ss impl dfb pg only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0581F	Pt transferred from anesth to cc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0581T	Abltj mal brst tum perq crtx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0582F	Not transferred from anesth to cc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0582T	Trurl abltj mal prst8 tiss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0583F	Transfer care checklist used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0584F	No transfer care checkelist used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
0600T	Ire abltj 1+tum organ perq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0601T	Ire abltj 1+tumors open	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0602T	Transdermal GFR measurements	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0603T	Transdermal GFR monitoring	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0604T	Rem OCT rta dev setup & educaj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0605T	Rem OCT rta techl sprt min 8	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0606T	Rem OCT rta phys/qhp ea 30d	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0607T	Rem mntr pulm flu mntr setup	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0608T	Rem mntr pulm flu mntr alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0609T	Mrs disc pain acquisj data	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0610T	Mrs disc pain transmis data	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0611T	Mrs disc pain alg alys data	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0612T	Mrs discogenic pain I & R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0613T	Perq tcat intratrl septl sht	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0614T	Rmvl & rplcmt ss impl dfb pg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0615T	Eye mvmt alys w/o calbrj I & R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0619T	Cysto w/prst commissurotomy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0620T	Evasc ven artlz tibl/prnl vn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0621T	Trabeculostomy interno laser	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0622T	Trabeculostomy int lsr w/scp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0623T	Auto quantification c plaque	HTCC Benefit Denial	Not a covered benefit per HTCC
0624T	Auto quan c plaq data prep	HTCC Benefit Denial	Not a covered benefit per HTCC
0625T	Auto quan c plaq cptr alys	HTCC Benefit Denial	Not a covered benefit per HTCC
0626T	Auto quan c plaq i&r	HTCC Benefit Denial	Not a covered benefit per HTCC
0627T	Perq njx algc fluor lmbr 1st	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0628T	Perq njx algc fluor lmbr ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0629T	Perq njx algc ct lmbr 1st	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0630T	Perq njx algc ct lmbr ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0631T	Tc vis lit hyperspectral img	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0632T	Perq tcat us abltj nrv p-art	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0633T	Ct breast w/3d uni c-	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0634T	Ct breast w/3d uni c+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0635T	Ct breast w/3d uni c-/c+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0636T	Ct breast w/3d bi c-	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0637T	Ct breast w/3d bi c+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0638T	Ct breast w/3d bi c-/c+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0639T	Wrls skn snr anisotropy meas	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0640T	Ncntc Nr Ifr Spctrsc Wnd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0643T	Tcat L Ventr Rstrj Dev Implt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0645T	Tcat Impltj C Sins Rdctj Dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0646T	Ttvi/Rplcmt W/Prstc Vlv Perq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0647T	Insj Gtube Perq Mag Gastrpxy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0655T	Tprnl Focal Abltj Mal Prst8	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0656T	Vrt Bdy Tethering Ant <7 Seg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0657T	Vrt Bdy Tethering Ant 8+ Seg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0658T	Elec Impd Spectrsc 1+Skn Les	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0659T	Tcat Intra-C Nfs Supersat O2	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0660T	Implt Ant Sgm Io Nbio Rx Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0661T	Rmvl&Rimpltj Ant Sgm Implt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0664T	Don Hysterectomy Open Cdvr	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0665T	Don Hysterectomy Open Liv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0666T	Don Hysterectomy Laps Liv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0667T	Don Hysterectomy Rcp Uter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0668T	Bkbench Prep Don Uter Algrft	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0669T	Bkbench Rcnstj Don Uter Ven	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0670T	Bkbench Rcnstj Don Uter Artl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0672T	Ndovag Cryg Rf Remdl Tiss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0674T	Laps Insj Nw/Rpcmt Prm Isdss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0675T	Laps Insj Nw/Rpcmt Isdss 1Ld	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0676T	Laps Insj Nw/Rpcmt Isdss Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0677T	Laps Repos Lead Isdss 1St Ld	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0678T	Laps Repos Lead Isdss Ea Add	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0679T	Laps Rmvl Lead Isdss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0680T	Insj/Rplcmt Pg Only Isdss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0681T	Rlcj Pulse Gen Only Isdss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0682T	Removal Pulse Gen Only Isdss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0683T	Prgrmg Dev Eval Isdss Ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0684T	Peri-Px Dev Eval Isdss Ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0685T	Interrog Dev Eval Isdss Ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0686T	Histotripsy Mal Hepatcel Tis	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0687T	Tx Amblyopia Dev Setup 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0688T	Tx Amblyopia Assmt W/Report	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0691T	Auto Alys Xst Ct Std Vrt Fx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0697T	Quan Mr Tis Wo Mri Mlt Orgn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0698T	Quan Mr Tiss W/Mri Mlt Orgn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0700T	Molec Fluor Img Sus Nev 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0701T	Molec Fluor Img Sus Nev Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0704T	Rem Tx Amblyopia Setup&Edu	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0705T	Rem Tx Amblyopia Tech Sprt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0706T	Rem Tx Amblyopia I&R Phy/Qhp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0710T	N-Invas Artl Plaq Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0711T	N-Nvs Artl Plaq Alys Dat Prp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0712T	N-Nvs Artl Plaq Alys Quan	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0713T	N-Nvs Artl Plaq Alys Rvw I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0714T	Tprnl Lsr Ablt B9 Prst8 Hypr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0716T	Car Acous Wavfrm Rec Cad Rsk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0717T	Adrc Ther Prtl Rc Tear	HTCC Benefit Denial	Not a covered benefit per HTCC
0718T	Adrc Ther Prtl Rc Tear Njx	HTCC Benefit Denial	Not a covered benefit per HTCC
0719T	Pst Vrt Jt Rplcmt Lmbr 1 Sgm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0723T	Qmrcp W/O Dx Mri Sm Anat Ses	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0724T	Qmrcp W/Dx Mri Same Anatomy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0725T	Vestibular Dev Impltj Uni	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0726T	Rmvl Implt Vstibular Dev Uni	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0727T	Rmvl&Rplcmt Implt Vstblr Dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0728T	Dx Alys Vstblr Implt Uni 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0729T	Dx Alys Vstblr Implt Uni Sbq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0730T	Trabeculotomy Lsr W/Oct Gdn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0731T	Augmnt Ai-Based Fcl Phnt A/R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0732T	Immntx Admn Electroporatn Im	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0737T	Xenograft Impltj Artclr Surf	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0738T	Tx Pln Mag Fld Abltj Prst8	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0739T	Abltj Mal Prst8 Mag Fld Ndct	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0743T	B1 Str & Fx Rsk Vrt Fx Assmt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0744T	Insj Bioprostc Vlv Fem Vn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0745T	Car Ablt Rad Arr N-Invas Loc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0746T	Car Ablt Rad Arr Cnv Loc Map	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0747T	Car Ablt Rad Arrhyt Dlvr Rad	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0748T	Njx Stm Cl Prdct Anl Sft Tis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0749T	B1 Str&Fx Rsk Assmt Dxr-Bmd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0750T	B1 Str&Fx Rsk Asmt Dxrbmd1Vw	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0764T	Asstv Alg Ecg Rsk Asmt Cncrt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0765T	Asstv Alg Ecg Rsk Asmt Prev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0766T	Tc Mag Stimj Pn 1St Tx 1Nrv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0767T	Tc Mag Stimj Pn 1St Tx Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0770T	Vr Technology Assist Therapy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0771T	Vr Px Dissoc Svc Sm Phy 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0772T	Vr Px Dissoc Svc Sm Phy Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0773T	Vr Px Dissoc Svc Oth Phy 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0774T	Vr Px Dissoc Svc Oth Phy Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0776T	Ther Indctj Ntrabrn Hypthrm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0779T	Gi Myoelectrical Actv Study	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0780T	Instlj Fecal Microbiota Ssp	HTCC Decision	Possible HTCC decision denial
0781T	Brnchsc Rf Dstrj Pulm Nrv Bi	HTCC Benefit Denial	Not a covered benefit per HTCC
0782T	Brnchsc Rf Dstrj Plm Nrv Uni	HTCC Benefit Denial	Not a covered benefit per HTCC
0783T	Tc Auriculr Neurostimulation	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0790T	Revj Rplcmt/Rmvl Vrt Tethrg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0793T	Prq Tcat Thrm Ablt Nrv P-Art	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0795T	Tcat Ins 2Chmbr Ldls Pm Cmpl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0796T	Tcat Ins 2Chmbr Ldls Pm Ra	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0797T	Tcat Ins 2Chmbr Ldls Pm Rv	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0801T	Tcat Rmv&Rpl 2Chmbr Ldls Pm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0802T	Tcat Rmv&Rpl2Chmb Ldls Pm Ra	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0803T	Tcat Rmv&Rpl2Chmb Ldls Pm Rv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0804T	Prgrmg Evl Ldls Pm 2Chmbr Ip	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0805T	Tcat S&Ivc Prstc Vl Impl Prq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0806T	Tcat S&Ivc Prstc Vl Impl Opn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0807T	Pulm Tiss Vntj Alys Prev Ct	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0808T	Pulm Tiss Vntj Alys W/Ct	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0810T	Subrta Njx Rx Agt W/Vtrc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0811T	Rem Mlt Day Uroflow Setup	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0812T	Rem Mlt Day Uroflow Dev Sply	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0813T	Egd Vol Adjmt Bariatric Balo	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0814T	Prq Njx Biod Osteo Matrl Fem	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0816T	Opn Insj/Rplcmt Ins Ptn Subq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0817T	Opn Insj/Rplcmt Ins Ptn Subf	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0818T	Revj/Rmvl Ins Ptn Subq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0819T	Revj/Rmvl Ins Ptn Subf	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0857T	Opto-Acoustic Img Breast Uni	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0859T	Ncntc Ifr Spctrsc O/T Pad Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0860T	Ncntc Ifr Spctrsc Scr Pad	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0861T	Rmvl Pg Wcs Lv Both Compnt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0862T	Rlcj Pg Wcs Lv Battery Only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0863T	Rlcj Pg Wcs Lv Trnsmtr Only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0864T	Low Ntsty Eswt Corpus Cvrnsm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0865T	Quan Mri Alys Brn W/O Dx Mri	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0866T	Quan Mri Alys Brn W/Dx Mri	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0867T	Tpla B9 Prst8 Hyprplsa>=50Ml	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0868T	Hi-Res Gastric Ep Mapping	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0870T	Imp Subq Prtl Ascts Pmp Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0871T	Rplcmt Subq Prtl Ascites Pmp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0872T	Rplcmt Ndwllg Bldr&Prtl Cath	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0873T	Revj Subq Prtl Asct Pmp Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0875T	Prgrm Subq Prtl Asct Pmp Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0876T	Duplex Scan Hemo Fstl Lmtd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0877T	Augmnt Alys Ch Ct Ild W/O Ct	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0878T	Augmnt Alys Ch Ct Ild W/Ct	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0879T	Augmnt Alys Ch Ct Ild Prep	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0880T	Augmnt Alys Ch Ct Ild I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0881T	Cryotherapy Oral Cavity	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0882T	Intraop Ther Estim Pn Ue 1St	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0883T	Intraop Ther Estim Pn Ue Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0884T	Esphgsc Flx 1St Tndsc Dilat	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0885T	Colsc Flx 1St Tndsc Dilat	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0886T	Sgmdsc Flx 1St Tndsc Dilat	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0888T	Histotripsy Mal Renal Tissue	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0893T	N-Invas Assmt Bld Oxygnation	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0897T	N-Invas Augmnt Arrhyt Alys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0898T	N-Invas Prst8 Cancer Est Map	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0901T	PLMT BONE MARROW SMPLG PORT	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0902T	QTC NTRVL AUGMNT ALG ALY ECG	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0903T	ECG ALG 12 LEAD REDUCED I&R	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0904T	ECG ALG 12 LD RDCD TRCG ONLY	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0905T	ECG ALG 12 LD RDCD TRCG ONLY	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0906T	COMS THER 1ST APPL<=50 SQ CM	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0907T	COMS THER EA ADDL<=50 SQ CM	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0915T	INSJ PERM CCM-D SYS PG&ELTRD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0916T	INSJ PERM CCM-D SYS PG ONLY	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0917T	INSJ PERM CCM-D SYS 1 LEAD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0918T	INSJ PERM CCM-D SYS DUAL LD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0919T	RMVL PERM CCM-D SYS PG ONLY	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
0920T	RMVL PERM CCM-D SYS 1 PAC LD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0921T	RMVL PERM CCM-D SYS 1 DFB LD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0922T	RMVL PERM CCM-D SYS DUAL LD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0923T	RMVL&RPLCMT PERM CCM-D PG	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0924T	RPOS PRV CCM-D TRNSVNS ELTRD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0925T	RLCJ SKIN POCKET CCM-D PG	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0926T	PRGRMG DEV EVAL CCM-D IP	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0927T	INTERROG DEV EVAL CCM-D IP	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0928T	REM INTERROG DEV CCM-D PHYS	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0929T	REM INTERROG DEV CCM-D TECH	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0930T	EPHYS EVAL CCM-D LD 1ST IMPL	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0931T	EPHYS EVAL CCM-D LD SEPARATE	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0932T	N-INVS DET HRT FAIL AUG ECHO	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0933T	TCAT IMPL WRLS L ATR PRS SNR	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0934T	REM MNTR WRLS L ATR PRS SNR	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0935T	CYSTO W/RNL PEL SYMP DNRVTJ	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0936T	PHOTOBIOMODULATION THER RTA	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0937T	XTRNL ECG REC>15D<30D	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0938T	XTRNL ECG REC>15D<30D REC	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0939T	XTRNL ECG REC>15D<30D SCAN	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
0940T	XTRNL ECG REC>15D<30D R&I	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0941T	CYSTO FLX INS&XPNS URTL SCAF	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0942T	CYSTO FLX RMV&RPLC URTL SCAF	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0943T	CYSTO FLX RMVL URTL SCAFFOLD	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0944T	3D CNTR SIMULA TRGT LVR LES	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0946T	ORTHO IMPL MVMT ALYS PAIR CT	Investigational Denial	Always considered investigational; investigational services are denied member liability.
0947T	MRGFUS STRTCTC BL-BR DISRPJ	Investigational Denial	Always considered investigational; investigational services are denied member liability.
1000F	Tobacco Use, Smoking, Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1002F	Assess Anginal Symptom/level	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1003F	Level Of Activity Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1004F	Clin Symp Vol Ovrld Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1005F	Asthma Symptoms Evaluate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1006F	Osteoarthritis Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1007F	Anti-inflm/anlgsc Otc Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1008F	Gi/renal Risk Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1010F	Severity angina by actvty	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1011F	Angina present	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1012F	Angina absent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1015F	Copd Symptoms Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1018F	Assess Dyspnea Not Present	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
1019F	Assess Dyspnea Present	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1022F	Pneumo Imm Status Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1026F	Co-morbid Condition Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1030F	Influenza Imm Status Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1031F	Smoking & 2nd hand assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1032F	Smoker/exposed 2nd hnd smoke	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1033F	Tobacco nonsmoker nor 2ndhnd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1034F	Current Tobacco Smoker	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1035F	Smokeless Tobacco User	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1036F	Tobacco Non-user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1038F	Persistent Asthma	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1039F	Intermittent Asthma	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1040F	Dsm-ivtm Info Mdd Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1050F	History Of Mole Changes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1052F	Type location activityassess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1055F	Visual Funct Status Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1060F	Doc Per/cont/parox Atr.fib	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1061F	Doc Lack Perm+cont+parox Fib	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1065F	Ischm Stroke Symp <3 Hrs B/4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1066F	Ischm Stroke Symp >3 Hrs B/4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
1070F	Alarm Symp Assessed-absent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1071F	Alarm Symp Assessed-1 + Prsnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1090F	Pres/absn Urin Incon Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1091F	Urine Incon Characterized	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1100F	Pt Falls Assess-doc'd>2+/yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1101F	Pt Falls Assessed-doc'd<1/yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1110F	Pt Lft Inpt Fac W/in 60 Days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1111F	Dschrg Med/current Med Merge	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1116F	Auric/peri Pain Assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1118F	Gerd Symptoms Assessed After 12 Months Of Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1119F	Initial Evaluation For Condition (hep C)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1121F	Subsequent Evaluation For Condition (hep C)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1123F	Advance Care Planning Discussed And Documented; Ad	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1124F	Advance Care Planning Discussed And Documented In	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1125F	Pain Severity Quantified; Pain Present (onc)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1126F	Pain Severity Quantified; No Pain Present (onc)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1127F	New episode for condtion	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1128F	Subsequent episode for condtion	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1130F	Back Pain And Function Assessed, Including All Of	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1134F	Episode Of Back Pain Lasting Six Weeks Or Less (bk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
1135F	Episode Of Back Pain Lasting Longer Than Six Weeks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1136F	Episode Of Back Pain Lasting 12 Weeks Or Less (bkp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1137F	Episode Of Back Pain Lasting Longer Than 12 Weeks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1150F	Doc Pt Rsk Death W/in 1yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1151F	Doc No Pt Rsk Death W/in 1yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1152F	Doc Advncd Dis Comfort 1st	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1153F	Doc Advncd Dis Cmfrt Not 1st	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1157F	Advnc Care Plan In Rcrd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1158F	Advnc Care Plan Tlk Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1159F	Med List Docd In Rcrd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1160F	Rvw Meds By Rx/dr In Rcrd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1170F	Fxnl Status Assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1175F	Function stat assessed rvwd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1180F	Thromboemb Risk Assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1181F	Neuropsychia sympts assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1182F	Neuropsychi sympt 1+present	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1183F	Neuropsychiatric symp absent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1200F	Seizure type(s)+ frq docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1205F	Epi etiol synd rvwd and docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1220F	Patient Screened For Depression	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
1400F	Parkinson's Disease diagnosis reviewed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1450F	Symptoms improved/consist	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1451F	Sympt show clin import drop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1460F	Qual card diag prior 12 mons	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1461F	No qual card diag prior12mon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1490F	Dem severity classified mild	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1491F	Dem severity classified mod	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1493F	Dem severity class severe	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1494F	Cognit assessed and reviewed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1500F	Symptom and sign symm polyneuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
15011	Hrv skn cll ssp agrft 1st 25	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15012	Hrv skn cll ssp agrft ea add	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15013	Prepj skn cll ssp agrft 1st	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15014	Prepj skn cll ssp agrft ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15015	App skn cl ssp agrft t/a/l 1	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15016	App skn cl ssp agrf t/a/l ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15017	App skn cll ssp f/n/g/hf 1st	Investigational Denial	Always considered investigational; investigational services are denied member liability.
15018	App skn cll ssp f/n/g/hf ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
1501F	Not initial eval for condition	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1502F	Pt queried pain function with instrument	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
1503F	Pt queried symptoms resp insuff	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1504F	Pt has respiratory insufficiency	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
1505F	Pt has no respiratory insufficiency	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
15775	Hair Transplant Punch Grafts	Medical Necessity	Review for medical necessity
15776	Hair Transplant Punch Grafts	Medical Necessity	Review for medical necessity
15780	Abrasion Treatment Of Skin	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15781	Abrasion Treatment Of Skin	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15782	Abrasion Treatment Of Skin	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15783	Abrasion Treatment Of Skin	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15786	Abrasion, Lesion, Single	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15787	Abrasion, Lesions, Add-on	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15824	Removal Of Forehead Wrinkles	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15825	Removal Of Neck Wrinkles	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15826	Removal Of Brow Wrinkles	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15828	Removal Of Face Wrinkles	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15829	Removal Of Skin Wrinkles	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15832	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15833	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15834	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15835	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
15836	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15837	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15838	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15839	Excise Excessive Skin Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15847	Exc Skin Abd Add-on	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15876	Suction Assisted Lipectomy	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15877	Suction Assisted Lipectomy	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15878	Suction Assisted Lipectomy	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15879	Suction Assisted Lipectomy	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
15999	Removal Of Pressure Sore	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
17999	Skin Tissue Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
19105	Cryosurg Ablate Fa, Each	Investigational Denial	Always considered investigational; investigational services are denied member liability.
19300	Removal Of Breast Tissue	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
19499	Breast Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
2000F	Blood Pressure Measure	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2001F	Weight Record	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2002F	Clin Sign Vol Ovrld Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2004F	Initial Exam Involved Joints	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2010F	Vital Signs Recorded	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2014F	Mental Status Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
2015F	Asthma impairment assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2016F	Asthma risk assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2018F	Hydration Status Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2019F	Dilated Macul Exam Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2020F	Dilated Fundus Eval Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2021F	Dilated Macul+exam Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2022F	Dil Retina Exam Interp Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2023F	Dilat rta xm w/o rtnopthy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2024F	7 Field Photo Interp Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2025F	7 fld rta photo w/o rtnopthy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2026F	Eye Image Valid To Dx Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2027F	Optic Nerve Head Eval Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2028F	Foot Exam Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2029F	Complete Phys Skin Exam Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2030F	H20 Stat Doc'd Normal	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2031F	H20 Stat Doc'd Dehydrated	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2035F	Tymp Memb/motion Exam'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2040F	Physical Examination On The Date Of The Initial Vi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2044F	Documentation Of Mental Health Assessment Prior To	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
2050F	Wound Char Size Etc Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
20552	Inj Trigger Point, 1/2 Muscl	HTCC Decision	Possible HTCC decision denial
20553	Inject Trigger Points, =/> 3	HTCC Decision	Possible HTCC decision denial
20560	Ndl insj w/o njx 1 or 2 musc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
20561	Ndl insj w/o njx 3+ musc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
2060F	Pt talk eval hlthwkr re mdd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
20930	Spinal Bone Allograft	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
20936	Spinal Bone Autograft	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
20983	Ablate bone tumor(s) perq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
20985	Cptr-asst Dir Ms Px	HTCC Decision	Possible HTCC decision denial
20999	Musculoskeletal Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
21089	Prepare Face/oral Prosthesis	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
21137	Reduction Of Forehead	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21138	Reduction Of Forehead	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21139	Reduction Of Forehead	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21270	Augmentation, Cheek Bone	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21280	Revision Of Eyelid	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21282	Revision Of Eyelid	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
21299	Cranio/maxillofacial Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
21499	Head Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
21899	Neck/chest Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
22510	Perq cervicothoracic inject	HTCC Benefit Denial	Not a covered benefit per HTCC
22511	Perq lumbosacral injection	HTCC Benefit Denial	Not a covered benefit per HTCC
22512	Vertebroplasty addl inject	HTCC Benefit Denial	Not a covered benefit per HTCC
22513	Perq vertebral augmentation	HTCC Benefit Denial	Not a covered benefit per HTCC
22514	Perq vertebral augmentation	HTCC Benefit Denial	Not a covered benefit per HTCC
22515	Perq vertebral augmentation	HTCC Benefit Denial	Not a covered benefit per HTCC
22526	Idet, Single Level	HTCC Benefit Denial	Not a covered benefit per HTCC
22527	Idet, 1 Or More Levels	HTCC Benefit Denial	Not a covered benefit per HTCC
22586	Prescrl fuse w/ instr L5/S1	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22836	Ant Thrc Vrt Body Tethrg <7	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22837	Ant Thrc Vrt Body Tethrg 8+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22838	Rev Rplc/Rmv Thrc Vrt Tethrg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22841	Insert Spine Fixation Device	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
22857	Lumbar Artif Diskectomy	HTCC Benefit Denial	Not a covered benefit per HTCC
22860	Tot Disc Arthrp 2Ntrspc Lmbr	HTCC Benefit Denial	Not a covered benefit per HTCC
22862	Revise Lumbar Artif Disc	HTCC Benefit Denial	Not a covered benefit per HTCC
22865	Remove Lumb Artif Disc	HTCC Benefit Denial	Not a covered benefit per HTCC
22867	Insj stablj dev w/dcmprn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22868	Insj stablj dev w/dcmprn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22869	Insj stablj dev w/o dcmprn	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
22870	Insj stablj dev w/o dcmprn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
22899	Spine Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
22999	Abdomen Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
23929	Shoulder Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
24999	Upper Arm/elbow Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
25999	Forearm Or Wrist Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
26989	Hand/finger Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
27299	Pelvis/hip Joint Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
27599	Leg Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
27899	Leg/ankle Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
28890	High Energy Eswt, Plantar F	HTCC Benefit Denial	Not a covered benefit per HTCC
28899	Foot/toes Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
29799	Casting/strapping Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
29874	Knee Arthroscopy/surgery	HTCC Benefit Denial	Not a covered benefit per HTCC
29877	Knee Arthroscopy/surgery	HTCC Benefit Denial	Not a covered benefit per HTCC
29999	Arthroscopy Of Joint	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3006F	Cxr Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3008F	Body mass index docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3011F	Lipid Panel Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3014F	Sceen Mammo Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3015F	Cerv cancer screen docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3016F	Pt Scrnd Unhlthy Oh Use	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3017F	Colorectal Ca Screen Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3018F	Pre-prxd Rsk Et Al Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3019F	Lvef assess planpost dschrge	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3020F	Lvf Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3021F	Lvef Mod/sever Depres Syst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3022F	Lvef >40% Systolic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3023F	Spirom Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3025F	Spirom Fev/fvc <70% W Copd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3027F	Spirom Fev/fvc >70% W/o Copd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3028F	O2 Saturation Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3035F	O2 Saturation <88% /pao<55%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3037F	O2 Saturation >88% /pao>55	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3038F	Pulm fx w/in 12 mon b/4 surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3040F	Fev <40% Predicted Value	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3042F	Fev >40% Predicted Value	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3044F	Hg A1c Level <7.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3045F	Hg A1c Level 7.0 - 9.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
30468	Rpr nsl vlv collapse w/implt	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
30469	Rpr Nsl Vlv Collapse W/Rmdlg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
3046F	Hemoglobin A1c Level > 9.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3048F	Ldl-c < 100 Mg/dl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3049F	Ldl-c 100-129 Mg/dl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3050F	Ldl-c = 130 Mg/dl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3051F	Hg a1c>equal 7.0%<8.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3052F	Hg a1c>equal 8.0%<equal 9.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3055F	Lvef less than/equal to 35%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3056F	Lvef greater than 35%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3060F	Pos Microalbuminuria Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3061F	Neg Microalbuminuria Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3062F	Pos Macroalbuminura Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3066F	Nephropathy Doc Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3072F	Low Risk For Retinopathy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3073F	Pre-surg Eye Measures Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3074F	Sust Bp < 130 Mmhg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3075F	Syst Bp >130 - 139 Mmhg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3077F	Syst Bp = 140 Mm Hg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3078F	Diast Bp < 80 Mm Hg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3079F	Diast Bp 80-89 Mm Hg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3080F	Diast Bp = 90 Mm Hg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3082F	Kt/v <1.2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3083F	Kt/v >= 1.2 And < 1.7	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3084F	Kt/v > 1.7	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3085F	Suicide Risk Assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3088F	Mdd Mild	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3089F	Mdd Moderate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3090F	Mdd Severe; W/o Psych	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3091F	Mdd Severe; W/psych	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3092F	Mdd In Remission	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3093F	Doc New Diag 1st/addl. Mdd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3095F	Central Dexa Results Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3096F	Central Dexa Ordered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
30999	Nasal Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3100F	Carot Blk Doc'd W/carot Ref	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3110F	Pres/absn Hmrhg/lesion Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3111F	Ct/mri Brain Done W/in 24 Hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3112F	Ct/mri Brain Done > 24 Hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3115F	Quant results activity +symp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3117F	Hf assessment tool completed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3118F	Ny heart assoc class docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3119F	No eval activity clin symp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3120F	12-lead Ecg Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
31242	Nsl/Sinus Ndsc Rf Abltj Pnn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
31243	Nsl/Sinus Ndsc Cryoabltj Pnn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
3126F	Esophageal biopsy report/dysplasia	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
31299	Sinus Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3130F	Upper Gi Endoscopy Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3132F	Doc Ref. Upper Gi Endoscopy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3140F	Forceps Esoph Biopsy Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3141F	Upper Gi Endo Shows Barrtt's	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3142F	Upper Gi Endo Not Barrtt's	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3150F	Forceps Esoph Biopsy Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3155F	Cytogen Test Marrow B/4 Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
31599	Larynx Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3160F	Doc Fe+ Stores B/4 Epo Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
31660	Bronch thermoplsty 1 lobe	HTCC Benefit Denial	Not a covered benefit per HTCC
31661	Bronch thermoplsty 2/> lobes	HTCC Benefit Denial	Not a covered benefit per HTCC
3170F	Flow Cyto Done B/4 Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
31830	Revise Windpipe Scar	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.

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Code	Description	Edit Type	Comment
31899	Airways Surgical Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3200F	Barium Swallow Test Not Req	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3210F	Grp A Strep Test Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3215F	Pt Immunity To Hep A Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3216F	Pt Immunity To Hep B Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3218F	Rna Testing For Hepatitis C Documented As Performe	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3220F	Hep C Quant Rna Tstng Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3230F	Note Hring Tst W/in 6 Mon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3250F	Noprim Loc Anat Bx Site Tumor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3260F	Pt Cat/pn Cat/hist Grd Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3265F	Ribonucleic Acid (rna) Testing For Hepatitis C Vir	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3266F	Hepatitis C Genotype Testing Documented As Perform	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3267F	Path report w/PT PN CAT ET AL	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3268F	Prostate-specific Antigen (psa), And Primary Tumor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3269F	Bone Scan Performed Prior To Initiation Of Treatme	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3270F	Bone Scan Not Performed Prior To Initiation Of Tre	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3271F	Low Risk Of Recurrence, Prostate Cancer (prca)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3272F	Intermediate Risk Of Recurrence, Prostate Cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3273F	High Risk Of Recurrence, Prostate Cancer (prca)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3274F	Prostate Cancer Risk Of Recurrence Not Determined	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3278F	Serum Levels Of Calcium, Phosphorus, Intact Parath	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3279F	Hemoglobin Level Greater Than Or Equal To 13 G/dl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3280F	Hemoglobin Level 11 G/dl To 12.9 G/dl (ckd, Esrd)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3281F	Hemoglobin Level Less Than 11 G/dl (ckd, Esrd)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3284F	Intraocular Pressure (iop) Reduced By A Value Of G	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3285F	Intraocular Pressure (iop) Reduced By A Value Less	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3288F	Falls Risk Assessment Documented (ger)5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3290F	Patient Is D (rh) Negative And Unsensitized (prena	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3291F	Patient Is D (rh) Positive Or Sensitized (prenatal	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3292F	Hiv Testing Ordered Or Documented And Reviewed Dur	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3293F	Abo rh blood typing docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3294F	Grp b strep screening docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
32999	Chest Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3300F	American Joint Committee On Cancer (ajcc) Stage Do	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3301F	Cancer Stage Documented In Medical Record As Metas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3315F	Estrogen Receptor (er) Or Progesterone Receptor (p	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3316F	Estrogen Receptor (er) And Progesterone Receptor (	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3317F	Pathology Report Confirming Malignancy Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3318F	Pathology Report Confirming Malignancy Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3319F	One Of The Following Diagnostic Imaging Studies Or	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
3320F	None Of The Following Diagnostic Imaging Studies O	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3321F	Ajcc Cncr O/ia Mela Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3322F	Melanoma >ajicc Stage 0 Or Ia	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3323F	Clin node stgng docdb/4 surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3324F	Mri ct scan ord rvwd rqstd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
33250	Ablate Heart Dysrhythm Focus	HTCC Decision	Possible HTCC decision denial
33251	Ablate Heart Dysrhythm Focus	HTCC Decision	Possible HTCC decision denial
3325F	Preoperative Assessment Of Functional Or Medical I	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
33276	Insj Phrnc Nrv Stim Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33277	Insj Phrnc Nrv Stim Transvns	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33278	Rmvl Phrnc Nrv Stim Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33279	Rmvl Phrnc Nrv Stim Transvns	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33280	Rmvl Phrnc Nrv Stim Pg Only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33281	Reposg Phrnc Nrv Stim Trnsvn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33287	Rmv&Rplcmt Phrnc Nrv Stim Pg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33288	Rmv&Rplcmt Phrnc Nrv Stim Ld	Investigational Denial	Always considered investigational; investigational services are denied member liability.
33289	Tcat impl wrls p-art prs snr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
3328F	Prfrmnc docd 2 wks b/4 surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3330F	Imaging Study Ordered (bkp)2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3331F	Imaging Study Not Ordered (bkp)2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3340F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3341F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3342F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3343F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3344F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3345F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3350F	Mammo Bx Proven Malig Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3351F	Neg Screen Dep Symp By Dep Tool	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3352F	No Sig Dep Symp By Dep Tool	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3353F	Mild-mod Dep Symp By Dep Tool	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
33548	Restore/remodel, Ventricle	Investigational Denial	Always considered investigational; investigational services are denied member liability.
3354F	Clin Sig Dep Symp By Dep Tool	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3370F	Ajcc Breast Cancer Stage 0 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3372F	Ajcc Breast Cancer Stage1 + Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3374F	Ajcc Brst Cancer Tumor Size >1cm To 2cm Stage 1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3376F	Ajcc Breast Cancer Stage 2 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3378F	AJCC Breast Cancer Stage III, documented (ONC)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3380F	Ajcc Breast Cancer Stage 4 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3382F	Ajcc Colon Cancer Stage 0 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3384F	Ajcc Colon Cancer Stage 1 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3386F	Ajcc Colon Cancer Stage 2 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3388F	Ajcc Colon Cancer Stage 3 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3390F	Ajcc Colon Cancer Stage 4 Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3394F	Quant HER2 IHC eval breast cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3395F	Quant HER2 IHC eval breast cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
33999	Cardiac Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3450F	Dyspnea Scrnd, No-mild Dysp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3451F	Dyspnea Scrnd Mod-high Dysp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3452F	Dyspnea Not Screened	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3455F	Tb Scrng Done-interpd 6mon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3470F	Ra Disease Activity, Low	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3471F	Ra Disease Activity, Mod	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3472F	Ra Disease Activity, High	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3475F	Disease Progn Ra Poor Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3476F	Disease Progn Ra Good Docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
34839	Plnning pt spec fenest graft	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
3490F	History - Aids-defining Cond	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3491F	Hiv Unsure Baby Of Hiv+moms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3492F	History Cd4+ Cell Count <350	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3493F	No Hist Cd4+cell Cnt<350	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3494F	Cd4+cell Count <200cells/mm3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3495F	Cd4+cell Cnt 200-499 Cells	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3496F	Cd4+ Cell Count =500 Cells	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3497F	Cd4+ Cell Percentage <15%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3498F	Cd4+ Cell Percentage =15%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3500F	Cd4 +cell Count% Documented As Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3502F	Hiv Rna Vrl Load <lmts Quantif	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3503F	Hiv Rna Vrl Load Below Limits Of Quantif	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3510F	Doc Tb Screening Results Interpreted	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3511F	Chlamydia And Gonorrhea Documented Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3512F	Syphilis Screening Documented As Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3513F	Hepatitis Screening Documented As Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3514F	Hepatitis C Screening Documented As Done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3515F	Patient Has Documented Immunity To Hep C	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3517F	Hbv assess&results intrp 1yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3520F	Cdifficile testing performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3550F	Low Risk Thromboembolism	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3551F	Intermediate Risk Thromboembolism	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3552F	High Risk For Thromboembolism	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3555F	Patient Inr Measurement Preformed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3570F	Report Scint X-ref With X-ray	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3572F	Patient Considered Poss Risk Fx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3573F	Patient Not Considered Poss Risk Fx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
36000	Place Needle In Vein	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
36299	Vessel Injection Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
36416	Capillary Blood Draw	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
36468	Injection(s), Spider Veins	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
36473	Endovenous mchnchem 1st vein	Investigational Denial	Always considered investigational; investigational services are denied member liability.
36474	Endovenous mchnchem add-on	Investigational Denial	Always considered investigational; investigational services are denied member liability.
3650F	EEG ordered rvwd reqstd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
36511	Apheresis Wbc	Medical Necessity	Review for medical necessity
3700F	Psychiatric disorder or disturbances assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3720F	Cognitive impairment or dysfunction assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3725F	Screen depression performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
37501	Vascular Endoscopy Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
3750F	Ptnotrcvngsteroid>/=10mg/day	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3751F	Electrodiag polyneuro 6 months	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3752F	No electrodiag polyneuro 6 months	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3753F	Pt has symp and signs neuropathy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3754F	Screeing tests dm done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
3755F	Cognitive and behav impairment scrng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3756F	Pt with pseudobulb affect ALS	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3757F	Pt with no pseudobulb affect ALS	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3758F	Pt referred pulmon fx test / peak flow	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3759F	Pt screened dysphag/wt loss/nutr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3760F	Pt w/ dysphag/wt loss/nutr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3761F	Pt w/o dysphag/wt loss/nutr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3762F	Patient is dysarthric	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3763F	Patient is not dysarthric	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3775F	Adenoma(s)/neoplasm detected during colonoscopy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
3776F	Adeonom(s)/neoplasm not detected in colonoscopy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
37799	Vascular Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
38129	Laparoscope Proc, Spleen	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
38204	Bl Donor Search Management	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
38225	Car-t hrv bld-drv t lymphcyt	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
38226	Car-t prep t lymphcyt f/trns	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
38227	Car-t receipt&prepj admn	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
38589	Laparoscope Proc, Lymphatic	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
38999	Blood/lymph System Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
39499	Chest Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
39599	Diaphragm Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4003F	Pt Ed Write/oral, Pts W/ Hf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4004F	Pt tobacco use done rcvd tlk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4005F	Pharm Thx For Op Rx'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4008F	Beta-blocker therapy rxd/tkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4010F	Ace/arb therapy rxd/taken	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4011F	Oral Antiplatelet Therapy Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4012F	Warfarin Therapy Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4013F	Statin therapy/currently tkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4014F	Written Discharge Instr Prvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4015F	Persist Asthma Medicine Ctrl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4016F	Anti-inflm/anlgsc Agent Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4017F	Gi Prophylaxis For Nsaid Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4018F	Therapy Exercise Joint Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4019F	Doc Recpt Counsl Vit/calc+	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4025F	Inhaled Bronchodilator Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4030F	Oxygen Therapy Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4033F	Pulmonary Rehab Rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4035F	Influenza Imm Rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4037F	Influenza Imm Order/admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
4040F	Pneumo Imm Order/admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4041F	Doc Order Cefazolin/cerfurox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4042F	Doc Antibio Not Given	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4043F	Doc Order Given Stop Antibio	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4044F	Doc Order Given Vte Prophylx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4045F	Empiric Antibiotic Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4046F	Doc Antibio Given B/4 Surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4047F	Doc Antibio Given B/4 Surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4048F	Doc Antibio Given B/4 Surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4049F	Doc Order Given Stop Antibio	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4050F	Ht Care Plan Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4051F	Referred For An Av Fistula	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4052F	Hemodialysis Via Av Fistula	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4053F	Hemodialysis Via Av Graft	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4054F	Hemodialysis Via Catheter	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4055F	Pt. Rcvng Perton Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4056F	Approp. Oral Rehyd Recomm'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4058F	Ped Gastro Ed Given Caregvr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4060F	Psych Svcs Provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4062F	Pt Referral Psych Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
4063F	Antidepres rxthxpy not rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4064F	Antidepressant Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4065F	Antipsychotic Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4066F	Ect Provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4067F	Pt Referral For Ect Doc'd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4069F	Vte prophylaxis rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4070F	Dvt Prophylx Recv'd Day 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4073F	Oral Antiplat Thx Rx Dischrg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4075F	Anticoag Thx Rx At Dischrg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4077F	Doc T-pa Adm Considered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
40799	Lip Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4079F	Doc Rehab Svcs Considered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4084F	Aspirin Recv'd W/in 24 Hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4086F	Aspirin/clopidogrel rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
40899	Mouth Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4090F	Pt Recvng Epo Thxpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4095F	Pt Not Rcvng Epo Thxpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4100F	Biphos Thxpy Vein Ord/rec'vd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4110F	Int Mam Art Used For Cabg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4115F	Beta Blckr Admin W/in 24 Hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
4120F	Antibiot Rx'd/given	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4124F	Antibiot Not Rx'd/given	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4130F	Topical Prep Rx, Aoe	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4131F	Syst Antimicrobial Thx Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4132F	No Syst Antimicrobial Thx Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4133F	Antihist/decong Rx/recom	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4134F	No Antihist/decong Rx/recom	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4135F	Systemic Corticosteroids	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4136F	Syst Corticosteroids Not Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4140F	Inhaled corticosteroids rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4142F	Corticoster sparng txmnt rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4144F	Alt long-term cntrl med rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4145F	2+ anti-hyprtnsv agents tkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4148F	Hep A Vaccine Injection Admin/recvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4149F	Hep B Vaccine Injection Admin/recvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4150F	Pt Recvng Antivir Txmnt Hepc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
41512	Tongue Base Suspension, Permanent Suture Technique	Investigational Denial	Always considered investigational; investigational services are denied member liability.
4151F	Pt Not Recvng Antiv Hep C	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
41530	Submucosal Ablation Of The Tongue Base, Radiofrequ	Investigational Denial	Always considered investigational; investigational services are denied member liability.
4153F	Combo Pegintf/rib Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
4155F	Hep A Vac Series Prev Recvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4157F	Hep B Vac Series Prev Recvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4158F	Pt Consld About Risk Of Alcoho	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
41599	Tongue And Mouth Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4159F	Contrcp Talk B/4 Antiv Txmnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4163F	Patient Counseling At A Minimum On All Of The Foll	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4164F	Adjuvant (ie, In Combination With External Beam Ra	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4165F	Three-dimensional Conformal Radiotherapy (3d-crt)	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4167F	Head Of Bed Elevation (30-45 Degrees) On First Ven	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4168F	Patient Receiving Care In The Intensive Care Unit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4169F	Patient Either Not Receiving Care In The Intensive	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4171F	Patient Receiving Erythropoiesis-stimulating Agent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4172F	Patient Not Receiving Erythropoiesis-stimulating A	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4174F	Counseling About The Potential Impact Of Glaucoma	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4175F	Best-corrected Visual Acuity Of 20/40 Or Better (d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4176F	Counseling About Value Of Protection From Uv Light	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4177F	Counseling About The Benefits And/or Risks Of The	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4178F	Anti-d Immune Globulin Received Between 26 And 30	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4179F	Tamoxifen Or Aromatase Inhibitor (ai) Prescribed (	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4180F	Adjuvant Chemotherapy Prescribed Or Previously Rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
4181F	Conformal Radiation Therapy Received (onc)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4182F	Conformal Radiation Therapy Not Received (onc)1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4185F	Continuous (12-months) Therapy With Proton Pump In	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4186F	No Continuous (12-months) Therapy With Either Prot	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4187F	Disease Modifying Anti-rheumatic Drug Therapy Pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4188F	Appropriate Angiotensin Converting Enzyme (ace)/an	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
41899	Dental Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4189F	Appropriate Digoxin Therapeutic Monitoring Test Or	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4190F	Appropriate Diuretic Therapeutic Monitoring Test O	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4191F	Appropriate Anticonvulsant Therapeutic Monitoring	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4192F	Pt Not Rcvng Glucoco Thxpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4193F	Pt Rcvng<10mg Daily Predniso	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4194F	Pt Rcvng>10mg Daily Predniso	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4195F	Pt Rcvng Anti-rheum Thxpy Ra	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4196F	Ptnot Rcvng Anti-rhm Thxpyra	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4200F	External Beam Radiotherapy To Prostate W/wo (prca)	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4201F	External Beam Radiotherapy For Prostate Cancer To	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4210F	Angiotensin Converting Enzyme (ace) Or Angiotensin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4220F	Digoxin Medication Therapy For 6 Months Or More (m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4221F	Diuretic Medication Therapy For 6 Months Or More (	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
42299	Palate/uvula Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4230F	Anticonvulsant Medication Therapy For 6 Months Or	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4240F	Instruction In Therapeutic Exercise With Follow-up	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4242F	Counseling For Supervised Exercise Program Provide	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4245F	Patient Counseled During The Initial Visit To Main	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4248F	Patient Counseled During The Initial Visit For An	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4250F	Active Warming Used Intraoperatively For The Purpo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4255F	Anesth >= 60 min as docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4256F	Anesth < 60 min as docd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4260F	Wound Srfc Culturetech Used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4261F	Tech Other Than Surfc Cultr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4265F	Wet-dry Dressings Rx-recmd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4266F	No Wet-dry Drssings Rx-recmd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4267F	Comprssion Thxpy Prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4268F	Pt Ed Re Comp Thxpy Rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
42699	Salivary Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4269F	Appropos Mthd Offloading Rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4270F	Patient Receiving Anti R-viral Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4271F	Patient Receiving Anti R-viral Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4274F	Flu Immunization Administered Received	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
4276F	Potent antivir thxpy rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4279F	Pcp Prophylaxis Rxd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4280F	Pcp Prophylax Rxd 3mon Low %	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4290F	Patient Screen For Injection Drug Use (hiv) 5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4293F	Patient Screened High-risk Sexual Behavior	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
42999	Throat Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4300F	Patient Receiving Warfin Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4301F	Patient Not Receiving Warfin Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4305F	Pt Ed Re Ft Care Inspct Rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4306F	Pt Tlk Psych & Rx Opd Addic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4320F	Patient Talk Psychsoc And Treatment Oh Dpnd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43210	Egd esophagogastrc fndoplsty	Investigational Denial	Always considered investigational; investigational services are denied member liability.
4322F	Crgvr prov w/ ed addl rsrcs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4324F	Patient queried Parkinson's Disease Complications	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43257	Uppr Gi Scope W/thrml Txmnt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
4325F	Med and surgical treatment options reviewed w/ pt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4326F	Patient asked regarding symptoms auto dysfxn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43284	Laps esophgl sphnctr agmntj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
43285	Rmvl esophgl sphnctr dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
43289	Laparoscope Proc, Esoph	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
4328F	Patient asked regarding sleep disturbances	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43290	Egd Flx Trnsorl Dplmnt Balo	Investigational Denial	Always considered investigational; investigational services are denied member liability.
43291	Egd Flx Trnsorl Rmvl Balo	Investigational Denial	Always considered investigational; investigational services are denied member liability.
4330F	Cnslng epi spec sfty issues	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4340F	Cnslng chldbrng+ women epi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43497	Transorl Lwr Esophgl Myotomy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
43499	Esophagus Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4350F	Cnslng provided symp mngmnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
43631	Removal Of Stomach, Partial	Medical Necessity	Review for medical necessity
43632	Removal Of Stomach, Partial	Medical Necessity	Review for medical necessity
43633	Removal Of Stomach, Partial	Medical Necessity	Review for medical necessity
43634	Removal Of Stomach, Partial	Medical Necessity	Review for medical necessity
43659	Laparoscope Proc, Stom	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
43770	Lap, Place Gastr Adjust Band	Investigational Denial	Always considered investigational; investigational services are denied member liability.
43842	V-band Gastroplasty	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
43999	Stomach Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4400F	Rehab therapy options with patient	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
44238	Laparoscope Proc, Intestine	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4450F	Self-care ed provided to pt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
44705	Prepare fecal microbiota	HTCC Decision	Possible HTCC decision denial

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Code	Description	Edit Type	Comment
4470F	Icd counseling provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
44799	Unlisted Procedure Intestine	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4480F	Pt rcvng ace/arb b-blockertx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4481F	Pt rcvng ace/arb blker<3mons	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
44899	Bowel Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
44979	Laparoscope Proc, App	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4500F	Ref to outpt card rehab prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4510F	Prev cardrehab qualcardevent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4525F	Neuropsychia interven order	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4526F	Neuropsychia interven rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
45399	Unlisted procedure colon	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4540F	Disease modifying pharmacothxpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4541F	Pt offered tx for pseudobulb	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
45499	Laparoscope Proc, Rectum	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
4550F	Noninvas resp support talk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4551F	Nutritional support offered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4552F	Pt ref for speech lang path	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4553F	Pt asst in planning for end of liffe issues	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4554F	Pt receieved inhalation anesthetic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4555F	Pt received no inhalation anesthetic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
4556F	Pt w/3 or more post op nausea and vomiting	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4557F	Pt w/o 3 or more post op nausea and vomiting	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4558F	Pt received 2 rx anti-emetic agents	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4559F	1 body temp >=35.5 cw/in 30 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4560F	Anesth w/o gen/neuraxial anesth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4561F	Pt w/ coronary artery stent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4562F	Pt w/o coronary artery stent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
4563F	Pt received aspirin within 24 hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
45999	Rectum Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
46707	Repair anorectal fist w/plug	Investigational Denial	Always considered investigational; investigational services are denied member liability.
46948	Int hrhc tranal dartlzj 2+	Investigational Denial	Always considered investigational; investigational services are denied member liability.
46999	Anus Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
47379	Laparoscope Procedure, Liver	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
47399	Liver Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
47579	Laparoscope Proc, Biliary	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
47999	Bile Tract Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
48999	Pancreas Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
49329	Laparo Proc, Abdm/per/oment	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
49659	Laparo Proc, Hernia Repair	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
49999	Abdomen Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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5005F	Pt Counsld On Exam For Moles	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
5010F	Macul+fndngs To Dr Mng Dm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
5015F	Doc Fx & Test/txmnt For Op	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
5020F	Treatment Summary Report Communicated To Physician	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
5050F	Treatment Plan Communicated To Provider(s) Managin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
50549	Laparoscope Proc, Renal	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
5060F	Findings From Diagnostic Mammogram Communicated To	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
5062F	Documentation Of Direct Communication Of Diagnosti	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
50949	Laparoscope Proc, Ureter	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
5100F	Rsk Fx Ref W/n 24 Hrs X-ray	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
51721	Ins trurl ablt trnsdc thr us	Investigational Denial	Always considered investigational; investigational services are denied member liability.
51999	Laparoscope Proc, Bladder	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
5200F	Eval appros surg thxpy epi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
52284	Cysto Rx Balo Cath Urtl Strx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
5250F	Asthma discharge plan presnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
53451	Tprnl Balo Cntnc Dev Bi	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53452	Tprnl Balo Cntnc Dev Uni	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53453	Tprnl Balo Cntnc Dev Rmvl Ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53454	Tprnl Balo Cntnc Dev Adjmt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53855	Insert prost urethral stent	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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53865	Cysto insj dev ischmc rmdlg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53866	Cathj rmvl dev ischmc rmdlg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
53899	Urology Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
54699	Laparoscope Proc, Testis	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
55559	Laparo Proc, Spermatic Cord	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
55881	Ablt trurl prst8 tis thrm us	Investigational Denial	Always considered investigational; investigational services are denied member liability.
55882	Ablt trurl prst8 tis trnsdcr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
55899	Genital Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
57465	Cam cervix uteri drg colp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
58578	Laparo Proc, Uterus	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
58579	Hysteroscope Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
58679	Laparo Proc, Oviduct-ovary	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
58999	Genital Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
59897	Fetal Invas Px W/us	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
59898	Laparo Proc, Ob Care/deliver	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
59899	Maternity Care Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
6005F	Care Level Rationale Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6010F	Dysphag Test Done B/4 Eating	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6015F	Pt Recvng/ok For Eatng/swallowing	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6020F	Npo (nothing-mouth) Ordered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
6030F	All Elements Of Maximal Sterile Barrier Technique	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6040F	Use Of Appropriate Radiation Dose Reduction Device	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6045F	Radiation Exposure Or Exposure Time In Final Repor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
60659	Laparo Proc, Endocrine	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
60699	Endocrine Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
6070F	Pt asked/cnsld aed effects	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6080F	Patient/Caregive queried about falls	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6090F	Patient/Caregive counseled about safety issues	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6100F	Verify pt site procedure documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6101F	Safety counseling dementia	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6102F	Safety counseling dem order	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6110F	Counsel prov driving risks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
6150F	Pt notrcvng1st antitnf txmnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
62263	Epidural Lysis Mult Sessions	Investigational Denial	Always considered investigational; investigational services are denied member liability.
62264	Epidural Lysis On Single Day	Investigational Denial	Always considered investigational; investigational services are denied member liability.
62287	Percutaneous Diskectomy	HTCC Benefit Denial	Not a covered benefit per HTCC
62292	Injection Into Disk Lesion	HTCC Benefit Denial	Not a covered benefit per HTCC
64505	N Block, Spenopalatine Gangl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64555	Implant Neuroelectrodes	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64575	Implant Neuroelectrodes	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
64624	Dstrj nulyt agt gnclr nrv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64625	Rf abltj nrv nrvtg si jt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64628	Trml Dstrj Ios Bvn 1St 2 L/S	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64629	Trml Dstrj Ios Bvn Ea Addl	Investigational Denial	Always considered investigational; investigational services are denied member liability.
64640	Injection Treatment Of Nerve	HTCC Benefit Denial	Not a covered benefit per HTCC
64999	Nervous System Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
66999	Eye Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
67299	Eye Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
67399	Eye Muscle Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
67599	Orbit Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
67999	Revision Of Eyelid	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
68399	Eyelid Lining Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
68899	Tear Duct System Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
69090	Pierce Earlobes	Cosmetic Denial	Always considered cosmetic; cosmetic services are denied member responsibility.
69399	Outer Ear Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
69420	Incision Of Eardrum	HTCC Decision	Possible HTCC decision denial
69421	Incision Of Eardrum	HTCC Decision	Possible HTCC decision denial
69424	Remove Ventilating Tube	HTCC Decision	Possible HTCC decision denial
69433	Create Eardrum Opening	HTCC Decision	Possible HTCC decision denial
69436	Create Eardrum Opening	HTCC Decision	Possible HTCC decision denial

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Code	Description	Edit Type	Comment
69799	Middle Ear Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
69949	Inner Ear Surgery Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
69979	Temporal Bone Surgery	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
7010F	Patient Information Entered Into A Recall System W	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
7020F	Breast Imaging-reporting And Data System (bi-rads-	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
7025F	Patient Information Entered Into A Reminder System	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
74263	Ct colonography, screen	HTCC Benefit Denial	Not a covered benefit per HTCC
75571	Ct hrt w/o dye w/ca test	HTCC Benefit Denial	Not a covered benefit per HTCC
76140	X-ray Consultation	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
76390	Mr Spectroscopy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
76496	Fluoroscopic Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
76497	Ct Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
76498	Mri Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
76499	Radiographic Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
76801	Ob Us < 14 Wks, Single Fetus	HTCC Decision	Possible HTCC decision denial
76805	Ob Us >/= 14 Wks, Sngl Fetus	HTCC Decision	Possible HTCC decision denial
76813	Ob Us Nuchal Meas, 1 Gest	HTCC Decision	Possible HTCC decision denial
76817	Transvaginal Us, Obstetric	HTCC Decision	Possible HTCC decision denial
76999	Echo Examination Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
77063	Breast tomosynthesis bi	HTCC Decision	Possible HTCC decision denial

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Code	Description	Edit Type	Comment
77085	Dxa bone density study	HTCC Benefit Denial	Not a covered benefit per HTCC
77086	Fracture assessment via dxa	HTCC Benefit Denial	Not a covered benefit per HTCC
77089	Tbs Dxa Cal W/I&R Fx Risk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
77090	Tbs Techl Prep&Transmis Data	Investigational Denial	Always considered investigational; investigational services are denied member liability.
77091	Tbs Techl Calculation Only	Investigational Denial	Always considered investigational; investigational services are denied member liability.
77092	Tbs I&R Fx Rsk Qhp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
77299	Radiation Therapy Planning	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
77399	External Radiation Dosimetry	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
77499	Radiation Therapy Management	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
77799	Radium/radioisotope Therapy	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78099	Endocrine Nuclear Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78199	Blood/lymph Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78299	Gi Nuclear Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78399	Musculoskeletal Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78499	Cardiovascular Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78599	Respiratory Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78699	Nervous System Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78799	Genitourinary Nuclear Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
78999	Nuclear Diagnostic Exam	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
79999	Nuclear Medicine Therapy	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
80299	Quantitative Assay, Drug	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
80320	Drug screen quantalcohols	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80321	Alcohols biomarkers 1or 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80322	Alcohols biomarkers 3/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80323	Alkaloids nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80324	Drug screen amphetamines 1/2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80325	Amphetamines 3or 4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80326	Amphetamines 5 or more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80327	Anabolic steroid 1 or 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80328	Anabolic steroid 3 or more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80329	Analgesics non-opioid 1 or 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80330	Analgesics non-opioid 3-5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80331	Analgesics non-opioid 6/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80332	Antidepressants class 1 or 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80333	Antidepressants class 3-5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80334	Antidepressants class 6/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80335	Antidepressant tricyclic 1/2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80336	Antidepressant tricyclic 3-5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80337	Tricyclic & cyclicals 6/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80338	Antidepressant not specified	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
80339	Antiepileptics nos 1-3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80340	Antiepileptics nos 4-6	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80341	Antiepileptics nos 7/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80342	Antipsychotics nos 1-3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80343	Antipsychotics nos 4-6	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80344	Antipsychotics nos 7/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80345	Drug screening barbiturates	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80346	Benzodiazepines1-12	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80347	Benzodiazepines 13 or more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80348	Drug screening buprenorphine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80349	Cannabinoids natural	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80350	Cannabinoids synthetic 1-3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80351	Cannabinoids synthetic 4-6	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80352	Cannabinoid synthetic 7/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80353	Drug screening cocaine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80354	Drug screening fentanyl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80355	Gabapentin non-blood	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80356	Heroin metabolite	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80357	Ketamine and norketamine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80358	Drug screening methadone	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
80359	Methylenedioxyamphetamines	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80360	Methylphenidate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80361	Opiates 1 or more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80362	Opioids & opiate analogs 1/2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80363	Opioids & opiate analogs 3/4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80364	Opioid &opiate analog 5/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80365	Drug screening oxycodone	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80366	Drug screening pregabalin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80367	Drug screening propoxyphene	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80368	Sedative hypnotics	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80369	Skeletal muscle relaxant 1/2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80370	Skel musc relaxant 3 or more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80371	Stimulants synthetic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80372	Drug screening tapentadol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80373	Drug screening tramadol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80374	Stereoisomer analysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80375	Drug/substance nos 1-3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80376	Drug/substance nos 4-6	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80377	Drug/substance nos 7/more	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80503	Path Clin Consltj Sf 5-20	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
80504	Path Clin Consltj Mod 21-40	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80505	Path Clin Consltj High 41-60	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
80506	Path Clin Consltj Prolng Svc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
81099	Urinalysis Test Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
81171	Aff2 gene detc abnor alleles	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81172	Aff2 gene charac alleles	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81226	Cyp2d6 gene com variants	HTCC Decision	Possible HTCC decision denial
81227	Cyp2c9 gene com variants	HTCC Benefit Denial	Not a covered benefit per HTCC
81230	CYP3A4 Gene common variants	HTCC Decision	Possible HTCC decision denial
81231	CYP3A5 Gene common variants	HTCC Decision	Possible HTCC decision denial
81232	DPYD Gene common variants	HTCC Decision	Possible HTCC decision denial
81291	Mthfr gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81313	Pca3/klk3 antigen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81327	Sept9 methylation analysis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81328	SLCO1B1 Gene common variants	HTCC Decision	Possible HTCC decision denial
81332	Serpina1 gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81346	TYMS Gene common variants	HTCC Decision	Possible HTCC decision denial
81355	Vkorc1 gene	HTCC Benefit Denial	Not a covered benefit per HTCC
81422	Fetal chrmoml microdeltj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81435	Hereditary colon cancer	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
81479	Unlisted molecular pathology	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
81490	Autoimmune rheumatoid arthr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81500	Onco (ovar) two proteins	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81503	Onco (ovar) five proteins	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81504	Oncology tissue of origin	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81517	Liver Ds Alys 3 Bmrk Srm Alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81525	Oncology colon mrna	HTCC Benefit Denial	Not a covered benefit per HTCC
81529	Onc cutan mlnma mrna 31 gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81535	Oncology gynecologic	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81536	Oncology gynecologic	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81538	Oncology lung	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81539	Oncology prostate prob score	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81540	Oncology tum unknown origin	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81554	Pulm ds ipf mrna 190 gen alg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81558	Trnspl rej kdn mrna qpcr 139	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81560	Onc Brst Mrna 70 Cnt 31 Gene	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81596	Nfct ds chrnc hcv 6 assays	Investigational Denial	Always considered investigational; investigational services are denied member liability.
81599	MAA	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
82075	Assay Of Breath Ethanol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
82233	Beta-amyloid 1-40 (abeta 40)	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
82234	Beta-amyloid 1-42 (abeta 42)	Investigational Denial	Always considered investigational; investigational services are denied member liability.
82306	Assay Of Vitamin D	Medical Necessity	Review for medical necessity
82310	Assay Of Calcium	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82330	Assay Of Calcium	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82340	Assay Of Calcium In Urine	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82523	Collagen Crosslinks	Investigational Denial	Always considered investigational; investigational services are denied member liability.
82652	Assay Of Dihydroxyvitamin D	Medical Necessity	Review for medical necessity
82670	Assay Of Estradiol	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82681	Assay dir meas fr estradiol	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82728	Assay Of Ferritin	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82746	Blood Folic Acid Serum	Medical Necessity	Review for medical necessity
82747	Assay Of Folic Acid, Rbc	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
82977	Assay Of Ggt	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
83540	Assay Of Iron	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
83550	Iron Binding Test	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
83698	Lipoprotein-associated Phospholipase A2 (lp-pla2)	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83700	Lipopro Bld, Electrophoretic	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83701	Lipoprotein Bld, Hr Fraction	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83704	Lipoprotein, Bld, By Nmr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83722	Lipoprtn dir meas sd ldl chl	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
83735	Assay Of Magnesium	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
83951	Oncoprotein; Des-gamma-carboxy-prothrombin (dcp)	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83970	Assay Of Parathormone	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
83987	Exhaled breath condesate	Investigational Denial	Always considered investigational; investigational services are denied member liability.
83992	Assay For Phencyclidine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
83993	Calprotectin, Fecal	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84100	Assay Of Phosphorus	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84105	Assay Of Urine Phosphorus	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84112	Placenta alpha micro ig c/v	Investigational Denial	Always considered investigational; investigational services are denied member liability.
84393	Tau phosphorylated ea	Investigational Denial	Always considered investigational; investigational services are denied member liability.
84394	Total tau	Investigational Denial	Always considered investigational; investigational services are denied member liability.
84402	Assay Of Testosterone	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84403	Assay Of Total Testosterone	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84410	Testosterone bioavailable	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84443	Assay Thyroid Stim Hormone	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84466	Assay Of Transferrin	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
84999	Clinical Chemistry Test (oncotype)	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
85651	Rbc Sed Rate, Nonautomated	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
85652	Rbc Sed Rate, Automated	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
85999	Hematology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
86001	Allergen Specific Igg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
86038	Antinuclear Antibodies	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86039	Antinuclear Antibodies (ana)	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86140	C-reactive Protein	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86152	Cell enumeration & id	Investigational Denial	Always considered investigational; investigational services are denied member liability.
86153	Cell enumeration phys interp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
86225	Dna Antibody	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86235	Nuclear Antigen Antibody	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86343	Leukocyte Histamine Release	Investigational Denial	Always considered investigational; investigational services are denied member liability.
86408	Neutrlzg antb SARSCOV2 SCR	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86409	Neutrlz antb SARSCOV2 titer	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
86849	Immunology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
86999	Transfusion Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
87472	Bartonella, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87482	Candida, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87483	Cns dna amp probe type 12-25	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87487	Chylmd Pneum, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87492	Chylmd Trach, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87512	Gardner Vag, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87523	Hepatitis D Quantification	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
87525	Hepatitis G, Dna, Dir Probe	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87526	Hepatitis G, Dna, Amp Probe	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87527	Hepatitis G, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87530	Hsv, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87542	Legion Pneumo, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87552	Mycobacteria, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87557	M.tuberculo, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87562	M.avium-intra, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87582	M.pneumon, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87592	N.gonorrhoeae, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87633	Resp virus 12-25 targets	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87652	Strep A, Dna, Quant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
87913	Nfct Agt Gntyp Alys Sarscov2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
87999	Microbiology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
88099	Necropsy (autopsy) Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
88199	Cytopathology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
88299	Cytogenetic Study	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
88399	Surgical Pathology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
88749	In vivo lab service	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
89240	Pathology Lab Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
89398	Unlisted reprod med lab proc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
9001F	Aortic aneurysm<5cm diam ct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9002F	Aortic aneurysm 5-5.4cm diam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9003F	Aortic anrysm5.5-5.4cm diam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9004F	Aortic anrysm 6/grtr cm diam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9005F	Asympt carot/vrtbrbas sten	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9006F	Sympt sten-tia/strk<120days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
9007F	Other carot sten120days/grtr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90393	Vaccina Ig, Im	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90399	Immune Globulin	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
90476	Adenovirus Vaccine, Type 4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90477	Adenovirus Vaccine, Type 7	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90593	CHIKUNGUNYA VACC RECOMB IM	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90634	Hep A Vacc, Ped/adol, 3 Dose	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90655	Flu Vaccine No Preserv 6-35m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90676	Rabies Vaccine, Id	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90749	Vaccine Toxoid	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
90863	Pharmacologic mgmt w/psytx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90865	Narcosynthesis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
90882	Environmental Manipulation	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
90885	Psy Evaluation Of Records	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
90887	Consultation With Family	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
90889	Preparation Of Report	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
90899	Psychiatric Service/therapy	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
91112	Gi wireless capsule measure	Investigational Denial	Always considered investigational; investigational services are denied member liability.
91299	Gastroenterology Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
92132	Cmptr ophth dx img ant segmt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
92352	Special Spectacles Fitting	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92353	Special Spectacles Fitting	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92354	Special Spectacles Fitting	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92355	Special Spectacles Fitting	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92358	Eye Prosthesis Service	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92371	Repair & Adjust Spectacles	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92499	Eye Service Or Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
92517	Vemp test i&r cervical	Investigational Denial	Always considered investigational; investigational services are denied member liability.
92518	Vemp test i&r ocular	Investigational Denial	Always considered investigational; investigational services are denied member liability.
92519	Vemp tst i&r cervical&ocular	Investigational Denial	Always considered investigational; investigational services are denied member liability.
92531	Spontaneous Nystagmus Study	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92532	Positional Nystagmus Test	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92533	Caloric Vestibular Test	Non-Reimbursable Services	CMS Status B, not reimbursed separately.

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Code	Description	Edit Type	Comment
92534	Optokinetic Nystagmus Test	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92562	Loudness Balance Test	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
92605	Eval For Nonspeech Device Rx	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92606	Non-speech Device Service	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92618	Ex for nonspeech dev rx add	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92700	Ent Procedure/service	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
92921	Prq cardiac angio addl art	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92925	Prq card angio/athrect addl	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92929	Prq card stent w/angio addl	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92934	Prq card stent/ath/angio	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92938	Prq revasc byp graft addl	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92944	Prq card revasc chronic addl	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
92972	Perq Trluml Coronry Lithotrp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93150	Therapy Activation Ipnss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93151	Interrog&Prgrmg Ipnss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93152	Interrog&Prgrmg Ipnss Polysm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93153	Interrog W/O Prgrmg Ipnss	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93264	Rem mntr wrls p-art prs snr	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93278	Ecg/signal-averaged	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
93356	Myocrd strain img spckl trck	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
93701	Bioimpedance, Thoracic	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93702	Bis xtracell fluid analysis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
93740	Temperature Gradient Studies	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
93770	Measure Venous Pressure	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
93799	Cardiovascular Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
93895	Carotid intima atheroma eval	Investigational Denial	Always considered investigational; investigational services are denied member liability.
94005	Home Vent Mgmt Supervision	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
94150	Vital Capacity Test	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
94760	Measure Blood Oxygen Level	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
94761	Measure Blood Oxygen Level	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
94799	Pulmonary Service/procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
95060	Eye Allergy Tests	Investigational Denial	Always considered investigational; investigational services are denied member liability.
95065	Nose Allergy Test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
95120	Immunotherapy, One Injection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95125	Immunotherapy, Many Antigens	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95130	Immunotherapy, Insect Venom	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95131	Immunotherapy, Insect Venoms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95132	Immunotherapy, Insect Venoms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95133	Immunotherapy, Insect Venoms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
95134	Immunotherapy, Insect Venoms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
95199	Allergy Immunology Services	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
95803	Actigraphy Testing, Recording, Analysis, Interpret	Investigational Denial	Always considered investigational; investigational services are denied member liability.
95905	Motor/sens nrve conduct test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
95999	Neurological Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
96041	Genetic counseling svc ea 30	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
96379	Unlisted Therapeutic, Prophylactic, Or Diagnostic	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
96549	Chemotherapy, Unspecified	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
96902	Trichogram	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
96904	Whole Body Photography	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
96931	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96932	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96933	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96934	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96935	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96936	Rcm celulr subcelulr img skn	Investigational Denial	Always considered investigational; investigational services are denied member liability.
96999	Dermatological Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
97010	Hot Or Cold Packs Therapy	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
97039	Physical Therapy Treatment	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
97124	Massage Therapy	HTCC Decision	Possible HTCC decision denial
97139	Physical Medicine Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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Code	Description	Edit Type	Comment
97602	Wound(s) Care Non-selective	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
97610	Low frequency non-thermal us	Investigational Denial	Always considered investigational; investigational services are denied member liability.
97799	Physical Medicine Procedure	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
97810	Acupunct W/o Stimul 15 Min	HTCC Decision	Possible HTCC decision denial
97811	Acupunct W/o Stimul Addl 15m	HTCC Decision	Possible HTCC decision denial
97813	Acupunct W/stimul 15 Min	HTCC Decision	Possible HTCC decision denial
97814	Acupunct W/stimul Addl 15m	HTCC Decision	Possible HTCC decision denial
98926	Osteopathic Manipulation	HTCC Decision	Possible HTCC decision denial
98927	Osteopathic Manipulation	HTCC Decision	Possible HTCC decision denial
98928	Osteopathic Manipulation	HTCC Decision	Possible HTCC decision denial
98929	Osteopathic Manipulation	HTCC Decision	Possible HTCC decision denial
98940	Chiropractic Manipulation	HTCC Decision	Possible HTCC decision denial
98941	Chiropractic Manipulation	HTCC Decision	Possible HTCC decision denial
98942	Chiropractic Manipulation	HTCC Decision	Possible HTCC decision denial
98943	Chiropractic Manipulation	HTCC Decision	Possible HTCC decision denial
98960	Self-mgmt Educ & Train, 1 Pt	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
98961	Self-mgmt Educ/train, 2-4 Pt	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
98962	Self-mgmt Educ/train, 5-8 Pt	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
98975	Rem Ther Mntr 1St Setup&Edu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
98976	Rem Ther Mntr Dev Sply Resp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
98977	Rem Ther Mntr Dv Sply Mscskl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
98980	Rem Ther Mntr 1St 20 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
98981	Rem Ther Mntr Ea Addl 20 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99000	Specimen Handling	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99001	Specimen Handling	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99002	Device Handling	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99024	Postop Follow-up Visit	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99026	In-hospital On Call Service	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99027	Out-of-hosp On Call Service	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99050	Medical Services After Hrs	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99051	Med Serv, Eve/wkend/holiday	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99053	Med Serv 10pm-8am, 24 Hr Fac	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99056	Med Service Out Of Office	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99058	Office Emergency Care	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99060	Out Of Office Emerg Med Serv	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99070	Special Supplies	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99071	Patient Education Materials	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99072	Addl supl matrl&staf tm phe	HTCC Benefit Denial	Not a covered benefit per HTCC
99078	Group Health Education	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99080	Special Reports Or Forms	Non-Reimbursable Services	CMS Status B, not reimbursed separately.

Clinical Edits by Code List
Complete List
Applies to Uniform Medical Plan (UMP)

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Code	Description	Edit Type	Comment
99100	Special Anesthesia Service	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99116	Anesthesia With Hypothermia	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99135	Special Anesthesia Procedure	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99140	Emergency Anesthesia	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99190	Special Pump Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99191	Special Pump Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99192	Special Pump Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99199	Special Service/proc/report	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
99288	Direct Advanced Life Support	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99360	Physician Standby Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99366	Medical Team Conference With Interdisciplinary Tea	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99367	Medical Team Conference With Interdisciplinary Tea	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99368	Medical Team Conference With Interdisciplinary Tea	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99374	Home Health Care Supervision	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99375	Home Health Care Supervision	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99377	Hospice Care Supervision	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99378	Hospice Care Supervision	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99379	Nursing Fac Care Supervision	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99380	Nursing Fac Care Supervision	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99429	Unlisted Preventive Service	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
99453	Rem mntr physiol param setup	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99454	Rem mntr physiol param dev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99457	Rem physiol mntr 20 min mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99458	Rem physiol mntr ea addl 20	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99485	Suprv interfacilty transport	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99486	Suprv interfac trnsport addl	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
99499	Unlisted E&m Service	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
99605	Medication Therapy Management Service(s) Provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99606	Medication Therapy Management Service(s) Provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
99607	Medication Therapy Management Service(s) Provided	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A0140	Nonemerg Trnsprt & Air Travel	HTCC Benefit Denial	Not a covered benefit per HTCC
A2001	Innovamatrix Ac, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2002	Mirragen Adv Wnd Mat Per Sq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2004	Xcellistem, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2005	Microlyte Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2006	Novosorb Synpath Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2007	Restrata, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2008	Theragenesis, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2009	Symphony, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2010	Apis, Per Square Centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
A2011	Supra Sdrm, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2012	Suprathel, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2013	Innovamatrix Fs, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2014	Omeza collag per 100 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2015	Phoenix wnd mtrx, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2016	Permeaderm b, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2017	Permeaderm glove, each	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2018	Permeaderm c, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2019	Kerecis Marigen Shld Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2020	Ac5 Wound System	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2021	Neomatrix Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2022	Innovabrn/Innovamatx Xl Sqcm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2023	Innovamatrix Pd, 1 Mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2024	Resolve Matrix or xenopatch Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2025	Miro3D Per Cubic Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2026	Restrata Minimatrix, 5 Mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2027	Matriderm Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2028	Micromatrix Flex Per Mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A2029	Mirotract Matrix Sheet	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4210	Needle-free Injection Device Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
A4212	Noncoring Needle/stylet W/wo Cath	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4220	Refill Kit Implantable Infus Pump	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4223	Infus Spl No Ext Infus Pump Cas/bag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4230	Infus Set Ext Insulin Pump Nonndle	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4231	Infus Set Ext Insulin Pump Needle	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4244	Alcohol Or Peroxide Per Pint	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4246	Betadine/phisohex Solution Per Pint	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4247	Betadine/iodine Swabs/wipes Per Box	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4248	Chlorhexidine Containing Antiseptic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4250	Urine Test/reagent Strips/tablets	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4252	Blood Ketone Test Or Reagent Strip, Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4262	Temp Absorb Lac Duct Implant Ea	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
A4263	Perm Nondissolv Lac Duct Impl Ea	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
A4268	Contracept Supply Condom Female Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4270	Disposable Endoscope Sheath Each	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
A4300	Impl Acss Catheter External Access	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
A4305	Dispbl Rx Del Sys Rate 50 Ml/>-hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4306	Dispbl Rx Del Sys Rate 5 Ml/<-hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4335	Incontinence Supply; Miscellaneous	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A4400	Ostomy Irrigation Set	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
A4421	Ostomy Supply; Miscellaneous	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A4465	Nonelastic Binder For Extremity	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4467	Belt strap sleev grmnt cover	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4490	Surg Stocking Above Knee Length Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4495	Surgical Stocking Thigh Length Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4500	Surg Stocking Below Knee Length Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4510	Surgical Stocking Full-length Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4540	Trans Elec Nerv Periph Nerv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4541	Monthly Supp Use With E0733	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4542	Supp Ext Up Limb Tremor Stim	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4543	Supply Trans Elec Nerve Stim	HTCC Benefit Denial	Not a covered benefit per HTCC
A4544	Electro Nerve Stimulator Rls	HTCC Benefit Denial	Not a covered benefit per HTCC
A4545	Suppl Accessor Tibial Stim	HTCC Benefit Denial	Not a covered benefit per HTCC
A4550	Surgical Trays	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
A4553	Nondisp underpads, all sizes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4555	Ca tx e-stim electr/transduc	HTCC Benefit Denial	Not a covered benefit per HTCC
A4560	Nmes Disposable	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4575	Topical Hyprbr Oxygen Chamb Dispbl	HTCC Benefit Denial	Not a covered benefit per HTCC
A4580	Cast Supplies	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4590	Special Casting Material	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
A4595	Elec Stim Supplies 2 Lead Per Month	HTCC Benefit Denial	Not a covered benefit per HTCC
A4596	Ces system monthly supp	Investigational Denial	Always considered investigational; investigational services are denied member liability.
A4600	Sleeve, inter limb comp dev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4611	Battry Hevy Duty; Repl Pt-ownd Vent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4612	Battry Cables; Repl Pt-owned Vent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4630	Repl Battry Trnsq Elec Stim Ownd Pt	HTCC Benefit Denial	Not a covered benefit per HTCC
A4649	Surgical Supply; Miscellaneous	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A4651	Calibrated Microcapillary Tube Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4652	Microcapillary Tube Sealant	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4657	Syringe With Or Without Needle Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4674	Chems/antisptc Sol Clean/sterl 8oz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4714	Treated H2o Periton Dialysis-gallon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4722	Dialysate Fl>1999<=2999cc Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4725	Dialysate Fl>4999<=5999cc Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4750	Bld Tubing Art/venous Hemodial Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4770	Bld Collection Tube Vac Dialysis-50	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4772	Bld Glu Test Strips Dialysis Per 50	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4774	Ammonia Test Strips Dialysis Per 50	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4860	Dispbl Cath Tip Periton Dialysis-10	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4911	Drain Bag/bottle For Dialysis Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
A4913	Miscellaneous Dialysis Supplies Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A4918	Venous Pressure Clamp Hemodial Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4927	Gloves Non-sterile Per 100	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4928	Surgical Mask Per 20	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A4930	Gloves Sterile Per Pair	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A5508	Dm Only Delux Featur Shoe/cstm Mold	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A5510	Diab Only Dir Form Comprs Mold Ft	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6025	Gel Sheet Dermal/epidrmal Applic Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6205	Compos Dress >48sq W/adhes Bordr Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6218	Gauze Non-impreg Nonsterl > 48 Sq	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6250	Skn Sealnt Protct Moisturzr Ointmnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6256	Spclty Absorb Dress > 48 Sq W/adhes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6260	Wound Cleansers Any Type Any Size	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6261	Wound Filler Gel/paste-fl Ounce Nec	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A6262	Wound Filler Dry Form Per Gram Nec	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A6404	Gauz Non-impreg Strl >48sq No Adhes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6412	Eye Patch Occlusive Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6413	Adhesive Bandage, First Aid Type, Any Size, Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A6512	Compression Burn Garment Noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
A6549	Gradient Compression Stocking Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
A7047	Resp suction oral interface	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9150	Nonprescription Drug	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9152	1 Vit/minerl/trace Elem Orldose Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9153	Multiple Vitamins Oral Per Dose Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9272	Disposable mech wound suct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9273	Hot/cold h2obot/cap/col/wrap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9275	Home Glu Dispbl Mon W/test Strips	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9279	Monitoring feature/deviceNOC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9280	Alert Or Alarm Device Noc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9284	Spirometer, Non-electronic, Includes All Accessori	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9285	Inversion eversion cor devic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9286	Any hygienic item, device	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9900	Dme Sup/access/srv-compon/oth Hcpcs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9901	Dme Del Set&/dspns Srvc Anoth Hcpcs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
A9999	Miscellaneous Dme Supply/access Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
B9999	Noc For Parenteral Supplies	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
C1062	Intravertebral fx aug impl	HTCC Benefit Denial	Not a covered benefit per HTCC
C1735	Cath renal denerv radiofreq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1736	Cath renal denerv ultrasnd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1748	Endoscope, single, ugi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
C1754	Catheter Intradiscal	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
C1761	Cath, Trans Intra Litho/Coro	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1821	Interspinous Implant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1824	Generator, ccm, implant	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1825	Gen, neuro, carot sinus baro	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1832	Auto Cell Process Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1833	Cardiac Monitor Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C1890	No device w/dev-intensive px	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
C2614	Probe Percut Lumbar Discectomy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C2624	Wireless pressure sensor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C7504	Perq Cvt&Ls Inj Vert Bodies	HTCC Benefit Denial	Not a covered benefit per HTCC
C7505	Perq Ls&Cvt Inj Vert Bodies	HTCC Benefit Denial	Not a covered benefit per HTCC
C7507	Perq Thor&Lumb Vert Aug	HTCC Benefit Denial	Not a covered benefit per HTCC
C7508	Perq Lumb&Thor Vert Aug	HTCC Benefit Denial	Not a covered benefit per HTCC
C8001	3d anat seg imaging preop	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C8002	Prep skin cell susp, automtd	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C8003	Imp extar knee shck absrb	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C8937	Cad breast mri	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
C9354	Acellular Pericardial Tissue Matrix Of Nonhuman Or	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9356	Tendoglide Tendon Prot, Cm2 (tenoglide)	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
C9358	SurgiMend, fetal	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9360	Dermal substitute, neonatal bovine	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9363	Skin sub., Integra Meshed Bilayer Wound Matrix	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9364	Porcine implant, Permacol, per sq centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9399	Unclassified Drugs Or Biologicals	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
C9727	Insert Palate Implants	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9760	Non-blind interatrial shunt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
C9762	Cardiac MRI seg dys strain	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9763	Cardiac MRI seg dys stress	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9764	Revasc intravasc lithotripsy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9765	Revasc intra lithotrip-stent	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9766	Revasc intra lithotrip-ather	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9767	Revasc lithotrip-stent-ather	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9772	Revasc lithotrip tibi/perone	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9773	Revasc lithotr-stent tib/per	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9774	Revasc lithotr-ather tib/per	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9775	Revasc lith-sten-ath tib/per	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9781	Arthro/Shoul Surg; W/Spacer	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9807	Nerve stim non-opioid dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9808	Cryo probe non-opioid dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Clinical Edits by Code List
Complete List
Applies to Uniform Medical Plan (UMP)

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

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Code	Description	Edit Type	Comment
C9809	Cryo needle non-opioid dev	Investigational Denial	Always considered investigational; investigational services are denied member liability.
C9899	Implanted Prosthetic Device, Payable Only For Inpa	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
E0144	Walker Enclos 4 Side Whl Post Seat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0172	Seat Lift Mech Place Ovr/top Toilet	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0175	Foot Rest Use W/commode Chair Each	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0231	Non-cntc Wnd Warm Devc W/card&covr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0232	Wound Warming Wound Cover	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0274	Over-bed Table	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0315	Bed Access: Board/tabl/supprt Devc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0350	Cntrl U Elec Bowel Irrig/evac Sys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0352	Dispbl Pack W/elec Bowel Irrig/evac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0430	Prtble Gaseous O2 Sys Purchase;	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0440	Station Liquid O2 Sys Purchase;	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0446	Topical Ox Deliver sys, nos	HTCC Benefit Denial	Not a covered benefit per HTCC
E0485	Orl Devc/appl Rduc Ua Collaps Prfab	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0490	Control Unit Nm Hw Remote	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0491	Oral Dv Nm Mouthpc Hw Remote	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0492	Control Unit Nm Stim W Phone	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0493	Oral Dv/App Neuromus Mouthpi	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0575	Nebulizer Ultrasonic Large Volume	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
E0620	Skn Pierc Devc Clct Caplry Bld Lasr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0676	Inter Limb Compress Dev Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0715	Intravag Pelvic Floor Kegel	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0716	Supp And Acces Intravag Pelv	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0720	Tens Two Lead Localized Stimulation	HTCC Benefit Denial	Not a covered benefit per HTCC
E0721	Trans Elec Stim Auricular	HTCC Benefit Denial	Not a covered benefit per HTCC
E0730	Tens Devc 4/more Leads Mx Nerv Stim	HTCC Benefit Denial	Not a covered benefit per HTCC
E0731	Form Fit Conduct Garm Tens/nmes	HTCC Benefit Denial	Not a covered benefit per HTCC
E0732	Ces System	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0733	Trans Elec Nerv For Trigemin	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0734	Ext Up Limb Tremor Stim Wris	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0737	Transcut Tibial Stim By App	HTCC Benefit Denial	Not a covered benefit per HTCC
E0738	Upper Extremity Rehab	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0739	Rehab Sys Active Assist Rt	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0740	Incont Tx Sys Pelv Flr Stim &/trner	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0743	Ext Low Ext Nerve Stimu Rls	HTCC Benefit Denial	Not a covered benefit per HTCC
E0744	Neuromuscular Stimulator Scoliosis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0745	Neuromusc Stim Elec Shock Unit	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0755	Elec Salivary Reflex Stimulator	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0761	Non-thrml Puls Radiowave Elecmagnet	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
E0762	Transcut Elec Joint Stim Devc Sys	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0764	Func Neuromusc Stim Cmpt Sc Inj	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0766	Elec stim cancer treatment	HTCC Benefit Denial	Not a covered benefit per HTCC
E0767	Intrabuc Am Rf Emf Cancer Tx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0769	Estim/elecmagnet Wound Tx Devc Noc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0770	Functional Electrical Stimulator, Transcutaneous S	Investigational Denial	Always considered investigational; investigational services are denied member liability.
E0840	Traction Frame Headboard Cerv Tract	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0850	Tract Stand Freestand Cerv Tract	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0856	Cervical Traction Device, Cervical Collar With Inf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0936	Cpm Device, Other Than Knee	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0983	Mnl Wc Acss Pwr Add-on Cnvrt Mnl Wc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E0984	Mnl Wc Acss Pwr Add-on Cnvrt Mnl Wc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1130	Std Whlchair; Fix Arm Dtach Footrst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1140	Whlchair; Dtachble Arms Footrests	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1220	Whlchair; Spclly Sized/constructed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1229	Wheelchair Pediatric Size Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1239	Power Wheelchair Pediatric Size Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
E1260	Lghtwt Whlchair; Dtach Arms Footrst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1354	Oxygen Accessory, Wheeled Cart For Portable Cylind	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1356	Oxygen Accessory, Battery Pack/cartridge For Porta	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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E1357	Oxygen Accessory, Battery Charger For Portable Con	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1358	Oxygen Accessory, Dc Power Adapter For Portable Co	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E1399	Dme Miscellaneous	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
E1699	Dialysis Equipment Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
E2230	Manual Wheelchair Accessory, Manual Standing Syste	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2358	Gr 34 nonsealed leadacid	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2360	Pwr Wc Acss 22 Nf Non-sealed Battry	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2362	Pwr Wc Acss Grp 24 Non-sealed Batt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2364	Pwr Wc Acss U-1 Non-sealed Battry	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2372	Pwr Wc Grp 27 Nonseal Led Acid Batt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
E2599	Access Speech Generating Device Noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
E3200	Gait Mod Systm Rhym Auditory	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0029	No Tob Scr/Cess Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0030	Pt Scr Tob & Cess Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0031	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0032	2+ Antipsy Schiz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0033	2+ Benzo Seiz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0034	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0035	Pt Ed Pos 23	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0036	Pt/Ptn Decln Assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G0037	Pt Not Able To Participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0038	Clin Pt No Ref	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0039	Pt No Ref, Rn Spec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0040	Pt Phys/Occ Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0041	Pt/Ptn Decln Referral	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0042	Ref To Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0043	Pt Mech Pros Ht Valv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0044	Pt Mitral Stenosis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0045	Mrs 90 Days Post Stk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0046	No Mrs 90 Days Post Stk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0047	Ped Blunt Hd Traum	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0048	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0049	Main Hemo In-Cntr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0050	Pt W/ Lmted Life Expec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0051	Pt Hospice Mnth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0052	Pt Peri Dialysis Dur Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0053	Adv Rheum Pt Care Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0054	Strk Cr Prev Pos Outcme Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0055	Adv Care Heart Dx Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0057	Best Pct Pt Safety Em Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G0058	Imprv Care Le Jnt Repr Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0059	Pt Sfty Pos Exp W Aneth Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0060	Allergy/Immunology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0061	Anesthesiology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0062	Audiology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0063	Cardiology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0064	Cert Nurse Midwife Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0065	Chiropractic Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0066	Clinical Social Work Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0067	Dentistry Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0071	Comm svcs by rhc/fqhc 5 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0076	Care manag h vst new pt 20 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0077	Care manag h vst new pt 30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0078	Care manag h vst new pt 45 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0079	Care manag h vst new pt 60 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0080	Care manag h vst new pt 75 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0081	Care man h v ext pt 20 mi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0082	Care man h v ext pt 30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0083	Care man h v ext pt 45 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0084	Care man h v ext pt 60 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G0085	Care man h v ext pt 75 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0086	Care man home care plan 30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0087	Care man home care plan 60 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0175	Sched Intrdiscipln Team Conf Pt Prs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0177	Trn&ed Pts Disabl Mentl Hlth-sess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0179	Phys Re-cert Mcr-covr Hom Hlth Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0180	Phys Cert Mcr-covr Hom Hlth Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0181	Phys Supv Pt Recv Mcr-covr Hom Hlth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0182	Phys Supv Pt Und Mcr-apprvd Hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0235	Pet Imaging Any Site Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
G0255	Cpt/snct Per Limb Any Nerve	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0269	Plcmt Occl Devc Post Surg/intrvnal	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
G0276	Pild/placebo control clinical trial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0281	E-stim 1/> Chrn Stage Iii&iv Ulcrs	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0282	E-stim 1/> Areas Wnd Care Not G0281	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0289	Scpe Knee Remv Fb Tm Surg Diff Comp	HTCC Benefit Denial	Not a covered benefit per HTCC
G0293	Noncovr Surg Sedat Anes-mcr Qual	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0294	Noncovr Proc No Anes/loc-mcr Qual	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0295	Elecmagnet Tx 1/>area Not G0329/oth	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0310	Immunize counsel 5-15 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G0311	Immunize counsel 16-30 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0312	Immunize couns < 21yr 5-15 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0313	Immunize couns < 21yr 6-30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0314	Counsel immune <21 16-30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0315	Counsel immune <21 5-15 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0327	Colon Ca Scrn;Bld-Bsd Biomrk	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0329	Em Tx Ulcers Not Healing 30 Da Care	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G0455	Fecal microbiota prep instil	HTCC Decision	Possible HTCC decision denial
G0460	Autologous PRP for ulcers	HTCC Benefit Denial	Not a covered benefit per HTCC
G0463	Hospital outpt clinic visit	Non-Reimbursable Services	Not considered a payable Professional service. Will be denied provider write-off.
G0465	Autolog Prp Diab Wound Ulcer	HTCC Benefit Denial	Not a covered benefit per HTCC
G0471	Venous blood collection SNF/HHA	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0482	Drug test definitive	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
G0483	Drug test definitive	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
G0501	Resource-inten svc during ov	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
G0519	New Pt-Cg Dyad Dem Low Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0520	New Pt-Cg Dyad Dem Mod Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0521	New Pt-Cg Dyad Dem Hig Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0522	Mgt Nw Pt Dementia Low Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0523	Mgt Nw Pt Dem Mod-High Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G0524	Est Pt-Cg Dyad Dem Low Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0525	Est Pt-Cg Dyad Dem Mod Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0526	Est Pt-Cg Dyad Dem Hig Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0527	Mgt Est Pt Dmentia Low Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0528	Mgt Est Pt Dem Mod-Hi Cmplx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0529	In Home Respite Care, 4 Hr U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0530	Adult Daycare Center, 8 Hr U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0531	Fclty-Based Respite, 24 Hr U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0539	Initial care training 30 m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0540	Train for caregiver add 15	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0541	No pt prsnt train initial 30	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0542	No pt prsnt train add 15	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0543	Group train w/o patient	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0913	Improve visual funct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0914	Survey not complete	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0915	No improve visual funct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0916	Satisfy with care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0917	Satisfy survey not complete	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G0918	No satisfy with care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G1025	Pt Mnth 1 Mcp Prov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G1026	Pt Hemo > 3Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G1027	Pt Hemo < 3Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2001	Post D/C home visit new pt 20 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2002	Post D/C home visit new pt 30 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2003	Post D/C home visit new pt 45 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2004	Post D/C home visit new pt 60 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2005	Post D/C home visit new pt 75 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2006	Post D/C home visit existing pt 20 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2007	Post D/C home visit existing pt 30 mintues	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2008	Post D/C home visit existing pt 45 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2009	Post D/C home visit existing pt 60 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2013	Post D/C home vist existing pt 75 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2014	Post D/C care plan oversight 30 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2015	Post D/C care plan oversight 60 minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2020	Hi inten serv for sip model	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2021	Hea care pract tx in place	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2022	Benef refuses service, mod	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2067	Med assist tx meth wk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2068	Med assist tx bupre oral	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2069	Med assist tx inject	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G2073	Med tx naltrexone	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2074	Med assist tx no drug	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2075	Med tx meds nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2076	Intake act w/med exam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2077	Periodic assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2078	Take-home meth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2079	Take-hom buprenorphine	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2080	Add 30 mins counsel	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2081	Pt 66+ snp or ltc pos > 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2090	Pt 66+ frailty and med dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2091	Pt 66+ frailty and adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2092	Ace arb arni	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2093	Med doc rsn no ace arn arni	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2094	Pt rsn no ace arn arni	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2096	No rsn ace arb arni	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2097	Child dx uri 3d of other dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2098	Pt 66+ frailty and med dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2099	Pt 66+ frailty and adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2100	Pt 66+ frailty and med dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2101	Pt 66+ frailty and adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G2105	Pt 66+ lt ints > 90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2106	Pt 66+ lt ints > 90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2107	Pt 66+ frailty and adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2112	Pred<=5 mg ra glu <6m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2113	Pred>5 mg >6m, no chg da	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2115	Pt 66+ frailty and med dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2116	Pt 66+ frailty and adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2118	Pt 81+ frailty	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2121	Psy dep anx ap and icd asse	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2122	Psy/dep/anx/apandicd noasse	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2125	Pt 81+ frailty	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2126	Pt 66+ frailty adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2127	Pt 66+ frailty med dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2128	No aspirin med rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2129	No bp outpt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2136	Bk pain vas 6-20wk = 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2137	Bk pain vas 6-20wk > 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2138	Bk pain vas 9-15mo = 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2139	Bk pain vas 9-20mo > 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2140	Leg pain vas 6-20wk = 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G2141	Leg pain vas 6-20wk > 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2142	Fs odi 9-15mo postop<= 22	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2143	Fs odi 9-15mo > 22	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2144	Fs odi 6-20wk postop > 22	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2145	Fsodi 6-20wk >22 or chg 30pt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2146	Leg pain vas 9-15mo <= 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2147	Leg pain vas 9-15mo > 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2148	Mpm used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2149	No mpm med rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2150	No mpm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2151	Dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2152	Res change sc =0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2167	Res change sc < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2168	Svs by pt in home health	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2169	Svs by ot in home health	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2172	Tx for opioid use demo proj	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2173	Uri w comorb 12m oth dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2174	Uri new rx antibiotic 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2175	Pt comorb dx 12m of epi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2176	Outpt ed obs w inpt admit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G2177	Bronch w rx antibx 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2178	Pt not elig low neuro ex	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2179	Med doc rsn no low ex	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2180	Inelig footwr eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2181	Bmi not doc medrsn ptref	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2182	Pt 1st biolog antirheum	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2183	Doc pt unable comm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2184	No caregiver	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2185	Caregiver dem trained	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2186	Pt ref app rsrcs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2187	Clin ind img hd trauma	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2188	Pt 50 yrs w/clin ind hd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2189	Img hd abnml neuro exam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2190	Ind img hd rad neck	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2191	Ind img hd pos hd ache	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2192	>55 yrs temp hd ache	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2193	<6yr new onset hd ache	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2194	New hdache ped pt dis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2195	Occip hdache child	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2196	Screen unhlthy etoh use	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G2197	Screen hlthy etoh use	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2199	Not scrn etoh no rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2200	Unhlthy etoh rcvd couns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2202	No rsn no brief couns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2204	Pt 50-85 w/ scope	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2205	Preg drng adjv trtmt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2206	Adjv trtmt chemo her2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2207	Rsn no trtmt chem her2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2208	No trtmt chemo and her2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2209	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G2210	No neck fs prom no rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4000	Dermatology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4001	Diagnostic Rad Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4002	Ep Cardio Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4003	Emergency Med Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4004	Endocrinology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4005	Family Medicine Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4006	Gastroenterology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4007	General Surgery Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4008	Geriatrics Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G4009	Hospitalists Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4010	Infectious Disease Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4011	Internal Medicine Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4012	Interventional Rad Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4013	Mentl/Behav Health Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4014	Nephrology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4015	Neurology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4016	Neurosurgical Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4017	Nutrition/Dietician Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4018	Ob/Gyn Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4019	Oncology/Hema Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4020	Ophthalmology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4021	Orthopedic Surgery Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4022	Otolaryngology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4023	Pathology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4024	Pediatric Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4025	Physical Medicine Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4026	Phys/Occ Therapy Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4027	Plastic Surgery Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4028	Podiatry Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G4029	Preventive Medicine Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4030	Pulmonology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4031	Radiation Oncology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4032	Rheumatology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4033	Skilled Nursing Facility Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4034	Speech Language Path Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4035	Thoracic Surgery Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4036	Urgent Care Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4037	Urology Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G4038	Vascular Surgery Ss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8395	Left Ventricular Ejection Fraction (lvef) >= 40% O	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8396	Left Ventricular Ejection Fraction (lvef) Not Perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8397	Dilated Macular Or Fundus Exam Performed, Includin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8399	Patient With Central Dual-energy X-ray Absorptiome	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8400	Patient With Central Dual-energy X-ray Absorptiome	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8404	Lower Extremity Neurological Exam Performed And Do	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8405	Lower Extremity Neurological Exam Not Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8410	Footwear Evaluation Performed And Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8415	Footwear Evaluation Was Not Performed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8416	Clinician Documented That Patient Was Not An Eligi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8417	Bmi >= 30 Was Calculated And A Follow-up Plan Was	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8418	Bmi < 22 Was Calculated And A Follow-up Plan Was D	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8419	Bmi >= 30 Or < 22 Was Calculated, But No Follow-up	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8420	Bmi < 30 And >= 22 Was Calculated And Documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8421	Bmi Not Calculated	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8427	Written Provider Documentation Was Obtained Confir	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8428	Current Medications With Dosages (includes Prescri	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8430	Documentation That Patient Is Not Eligible For Med	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8431	Documentation Of Clinical Depression Screening Usi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8432	No Documentation Of Clinical Depression Screening	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8433	Patient Not Eligible/not Appropriate For Clinical	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8450	Beta-blocker Therapy Prescribed For Patients With	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8451	Clinician Documented Patient With Left Ventricular	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8452	Beta-blocker Therapy Not Prescribed For Patients W	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8465	High Risk Of Recurrence Of Prostate Cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8473	Angiotensin Converting Enzyme (ace) Inhibitor Or A	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8474	Angiotensin Converting Enzyme (ace) Inhibitor Or A	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8475	Angiotensin Converting Enzyme (ace) Inhibitor Or A	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8476	Most Recent Blood Pressure Has A Systolic Measurem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8477	Most Recent Blood Pressure Has A Systolic Measurem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8478	Blood Pressure Measurement Not Performed Or Docume	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8510	Negative Screen For Clinical Depression Using A St	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8511	Screen For Clinical Depression Using A Standardize	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8535	No Documentation Of An Elder Maltreatment Screen,	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8536	No Documentation Of An Elder Maltreatment Screen,	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8539	Documentation Of A Current Functional Outcome Asse	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8540	Documentation That The Patient Is Not Eligible For	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8541	No Documentation Of A Current Functional Outcome A	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8542	Documentation Of A Current Functional Outcome Asse	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8543	Documentation Of A Current Functional Outcome Asse	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8559	Pt ref doc oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8560	Pt hx act drain prev 90 days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8561	Pt inelig for ref oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8562	Pt no hx act drain 90 d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8563	Pt no ref oto reas no spec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8564	Pt ref oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8565	Ver doc hear loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8566	Pt inelig ref oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8567	Pt no doc hear loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8568	Pt no ref otolo no spec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8569	Prol intubation req	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8570	No prol intub req	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8575	Postop ren insuf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8576	No postop ren insuf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8577	Reop req bld grft oth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8578	No reop req bld grft oth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8598	Asp therp used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8599	No asp therp used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8600	tPA initi w/in 3 hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8601	No elig tPA init w/in 3 hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8602	No tPA init w/in 3 hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8633	Pharm ther osteo rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8635	No pharm ther osteo rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8647	Fun stat score knee >= 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8648	Fun stat score knee < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8650	Fun stat score knee not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8651	Fun stat score hip >= 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8652	Fun stat score hip < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8654	Fun stat score hip not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8655	Fun stat score LE >= 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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G8656	Fun stat score LE < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8658	Fun stat score LE not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8659	Fun stat score LS >= 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8660	Fun stat score LS < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8661	Fun stat score LS pt no elg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8662	Fun stat score LS not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8663	Fun stat score shdl >=0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8664	Fun stat score shdl < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8666	Fun stat score shdl not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8667	Fun stat score UE >=0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8668	Fun stat score UE < 0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8670	Fun stat score UE not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8694	Lvef <40%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8708	Antibiotic not pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8709	Med reas antibiotic pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8710	Pt pres antibiotic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8711	Pres antibiotic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8712	Not pres antibiotic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8721	Pt, pn, hist grade doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8722	Med reas pt, pn, not doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G8723	Spec sit not prim tumor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8724	Pt, pn, hist grade not doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8733	Doc pos elder mal scrn plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8734	Doc neg elder mal no plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8735	Eld mal scrn pos no plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8749	Signs of melanoma absent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8752	Sys bp less 140	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8753	Sys bp > or = 140	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8754	Dias bp less 90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8755	Dias bp > or = 90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8756	No bp measure doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8783	Bp scrn perf rec interval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8785	Bp scrn no perf at interval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8797	Specimen site not esophagus	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8798	Specimen site not prostate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8806	Transab or transvag us	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8807	Doc reas no us	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8808	No transab or transvag us	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8815	Doc reas no statin therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8816	Statin med pres at disch	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8817	Doc reas no statin med disch	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8826	Pt disch home day #2 evar	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8833	Pt not disch home day#2 evar	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8834	Pt disch home day #2 cea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8838	Not disch home by day #2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8839	Sleep apnea assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8840	Doc reas no sleep apnea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8841	No sleep apnea assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8842	Ahi or rdi initial dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8843	Doc reas no ahi or rdi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8844	No ahi or rdi initial dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8845	Pos airway press prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8846	Mod or severe osa	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8849	Doc reas no pos air press	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8850	No pap prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8851	Adhere pos air press therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8854	Reas no adhere pos air pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8855	Pos air press adhere no perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8856	Ref for oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8857	No elig ref for oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8858	Not ref for oto eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8863	No assess bone loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8864	Pneumococcal vaccine admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8865	Doc med reas no pneumococcal	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8866	Doc pt reas no pneumococcal	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8867	No pneumococcal admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8869	Doc immun hep b 1st antitnf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8875	Breast cancer dx min invsive	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8876	Doc reas no min inv dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8877	No brst cncr dx min invasive	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8878	Sent lymph node biopsy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8880	Doc reas no lymph node biop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8881	Brst cncr stage > t1n0m0	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8882	No sent lymph node biopsy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8907	Pt doc no events on discharge	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8908	Pt doc with burn prior to discharge	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8909	Pt doc with no burn prior to discharge	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8910	Pt doc to have fall in ASC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8911	Pt doc no fall in ASC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8912	Pt doc with wrong event	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8913	Pt doc with no wrong event	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8914	Pt trans to hospital post discharge from ASC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8915	Pt not trans to hospital at discharge from ASC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8916	Pt with IV AB given on time	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8917	Pt with IV AB not given on time	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8918	Pt w/o preop order IV AB prop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8923	LVEF < 40% or lvsd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8924	Spiro EV1/FVC <60% COPD sym	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8934	LVEF <40% or dep lv sys fcn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8935	Rx ACE or ARB therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8936	Pt not eligible ACE/ARB	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8937	No rx ACE/ARB therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8942	Doc fcn/care plan w/30 days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8944	AJCC Mel cnr stg 0 - IIC	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8946	MIBM but no dx of breast CA	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8950	Pre-htn or htn doc, f/u indc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8952	Pre-htn/htn, no f/u, not gvn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8955	Most recent assess vol mgmt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8956	Pt rcv HeDia outpt dyls fac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8958	Assess vol mgmt not doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G8961	CSIT lowrisk surg pts preop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8962	CSIT on pt any reas 30 days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8967	Wrfrn or oral antigoag pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8968	Md rsn no pres Wrfrn or othr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8969	Pt rsn no pres Wrfrn or othr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G8970	No rsk fac or 1 mod risk TE	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9001	Coordinated Care Fee Initial Rate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9002	Coordinated Care Fee Maint Rate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9003	Coord Care Fee Risk Adjustd Hi Init	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9004	Coord Care Fee Risk Adjustd Lw Init	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9005	Coord Care Fee Risk Adjusted Maint	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9006	Coord Care Fee Home Monitoring	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9007	Coord Care Fee Schedule Team Conf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9008	Coord Care Fee Phys Ovrsight Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9009	Coord Care Fee Risk Adj Maint Lvl 3	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9010	Coord Care Fee Risk Adj Maint Lvl 4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9011	Coord Care Fee Risk Adj Maint Lvl 5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9012	Coord Care Fee Risk Adj Maint Oth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9013	Esrd Demo Basic Bundle Level I	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9014	Esrd Demo Expnd Bundle W/venus Acss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9016	Smok Cessatn Cnsl Ind Absnc/add E&m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9037	Intrpro Req Fr Rec Phys/Qhcp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9038	Co-Management Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9050	Onc; Prim Focus; Wrkup Eval/stag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9051	Onc; Prim Focus; Tx Decision Optns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9052	Onc; Prim; Surveillance Recur;	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9053	Onc; Prim; Expect Mgmt Evidence Ca;	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9054	Onc;prim;sup Pt Term Ca;palliatv Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9055	Onc;prim;oth Uns Not Otherwise List	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9056	Onc;prac Guide;mgmt Adhers To Guide	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9057	Onc; Prac; Mgmt Differ Clin Trial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9058	Onc; Mgmt Diffr Phys Disagree Guide	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9059	Onc;prac;mgmt Differs Pt Opt Alt Tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9060	Onc; Prac; Mgmt Differ Comorbid Ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9061	Onc; Pts Cond Not Addressed Guide	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9062	Onc; Prac; Mgmt Differs Oth Reason	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9063	Onc; Status; Nsclc; St I No Progrsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9064	Onc; Status; Nsclc;st Ii No Progrsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9065	Onc;nsclc; St Iii A No Progressn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9066	Onc; Status; Nsclc; St Iii B-4 Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9067	Onc; Status; Nsclc; Extent Dz Unkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9068	Onc; Status; Sc&comb;ltd No Progrsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9069	Onc; Status; Sclc Sc&comb; Ext Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9070	Onc;status;sclc Sc&comb;extent Unkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9071	Onc; Brst; Aca;st I/ii;pos; No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9072	Onc; Brst; Aca; St I/ii;neg;no Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9073	Onc; Brst; Aca; St Iii; Pos;no Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9074	Onc; Brst; Aca; St Iii; Neg;no Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9075	Onc; Status; F Brst Ca; Aca; M1 Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9077	Onc;pros Ca;t1-t2c& Psa</=20no Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9078	Onc; Pros Ca; T2 Psa >20 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9079	Onc;pros Ca; T3b-t4 N; T N1 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9080	Onc; Pros Ca; Tx Rising Psa	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9083	Onc; Pros Ca Aca; Extent Unkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9084	Onc; Colon Ca; T1-3 N0 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9085	Onc; Colon Ca; T4 N0 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9086	Onc; Colon Ca; T1-4 N1-2 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9087	Onc; Colon Ca; M1 Met W/curr Dz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9088	Onc; Colon Ca; M1 Met No Curr Dz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9089	Onc; Status; Colon Ca; Extent Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9090	Onc; Rectal Ca; T1-2 N0 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9091	Onc; Rectal Ca; T3 N0 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9092	Onc; Rectal Ca;t1-3 N1-2 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9093	Onc; Rectal Ca; T4 Any N M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9094	Onc; Status; Rectal Ca; M1 Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9095	Onc; Status; Rectal Ca; Extent Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9096	Onc;esoph Ca;t1-t3 N0-n1/nx No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9097	Onc; Esoph Ca; T4 Any N M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9098	Onc; Status; Esoph Ca ; M1 Metastat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9099	Onc; Status; Esoph Ca; Extent Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9100	Onc; Gastr Ca; R0 Resect No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9101	Onc; Gastr Ca; R1/r2 Resect No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9102	Onc; Gastr Ca; M0 Unresect No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9103	Onc; Status; Gastr Ca; Clin M1 Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9104	Onc; Status; Gastr Ca ; Extent Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9105	Onc; Pan Ca; R0 Resect No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9106	Onc; Pan Ca; R1/r2 Resect No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9107	Onc; Pan Ca; Unresectbl M1 Met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9108	Onc; Status; Pan Ca; Extent Dz Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9109	Onc; H&n Ca; T1-t2&n0 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9110	Onc;h&n Ca; T3-4&/n1-3 M0 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9111	Onc; Status; H&n Ca; M1 Met Loc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9112	Onc; Status; H&n Ca; Extent Unkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9113	Onc; Ov Ca; St Ia-b Gr 1 No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9114	Onc; Ov Ca; St Ia-b; Ic; Ii;no Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9115	Onc; Ov Ca; St Iii-iv; No Prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9116	Onc; Ov Ca; Progrssn&/platinm Rsist	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9117	Onc; Status; Ov Ca; Extent Unkn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9123	Onc; Nhl Transto Dlbcl; Relapsed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9124	Onc; Nhl; Relapsed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9125	Onc;nhl; Stage Not Detrm Poss Relap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9126	Onc; Status; Ov Ca; Stage Ia/ib	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9128	Onc; Status; Mm; Stage Ii /higher	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9129	Onc; Cml; Extnt Unk Tx Opt Considrd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9130	Onc; Status; Mx Myeloma; Extent Unk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9131	Onc Dx Brst Unknown Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9132	Onc Dx Prostate Mets No Cast	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9133	Onc Dx Prostate Clinical Mets	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9134	Onc Nhlstg 1-2 No Relap No	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9135	Onc Dx Nl Stg 3-4 Not Relap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9136	Onc Dx Nhl Trans To Ig Bcell	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9137	Onc Dx Nhl Relapse/refractor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9138	Onc Dx Nhl Stg Unknown	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9139	Onc Dx Coml. Dx Status Unknown	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9140	Frontier Extended Stay Clin Demo;	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9143	Warfarin respon genetic test	Investigational Denial	Always considered investigational; investigational services are denied member liability.
G9148	Medical Home Level I	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9149	Medical Home Level II	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9150	Medical Home Level III	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9151	MAPCP demo state	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9152	MAPCP demo community	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9153	MAPCP demo physician	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9187	BPCI home visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9188	Beta not given no reason	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9189	Beta pres or already taking	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9190	Medical reason for no beta	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9191	Pt reason for no beta	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9212	Doc of dsm-iv init eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9213	No doc of dsm-iv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9223	Pjp proph ordered cd4 low	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9225	Norsn no foot exam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9226	3 comp foot exam completed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9227	Docrsn no care plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9228	Gc chl syp documented	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9230	Norsn for gc chl syp test	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9231	Doc esrd dia trans preg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9242	Doc viral load >=200	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9243	Doc viral load <200	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9246	No med visit in 24mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9247	1 med visit in 24mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9254	Doc pt dischg >2d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9255	Doc pt dischg <=2d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9273	Sys<140 and dia<90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9274	Bp out of nrml limits	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9275	Doc of non tobacco user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9276	Doc of tobacco user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9277	Doc daily aspirin or contra	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9278	Doc no daily aspirin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9279	Pne scrn done doc vac done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9280	Pne not given norsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9281	Pne scrn done doc not ind	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9282	Doc medrsn no histo type	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9283	Hist type doc on report	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9284	No hist type doc on report	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9285	Site not small cell lung ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9286	Doc antibio order w in 7d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9287	No doc antibio order w in 7d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9288	Doc medrsn no hist type rpt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9289	Doc type nsm lung ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9290	No doc type nsm lung ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9291	Not nsm lung ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9292	Medrsn no pt category	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9293	No pt category on report	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9294	Pt cat and thck on report	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9295	Non cutaneous loc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9296	Doc share dec prior proc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9297	No doc share dec prior proc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9298	Eval risk vte card 30d prior	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9299	No eval riskk vte card prior	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9305	No interv req for leak	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9306	Interv req for leak	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9307	No ret for surg w in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9308	Unplnd ret to surg w in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9309	No unplnd hosp readm in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9310	Unplnd hosp readm in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9311	No surg site infection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9312	Surgical site infection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9313	Docrsn not first line amox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9314	Norsn not first line amox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9315	Doc first line amox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9316	Doc comm risk calc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9317	No doc comm risk calc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9318	Image std nomenclature	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9319	Image not std nomenclature	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9321	Doc count of ct in 12mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9322	No doc count of ct in 12mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9341	Srch for ct w in 12 mos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9342	No srch for ct in 12mo norsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9344	Sysrsn no dicom srch	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9345	Follow up pulm nod	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9347	No follow up pulm nod norsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9351	Doc >1 sinus ct w 90d dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9352	Not >1 sinus ct w 90d dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9353	Medrsn >1 sinus ct w 90d dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9354	Norsn >1 sinus ct w 90d dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9355	No early ind/delivery	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9356	Early ind/delivery	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9357	Pp eval/edu perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9358	Pp eval/edu not perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9361	Medical indication for induction	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9364	Sinus caus bac inx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9367	2high risk med ord	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9368	2high risk no ord	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9380	Off assis eol iss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9382	No off assis eol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9383	Recd scrn hcv infec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9384	Doc med reas no offer eol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9385	Doc pt reas not rec hcv srn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9386	Scrn hcv infec not recd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9393	Ini phq9 >9 remiss <5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9394	Dx bipol, death, nhres, hosp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9395	Ini phq9 >9 no remiss >=5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9396	Ini phq9 >9 not assess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9408	Card tamp w/in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9409	No card tamp e/in 30d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9410	Admit w/in 180d req remov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9411	No admit w/in 180d req remov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9412	Admit w/in 180d req surg rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9413	No admit req surg rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9414	1dose menig vac btwn 11 & 13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9415	No 1dose meni vac btwn 11&13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9416	Tdap or td or 1tet/dipth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9417	No tdap or td or 1tet/dipth	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9418	Lungcx bx rpt docs class	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9419	Med reas no rpt histo type	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9420	Spec site no lung	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9421	Lung cx bx rpt no doc class	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9422	Rpt doc class histo type	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9423	Med reas rpt no histo type	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9424	Site no lung or lung cx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9425	Spec rpt no doc class histo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9426	Impr med time edarr pain med	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9427	No impro med time pain med	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9428	Rpt pt cat and pt1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9429	Doc med reas no pt cat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9430	Spec site no cutaneous	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9431	No pt cat and pt1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9432	Asth controlled	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9434	Asth not controlled	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9452	Doc med reas no scrn hcv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9455	Abd imag w/us, ct or mri	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9456	Doc med pt reas no hcc scrn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9457	No abd imag w/o reason	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9468	No recd cortico>=10mg/d >60d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9470	No rec cortico>60d 1rx 600mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9471	W/in 2yr dxa not order	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9474	Diet counsel at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9475	Other counselor at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9476	Volun service at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9477	Care coord at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9478	Othe therapist at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9479	Pharmacist at hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9480	Admission to mccm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9481	Remote E/M new pt 10 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9482	Remote E/M new pt 20 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9483	Remote E/M new pt 30 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9484	Remote E/M new pt 45 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9485	Remote E/M new pt 60 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9486	Remote E/M est. pt 10 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9487	Remote E/M est. pt 15 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9488	Remote E/M est. pt 25 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9489	Remote E/M est. pt 40 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9490	Joint replac mod home visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9497	Preop anes or proxy b/4 surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9498	Abx reg prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9500	Rad exp time w/fluor doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9501	Rad exp time w/o fluor doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9502	Med reas no perf foot exam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9504	Doc reas no hbv status	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9505	Abx pres w/in 10 dys of symp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9507	Doc reas on statin or contra	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9508	Doc pt not on statin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9509	Remis 12m phq-9 score <5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9510	Remis 12m not phq-9 score <5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9511	Phq-9 >9 during 12m time	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9512	Indiv pdc > 0.8	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9513	Indiv pdc not > 0.8	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9514	Req ret or w/in 90d of surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9515	No reas, no ret or w/in 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9516	Impr vis acuit w/in 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9517	No impr vis acuit w/in 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9518	Doc active inj drug use	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9519	Final refract +/- 1.0 in 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9520	Refract not +/- 1.0 w/in 90d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9521	Er and ip hosp <2 in 12 mos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9522	Er/ip hosp =/>2 in 12 mos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9529	Minor blunt trauma w/head ct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9530	Min hd traum gcs=15 w/ct ed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9531	Indic for head ct valid	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9533	Indic for head ct not valid	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9534	Adv brain image not ordered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9535	Normal neuro exam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9536	Doc med reas adv brain image	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9537	Doc system reas adv imaging	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9538	Adv brain image ordered	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9539	Intent pot remv time placemt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9540	Pt alive 3 mos post proc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9541	Filter gone aft 3mos placmt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9542	Doc reass appr remo filt 3ms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9543	Doc 2x re-assess filt remov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9544	No filt remov w/in 3mos plcm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9547	Incid ct liver/kid/adre fdg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9548	Abd imag and followup rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9549	Doc med reas no follow imag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9550	Abd imag and followup no rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9551	Abd imag w/o liv/kid/adr les	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9552	Inc thyr node <1.0 in rpt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9553	Prior thyroid dise dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9554	Ct/mri chest/neck follup rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9555	Doc med reas no follow imag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9556	Ct/mri chest follup not rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9557	Ct/mri chest/neck no thy nod	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9580	Door to punc time <2hrs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9582	Door to punc time >2hr, nrg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9593	Low pecarn ped head trauma	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9594	Gsc >15 & hd ct by ed md	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9595	Val rsn hd ct ord reg indic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9597	No low pecarn ped head traum	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9598	Aor ane 5.5-5.9 cm max diam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9599	Aor ane >=6.0 cm max diam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9603	Pt surv improv bsline tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9604	Pt surv results not avail	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9605	Surv score no improv w/tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9606	Intraop cyst eval trac inj	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9607	Pt not elig	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9608	Intraop cyst eval not done	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9609	Doc order anti-plat or p2y12	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9610	Doc md rsn no antipla/p2y12	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9611	No antipla/p2y12 ord, rs nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9621	Scr unheal etoh w/counsel	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9622	No unheal etoh user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9624	No etoh scr/no counc/nrg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9625	Bld inj at surg/1mos post	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9626	Pt not elig	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9627	No bld inj at surg/1mos post	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9628	Vis inj at surg/1mos post	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9629	Pt not elig	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9630	No vis inj at surg/1mos post	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9637	Doc >1 dose reduc tech	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9638	No doc >1 dose reduc tech	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9642	Current cig smoker	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9643	Elective surgery	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9644	No smok b/4 anes day of surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9645	Had smoke b/4 anes day surg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9646	Pt w/90d mrs 0-2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9648	Pt w/90d mrs >2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9649	Psori tool doc w/benchmk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9651	Psori tool doc/no bnchmk met	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9654	Mon anesth care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9655	Toc tool incl key elem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9656	Pt direct anesth loc to pacu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9658	Toc tool incl elem not used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9659	>85y no hx colo ca/rsn scope	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9660	Doc med rsn scope pt >85y	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9661	>85y scope othr rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9662	Prior dx/active clin ascvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9663	Fast/dir ldl = 190 mg/dl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9664	Taking statin or rec'd order	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9665	No statin/no order statin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9674	Pt w/clin ascvd dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9675	Pt w/fast/dir lab ldl-c >190	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9676	40-75y w/type 1/2 w/ldl-c rs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9679	Acute care pneumonia	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9680	Acute care congestive heart	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9681	Acute care chronic obstruct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9682	Acute care skin infection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9683	Actue care fluid or electrolyte disorder	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9684	Acute care urinary tract infection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9685	Acute nursing facility care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9687	Hospice anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9688	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9689	Inpt elect carotid intervent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9690	Pt rec hospice dur msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9691	Pt hosp dur msmt period	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9692	Hosp recd by pt dur msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9693	Pt use hosp during msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9694	Hosp srv used pt in msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9695	Long act inhal bronchdil pre	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9696	Med rsn no presc bronchdil	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9698	Sys rsn no presc bronchdil	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9699	Long inhal bronchdil no pres	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9700	Pt is w/hosp during msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9702	Pt use hosp during msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9703	Child anbx 30 prior dx phary	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9704	Ajcc br ca stg i: t1 mic/t1a	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9705	Ajcc br ca stg ib	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9706	Low recur prost ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9708	Bilat mast/hx bi /unilat mas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9709	Hosp srv used pt in msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9710	Pt prov hosp srv msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9711	Pt hx tot col or colon ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9712	Doc med rsn presc anbx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9713	Pt use hosp during msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9714	Pt is w/hosp during msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9716	Bmi not norm, no follow, doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9717	Doc dx depr/dx bipol, no scr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9719	Pt not ambul/immob/wc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9720	Hospice anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9721	Pt not ambul/immob/wc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9722	Doc hx renal fail or cr+ >4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9723	Hosp recd by pt dur msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9724	Pt w/doc use anticoag mst yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9726	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9727	No knee intake prom, no prox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9728	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9729	No hip intake prom, no proxy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9730	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9731	No foot prom, no proxy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9732	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9733	No back intake prom, no prox	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9734	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9735	Pt no foto knee and no proxy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9736	Refused to participate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9737	Pt no foto elbow, no proxy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9740	Hosp srv to pt dur msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9741	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9742	Psych sympt assessed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9743	Psych symp not assessed, rns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9744	Pt not elig, dx htn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9745	Doc rsn no scr high bp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9746	Mit sten, valve or trans af	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9752	Urgent surgery	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9753	Doc no dicom, ct other fac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9754	Incid pulm nodule	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9755	Doc med rsn for imaging	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9756	Surg proc w/silicone oil	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9757	Surg proc w/silicone oil	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9758	Hospice or term phase	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9761	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9762	Pt had hpv b/t 9-13 yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9763	Pt no hpv b/t 9-13 yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9764	Pt tx oral syst/bio med psor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9765	Pt decl chan/conind or <6m	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9766	Cva stroke dx tx transf fac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9767	Hosp new dx cva consid evst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9768	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9769	Bn den 2yr/got ost med/ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9770	Perip nerve block	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9771	Anes end, 1 temp >35.5(95.9)	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9772	Doc temp >35.5(95.9), anest	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9773	No temp >35.5(95.9), anes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9775	Recd 2 anti-emet pre/intraop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9776	Doc med rsn no proph antiem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9777	Pt no antiemet pre/intraop	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9779	Pts breastfeeding	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9780	Pts dx w/rhabdomyolysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9781	Doc rsn no statin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9782	Hx dx fam/pure hypercholes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9784	Path/derm 2nd opin bx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9785	Path rpt snt path/derm in 7d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9786	No path rpt sent in 7d	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9787	Pt alive lst day msmt yr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9788	Most rct bp </= 140/90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9789	Record bp ip, er, urg/self	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9790	Most rct bp >/= 140/90	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9791	Most rct tob stat free	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9792	Most rct tob stat not free	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9793	Pt on daily asa/antiplat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9794	Doc med rsn no asa/antiplat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9795	Pt no daily asa/antiplat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9796	Pt not currently on statin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9797	Pt currently on statin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9805	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9806	Pt recd cerv cyto/hpv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9807	Pt no recd cerv cyto/hpv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9812	Pt died during inpt/30d aft	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9813	Pt not died w/in 30d of proc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9818	Doc sex activity	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9819	Pt w/hosp anytime msmt per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9820	Doc chlam scr test w/follow	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9821	No doc chlam scr ts w/follow	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9822	Endo abl proc yr prev ind dt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9823	Endo smpl/hyst bx res doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9824	Endo smpl/hyst bx res no doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9830	Her-2 pos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9831	Ajcc stg brt ca dx ii or iii	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9832	Brt ca dx i, no t1/t1a/t1b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9838	Pt met dis at dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9839	Anti-egfr mon anti ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9840	Kras tst bfr beg anti moab	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9841	No kras tst bfr beg ant moab	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9842	Pt met dis at dx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9843	Kras gene mut	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9844	Pt no recd anti-egfr ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9845	Pt recd anti-egfr ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9846	Pt died from cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9847	Pt recd chemo last 14d life	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9848	Pt no chemo last 14d life	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9858	Pt enroll hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9859	Pt died from cancer	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Clinical Edits by Code List
Complete List
Applies to Uniform Medical Plan (UMP)

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

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Code	Description	Edit Type	Comment
G9860	Pt less 3d hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9861	Pt more than 3d hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9862	Doc rsn no 10 yr follow	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9868	Asynch telehealth derm/ophth 10 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9869	Asynch telehealth derm/ophth 10-20 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9870	Asynch telehealth derm/ophth 20 or> min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9873	1 EM core session	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9874	4 EM core sessions	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9875	9 EM core sessions	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9876	2 EM core MS mo 7-9 no weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9877	2 EM core MS mo 10-12 no weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9878	2 EM core MS mo 7-9 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9879	2 EM core MS mo 10-12 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9880	EM 5 percent weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9881	EM 9 percent weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9882	2 EM ongoing MS mo 13-15 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9883	2 EM ongoing MS mo 16-18 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9884	2 EM ongoing MS mo 19-21 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9885	2 EM ongoing MS mo 22-24 weight loss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9886	In-person attendance g code	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
G9887	Distance learning attendance	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9888	Maintenance 5% WL from baseline weight in months 7-12	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9890	EM Bridge Payment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9891	EM session reporting	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9894	Adr dep thrpy prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9895	Doc med rsn no adr dep thrpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9896	Doc pt rsn no adr dep thrpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9897	Pt nt prsc adr dep thrpy rng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9898	Snp/lg trm cre pt w/pos cde	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9899	Scrn mam perf rslts doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9900	Scrn mam perf rslts not doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9901	Snp/lg trm cre pt w/pos cde	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9902	Pt scrn tbco and id as user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9903	Pt scrn tbco id as non user	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9905	No pt tbco scrn rng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9906	Pt recv tbco cess interv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9908	No pt tbco cess interv rng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9910	Snp/lg trm cre pt w/pos cde	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9911	Node neg pre/post syst ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9912	Hbv status assesed and int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9913	No hbv status assesd and int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9914	Pt receiving anti-tnf agent	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9915	No documntd hbv results rcd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9916	Funct status past 12 months	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9917	Doc med rsn no funct status	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9918	No funct stat perf, rsn nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9922	Sfty cncrns scrn nd mit recs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9923	Safty cncrns scrn and neg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9925	No scrn prov rsn nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9926	Sfty cncrns scrn but no recs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9928	No warf or fda drug presc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9929	Trs/rev af	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9930	Com care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9931	No chad or chad scr 0 or 1	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9938	Snp/lg trm cre pt w/pos cde	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9939	Same path/derm perf biopsy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9940	Doc reas no statin therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9943	Bk pn nt msr vas scl pre/pst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9945	Pt w/cancer scoliosis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9946	Bk pn nt msr vas pre-pst 1y	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9949	Lg pn nt msr vas scl pre/pst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9954	Pt >2 rsk fac post-op vomit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9955	Inhlnt anesth only for induc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9956	Combo thrpy of >= 2 prophly	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9957	Doc med rsn no combo thrpy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9958	No combo prohpyl thrp for pt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9959	Systemic antimicro not presc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9960	Med rsn sys antimi nt rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9961	Systemic antimicro presc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9962	Embolization doc separatly	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9963	Embolization not doc separat	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9964	Pt recv >=1 well-chld visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9965	No well-chld vist recv by pt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9968	Pt refrd 2 pvdr/spclst in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9969	Pvdr rfrd pt rprt rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9970	Pvdr rfrd pt no rprt rcvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9976	Doc pat rsn no mac exm perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9977	Dil mac exam no perf rsn nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9978	Remote E/M new patient 10 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9979	Remote E/M new patient 20 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
G9980	Remote E/M new patient 30 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9981	Remote E/M new patient 45 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9982	Remote E/M new patient 60 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9983	Remote E/M est. patient 10 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9984	Remote E/M est. patient 15 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9985	Remote E/M est. patient 25 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9986	Remote E/M est. patient 40 mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9987	BPCI advanced in home visit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9988	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9992	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9993	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9994	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9996	Doc Pt Pal Or Hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9997	Doc Pt Preg Dur Msrmt Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9998	Doc Med Rsn <3 Colon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
G9999	Doc Sys Rsn <3 Colon	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0001	Alcohol And/or Drug Assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0003	Alcohl&/rx Scr;lab Analy Alcohl&/rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0004	Behavioral Health Cnsl&tx-15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0005	Alcohl&/rx Srvc; Grp Cnsl Clinician	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
H0008	Alcohl&/rx Srvc;sub-ac Dtox Hosp Ip	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0009	Alcohl&/rx Srvc; Acute Dtox Hosp Ip	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0010	Alcohl&/rx Srvc; Sub-ac Dtox Res Ip	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0011	Alcohl&/rx Srvc;ac Dtox Res Prog Ip	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0012	Alcohl&/rx Srvc; Sub-ac Dtox Res Op	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0013	Alcohl&/rx Srvc;ac Dtox Res Prog Op	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0014	Alcohl &/ Rx Srvc; Amb Dtoxfication	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0016	Alcohl &or Rx Srvc; Medical/somatic	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0017	Bhval Health; Res W/o Room&bd-diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0018	Bhval Hlth; Shrt-term Res Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0019	Bhval Hlth; Lng-term Res Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0031	Mental Health Assess Non-physician	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0032	Mentl Hlth Srvc Plan Dvlp Non-phys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0035	Mental Health Part Hosp Tx < 24 Hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0046	Mental Health Services Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0049	Alcohol/drug Screening	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0050	Alcohol/drug Service 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0052	Mmip mental health and care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H0053	Ht mental health and care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H1000	Prenatal Care At-risk Assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
H1001	Prenatal at risk Enhncd Srvc; Antprtm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H1002	Prenatal at risk Enhncd Srvc; Coord	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H1003	Prenatal at risk Enhncd Srvc; Ed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H1004	Prenatal at risk Enhncd Srvc; F/u Hom	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H1005	Prenatal at risk Enhncd Srvc Pkg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2013	Psyc Health Facl Service Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2014	Skills Training&dvlp Per 15 Minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2035	Alcohol &or Oth Drug Tx Progm-hour	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2036	Alcohol &or Oth Drug Tx Progm-diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2038	Skill Train And Dev/Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2040	Coord Specialty Care, Month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
H2041	Coord Special Care Encounter	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0120	Injection Tetracycline Up To 250 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0190	Injection Biperiden Lactat Per 5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0200	Inj Alatrofloxacin Mesylate 100 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0205	Injection Alglucerase Per 10 Units	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0288	Inj Amphotericin B Cholestryl 10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0350	Injection Anistreplase Per 30 Units	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0365	Injection Aprotonin 10000 Kiu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0380	Inj Metaraminol Bitartrate 10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
J0390	Injection Chloroquine Hcl Up 250 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0395	Injection Arbutamine Hcl 1 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0400	Aripirazole Injection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0520	Inj Bethanechol Chlorid Up 5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0620	Inj Calcm Glycrophsphte&lactat-10ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0710	Inj Cephapirin Sodium To 1 Gm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0715	Inj Ceftizoxime Sodium Per 500 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0745	Inj Codeine Phosphate Per 30 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0890	Peginesatide injection	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J0945	Inj Brompheniramine Maleate-10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1180	Injection Dyphylline Up To 500 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1320	Inj Amitriptyline Hcl To 20 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1330	Inj Ergonovine Maleate Up To 0.2 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1435	Injection Estrone Per 1 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1436	Inj Etidronate Disodium Per 300 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1452	Inj Fomivirsen Sodium Io 1.65 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1457	Injection Gallium Nitrate 1 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1562	Immune Globulin Subcutaneo/brand Name - Vivaglobin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1600	Inj Gold Sodium Thiomalate To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1620	Inj Gonadoreln Hydrochlorid 100 Mcg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
J1642	Injection Heparin Sodium 10 Units	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1655	Injection Tinzaparin Sodium 1000 Iu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1675	Inj Histrelin Actat 10 Microgms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1700	Inj Hydrocortisone Actat To 25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1710	Inj Hydrocortison Sod Phos To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1730	Injection Diazoxide Up To 300 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1835	Injection Itraconazole 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1945	Injection Lepirudin 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1960	Inj Levorphanol Tartrate To 2 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J1990	Inj Chlordiazepoxide Hcl To 100 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2180	Inj Mepridin&promthzin Hcl To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2320	Inj Nandrolone Decanoate To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2460	Inj Oxytetracycline Hcl To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2513	Inj Pentastarch 10% Sol 100 Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2650	Inj Prednisolone Acetate To 1 Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2670	Injection Tolazoline Hcl To 25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2725	Injection Protirelin Per 250 Mcg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2910	Injection Aurothioglucose To 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2940	Injection Somatrem 1 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J2950	Injection Promazine Hcl Up To 25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
J2995	Inj Streptokinase Per 250000 Iu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3280	Inj Thiethylprazine Maleat To 10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3302	Inj Triamcinolone Diactat 5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3305	Inj Trimetrexate Glucoronate 25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3310	Injection Perphenazine Up To 5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3320	Inj Spctnomycn Dhydrochlord To 2 Gm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3350	Inj Urea Up To 40 Gm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3364	Injection Urokinase 5000 Iu Vial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3400	Inj Triflupromazine Hcl To 20 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3472	Inj Hyaluronidase Ovine 1000 Usp U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3490	Unclassified Drugs	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J3520	Edetate Disodium Per 150 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3530	Nasal Vaccine Inhalation	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J3535	Drug Admin Thru Metered Dose Inhal	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3570	Laetrile Amygdalin Vitamin B17	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J3590	Unclassified Biologics	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J7110	Infusion Dextran 75 500 Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7191	Factor Viii Ahf Procine Per Iu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7196	Antithrombin recombinant	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7199	Hemophilia Clotting Factor Noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
J7306	Levonorgestrel Contracptv Impl Sys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7402	Mometasone sinus sinuva	Investigational Denial	Always considered investigational; investigational services are denied member liability.
J7505	Muromonab-cd3 Parenteral 5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7513	Daclizumab Parenteral 25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7599	Immunosuppressive Drug Noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J7633	Budesonide Inhal Sol Dme-0.25 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7648	Isoetharine Hcl Inhal Sol Conc-mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7649	Isoetharine Hcl Inhal Sol U-mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7658	Isoproterenol Hcl Inhal Sol Conc-mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7659	Isoproterenol Hcl Inhal Sol U-mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7668	Metaproterenol Inhal Sol Conc-10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7669	Metaproterenol Inhal Sol U-10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J7699	Noc Rx Inhal Sol Admined Thru Dme	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J7799	Noc Rx Not Inhal Rx Admned Thru Dme	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J7999	Compounded drug, noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J8498	Antiemetic Drug Rectal/supp Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J8499	Prsc Rx Oral Nonchemothapeutic Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J8562	Oral fludarabine phosphate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J8565	Gefitinib Oral 250 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J8597	Antiemetic Drug Oral Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
J8999	Prsc Drug Oral Chemothapeutic Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
J9165	Diethylstilbestrol Diphoshat 250 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J9212	Inj Intrfern Alfacon-1 Recomb 1 Mcg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J9213	Intrferon Alfa-2a Recombinant 3 M U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J9219	Leuprolide Acetate Implant 65 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J9270	Plicamycin 2.5 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
J9999	Not Othwise Class Antineoplstc Drug	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K0008	Cstm manual wheelchair/base	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0009	Other Manual Wheelchair/base	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K0014	Oth Motorized/power Wheelchair Base	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K0108	Wc Component/accessory Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K0669	Wc Accss Seat/back Cushn No Sadmerc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0740	Repair/service oxygen equipment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0743	Portable home suction pump	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0806	POV group 2 std up to 300 lbs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0807	POV group 2 hd 301-450 lbs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0808	POV group 2 vhd 451-600 lbs	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0868	Pwc Gp 4 Std Seat/back	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0869	Pwc Gp 4 Std Cap Chair	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0870	Pwc Gp 4 Hd Seat/back	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
K0871	Pwc Gp 4 Vhd Seat/back	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0877	Pwc Gp 4 Std Sing Pow Opt S/b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0878	Pwc Gp 4 Std Sing Pow Opt Cap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0879	Pwc Gp 4 Hd Sing Pow Opt S/b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0880	Pwc Gp 4 Vhd Sing Pow Opt S/b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0884	Pwc Gp 4 Std Mult Pow Opt S/b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0885	Pwc Gp 4 Std Mult Pow Opt Cap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0886	Pwc Gp 4 Hd Mult Pow S/b	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
K0898	Power Wheelchair Noc	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K0900	Custom DME other than wheelchair	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
K1007	Bil hkaf pc s/d micro sensor	Investigational Denial	Always considered investigational; investigational services are denied member liability.
K1030	Ext Recharge Bat Replacement	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L0999	Addition To Spinal Orthosis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L1320	Pectus Carinatum Ortho Cust	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
L1499	Spinal Orthosis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L2006	Kaf sng/dbl swg/stn mcpr cus	HTCC Benefit Denial	Not a covered benefit per HTCC
L2840	Add Lw Ext Orthos Tib Len Sock Fx/=	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L2850	Add Lw Ext Ortho Fem Len Sock Fx/=	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L2861	Torsion mechanism knee/ankle	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L2999	Lower Extremity Orthoses Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
L3257	Orthoped Footwear Add Chrg Split Sz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L3649	Orthoped Shoe Mod Add/transfer Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L3999	Upper Limb Orthosis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L4394	Repl Sft Intrfce Matl Ft Drop Splnt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L4398	Ft Drop Splnt Recumbnt Pstn Devc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L5783	Add Low Ext Mec Limb Vol Sys	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
L5859	Knee-shin pro flex/ext cont	HTCC Benefit Denial	Not a covered benefit per HTCC
L5969	Ak/ft power asst incl motors	HTCC Benefit Denial	Not a covered benefit per HTCC
L5973	Ank-foot sys dors-plant flex	HTCC Benefit Denial	Not a covered benefit per HTCC
L5990	Add Lw Extrm Prosth Use Adj Heel Ht	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L5999	Lower Extremity Prosthesis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L7499	Upper Extremity Prosthesis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L7600	Prosetic Donning Sleeve Material Ea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L8031	Breast prosthesis w adhesive	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L8035	Cstm Brst Prosth Post Mastect Mold	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L8039	Breast Prosthesis Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L8048	Uns Maxlofce Prosth Br Prov Non-md	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L8499	Unlisted Proc Misc Prosth Services	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L8605	Inj bulking agent anal canal	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L8608	Arg ii ext com/sup/acc misc	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
L8678	Ext Sply Implt Neurostim	HTCC Benefit Denial	Not a covered benefit per HTCC
L8699	Prosthetic Implant Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
L8701	Pow ue rom dev ewh uprt cust	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L8702	Pow ue rom dev ewhf uprt cus	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L8720	Ext Low Ext Sens Prosthe Mec	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L8721	Receptor Sole L8720 Replace	Investigational Denial	Always considered investigational; investigational services are denied member liability.
L9900	Ortho/prosth Supp Acces &/ Serv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
L9900	Ortho/prosth Supp Acces &/ Serv	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
M0001	Advancing Cancer Care Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M0002	Opt Care Kidney Hlth Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M0004	Support Care Neur Cond Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M0005	Promot Wellness Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M0010	Eom Meos Payment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M0076	Prolotherapy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
M1003	Tb scr 12 mo pri fst bio dz	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1004	Doc med rsn no srn tb	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1005	Tb scr no perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1006	Dz not ases, no rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1007	>=50% total pt outpt ra enct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1008	<50% total pt outpt ra encts	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
M1009	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1010	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1011	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1012	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1013	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1014	Pt tx and final eval comp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1016	Pt dx meop or sur steri	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1018	Pt dx hst cr pt sk lg cr scr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1019	Adl pt mj dep ds rs 12 phq<5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1020	Adl pt mj dep ds no rs 12 mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1021	Pt uc in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1027	Img head (ct or mri) obtnd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1028	Doc of pt prm hda dx and otr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1029	Doc sysm rsn img hd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1032	Adt tkng pharmthry for oud	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1034	Adt 180 dys pharmthry oud	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1035	Adt pd out mat pr 180 dys tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1036	Adt no 180 dys pharmthry oud	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1037	Pt dx lum sp reg cacr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1038	Pt dx lum sp reg fract	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1039	Pt dx lum sp reg inf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1040	Pt dx lum idi or cong scol	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1041	Pt cr ft inf lm or pt id sl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1043	Ftl st mea sco no ot odi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1045	Fsm wth scr oks pre and post	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1046	Fsm wth scr no oks pre and p	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1049	Fsm wth scr no odi pre and p	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1051	Pt w/cancer scoliosis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1052	Lg pn nt msr vas scl pre/pst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1054	Pt uc in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1055	Aspirin used	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1056	Presc antico med in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1057	Aspirin not used, no rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1058	Pt prm nurs hm res in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1059	Pt no prm nurs hm res in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1060	Pt died in pp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1067	Hspc pt prv time meam per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1068	Pt not ambulatory	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1069	Pt scr ft fall rsk	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1070	Pt not scrn fut fall no rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1106	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1107	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1108	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1109	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1110	Oc ni pt selfdc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1111	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1112	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1113	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1114	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1115	Oc ni pt selfdc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1116	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1117	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1118	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1119	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1120	Oc ni pt selfdc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1121	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1122	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1123	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1124	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1125	Oc ni pt selfdc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
M1126	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1127	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1128	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1129	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1130	Oc ni pt self dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1131	Docu dx degen neuro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1132	Oc ni pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1133	Oc ni pt dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1134	Oc ni pt self dc 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1135	Start eoc doc med rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1141	Fs no oks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1142	Emerge cases	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1143	Ni rehab med chiro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1144	Oc no ind pt 1-2 vis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1146	Ongoing care not ind	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1147	Care not poss med rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1148	Pt self dschg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1149	No neck fs prom incap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1150	Lvef <=40% Or Mod/Sev L Vsf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1151	Pt W/ Hx Trnsplt Or Lvad	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1152	Pt W/ Hx Trnsplt Or Lvad	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1153	Pt W/ Dx Osteo Doe	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1159	Hospc Serv Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1160	Pt Anphx Due To Mengb Bef 13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1161	Pt Anphx Due To Dtp Bef 13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1162	Pt Enceph Due To Dtp Bef 13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1163	Pt Anphx Due To Hpv Bef 13	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1164	Pt W/ Dementia Any Time	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1165	Pt Use Hspc Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1166	Path Rpt Tis Spec Wle/Reexc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1167	Hspc Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1168	Pt Recd Flu Vax 7/1-6/30	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1169	Doc Med Rsn No Flu Vax	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1170	Pt W/O Flu Vax 7/1-6/30	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1171	Pt Recd 1 Td/Tdap 9Yrs Prior	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1172	Doc Med Rsn No Td/Tdap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1173	Pt No Rec Td/Tdap 9Yrs Prior	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1174	Pt W/ 1 Hzv Lv Or 2 Hzv Recm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1175	Doc Med Rsn No Hzv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1176	Pt W/O Hzv On/Aft Age 50	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1177	Pt Recd Pcv On/Aft 60	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1178	Doc Med Rsn No Pcv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1179	No Pcv Recd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1180	Pt Imm Ckpt Inhib Therapy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1181	Gr 2 Or> Dia Or Gr2 Or> Col	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1182	Not Elg Pre Ex Ibd/Uc/Crohn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1183	Doc Imm Ckpt Inhib Hld	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1184	Doc Med Rsn No Cst/Ist Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1185	Imm Ckpt Inhib Not Hld No Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1186	Pt W/ Rx For Hspc/Plltv Care	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1187	Pt W/ Esrd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1188	Pt W/ Ckd Stg 5	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1189	Doc Khe Pef W/Efgr/Uacr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1190	Doc Khe Not Pef W/Efgr/Uacr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1191	Hspc Svc Any Time In Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1192	Pt W/ Dx Sq Cell Ca Of Esoph	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1193	Rpts W/ Imp/Con Mmr/Msi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1194	Med Rsn No Imp/Con Mmr/Msi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1195	Rpt Wo Imp/Con Mmr/Msi	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1196	Ixv Nrs Vrs Iqa >=4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
M1197	Isa Red >=2 Fr Ixv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1198	Isa Not Red 2Pts Fr Ixv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1199	Pt Rec'G Rrt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1200	Ace-I/Arb Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1201	Med Rsn No Ace-I/Arb Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1202	Pt Rsn No Ace-I/Arb Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1203	No Rsn Ace-I/Arb Rx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1204	Ixv Nrs Vrs Iqa >=4	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1205	Isa Red >=2 Fr Ixv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1206	Isa Not Red 2Pts Fr Ixv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1207	#Pts Scrn Sdoh	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1208	#Pts No Scrn Sdoh	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1209	>=2 Same Hi-Rsk Med W/O Diag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1210	>=2 Same Meds Tbl4 Not Ord	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1211	Hemoglobin A1C Level >9.0%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1212	Missing Hb A1C Level	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1213	No Hx Spiro Prs Spiro>=70%	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1214	Spiro Results Wth Obs Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1215	Med Rsn For No Doc Spiro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1216	No Spiro Doc No Res Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1217	Sys Rsn No Doc Spiro	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1218	Pt Copd Symptoms	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1220	Dre Wth Interp Rtnopthy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1221	Dre W/O Rtnopthy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1222	Glaucoma Pln Of Care Not Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1223	Glaucoma Plan Of Care Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1224	Iop Dec <20% From Base	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1225	Iop Dec>=20% From Base	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1226	Iop Not Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1227	Eb Therapy Prescribed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1228	Pt + Hcv Aby +Vir W/ Rx 3 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1229	Pt W/ +Hcv +Vir Ref Win 1 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1230	Pt Hcv Rctv Aby No F/U Tst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1231	Pt Hcv Tst No Reactive Res	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1232	Pt Hcv Tst Reactive Result	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1233	Pt No Hcv Aby Or Result	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1234	Pt Hcv Rctv Aby F/U Neg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1235	Doc Pt Hcv Aby Rna Tst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1236	Baseline Mrs > 2	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1237	Pt Rsn No Scrn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1238	Doc 2Nd Recom Hzv 2-6 Mo Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1239	Pt No Resp Heard	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1240	Pt No Resp Best Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1241	Pt No Resp Seen As Person	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1242	Pt No Resp Imprt To Me	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1243	Pt Othr Thn True Heard	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1244	Pt Othr Thn True Best Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1245	Pt Othr Thn True Person	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1246	Pt Othr Thn True Imprt To Me	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1247	Pt Resp True Best Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1248	Pt Resp True Seen As Person	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1249	Pt Resp True Imprt To Me	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1250	Pt Resp True Heard	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1251	Pts Proxy Cmplt Hu Surv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1252	Pts No Cmplt Hu Survey	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1253	Pts Hu Surv No Amb Plltv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1254	Pts Deceased Prior Hu Surv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1255	Pts W/ Othr Rsn Vst,+Prg Tst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1256	Prior History Of Known Cvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1257	Cvd Risk Assess Not Perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1258	Cvd Risk Assess Perf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1259	Pt Kid Transplt Wtlst Lv Don	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1260	Pt No Kd Trnsplt Wtlst Lv Do	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1261	Pts On Wtlist Bef Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1262	Pts Transplt Bef Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1263	Pts Hosp Dialysis Dt	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1265	Cms 2728 Completed	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1266	Pts Admit Snf	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1267	Pt No Act Kid Transplt Wtlst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1268	Pt Ac Stat Kid Trnsplt Wtlst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1269	Rec'D Esrd Mcp Lst Day Of Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1270	Pts No Kid Transplt Wtlst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1271	Pts Dem Any Time/Dur Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1272	Pts Kid Transplt Wtlst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1273	Pts Snf 1 Yr Dialysis	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1274	Pts Snf Exl Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1275	Pts Hosp Exl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1276	Calc Bmi Out Nrm Param Nof/U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1277	Colorectal Ca Screen Doc Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1278	Pre-Htn Or Htn Doc, F/U Indc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1279	Pre-Htn/Htn, No F/U, Not Gvn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1280	Bilat Mast/Hx Bi /Unilat Mas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1281	Bp Scrn No Perf At Interval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1282	Pt Scrn Tbco Id As Non User	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1283	Pt Scrn Tbco And Id As User	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1284	Pt 66+ Snp Or Ltc Pos > 90D	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1285	Scrn Mam Perf Rslts Not Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1286	Bmi Doc Onl Fup Not Cmpltd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1287	Calc Bmi Blw Low Param F/U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1288	Doc Rsn No Hbp Scrn Or F/U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1289	No Pt Tbco Cess Interv Rng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1290	Pt Not Eli D/T Act Dig Htn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1291	Pt 66+ Frailty And Med Dem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1292	Pt 66+ Frail Inpt Adv Ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1293	Calc Bmi Abv Up Param F/U	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1294	Bp Scrn Perf Rec Interval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1295	Pt Hx Tot Col Or Colon Ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1296	Calc Bmi Norm Parameters	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1297	Bmi Not Doc Medrsn Ptref	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1298	Doc Pt Preg Dur Msrmt Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
M1299	Flu Immunize Order/Admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1300	Flu Imm No Admin Doc Rea	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1301	Pt Recv Tbco Cess Interv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1302	Scrn Mam Perf Rslts Doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1303	Hospc Serv Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1304	No Pneum Vax Admin 19+	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1305	Pneum Vax Admin 19+	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1306	Pt Anphx Due To Pneum	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1307	Doc Pt Pal Or Hospice	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1308	Flu Immunize No Admin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1309	Pall Serv During Meas	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1310	Pt Scr Tob & Cess Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1311	Aphlx To Vax Bef Enc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1312	No Pt Tbco Scrn Rng	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1313	No Tob Scr/Cess Int	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1314	Bmi Not Calculated	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1315	Crc No Doc No Rsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1316	Tobacco Non-User	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1317	Pts Counsl Cpt Opt Out	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1318	Pts No Csp Doc Contact	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1319	Pts Csp Doc Contact	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1320	Pts Scrn + Hrsn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1321	Pts No 7Wk Inj,No Iop,Iop>25	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1322	Pts 7Wk Inj, Scrn Iop =<25	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1323	Pts 7Wk Inj, Scrn Iop >25	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1324	Pts Intravitreal/Pci	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1325	Doc Med Rsn Not Seen	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1326	Pts Dx Hypotony	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1327	Pts No Eval Ini Xm No 8 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1328	Pts Dx Acute Vitreous Hem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1329	Pts Act Pvd 2 Wks 8 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1330	Doc Pts Rsn No F/U Xm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1331	Pts Eval Ini Xm 8 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1332	Pts No Eval Ini Xm No 2 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1333	Acute Vitreous Hemorrhage	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1334	Pts Act Pvd 2 Wks 2 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1335	Doc Pts Rsn No F/U Xm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1336	Pts Eval Ini Xm 2 Wks	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1337	Acute Pvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1338	Pt F/U 30-180 Dys No + Imprv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1339	Pts F/U 30-180 Dys + Improv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1340	Indx Whodas 2.0 Or Sds	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1341	Pt No F/U 30-180 Dys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1342	Pts Died Perf Per	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1343	Pt Pam Lvl 4 Base Or Srt Lin	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1344	Pts No Bsln Or 2Nd Pam Score	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1345	Pt Bsln Pam, 2Nd Scr 6-12 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1346	Pts No Pam 6 Pts 6-12 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1347	Pt Pam Incr 3 Pt 6-12 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1348	Pt Pam Incr 6 Pt 6-12 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1349	Pt No Pam 3 Pts 6-12 Mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1350	Pt W/ Suic Saf Pln Init Rev	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1351	Pt Cmplt Suicd Saf Pln 120Dy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1352	Suicd C-Ssrs Assessment, Equ	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1353	Pts No Cmplt Suicd Saf Pln	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1354	Pt No Suicd Saf Pln 120Dy	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1355	Suicd Based Cln Eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1356	Pt Died Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1357	Pt W/Red Suic Idea 120 Days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1358	Pts No <Suicd Idea 120 Dys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1359	Indx Suicd Idea, No 0 Scr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1360	Suicd C-Ssrs Assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1361	Suicd Based Cln Eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1362	Pt Died Dur Meas Pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1363	Pts No F/U 120 Dys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1364	Ascvd Risk >=20Pct	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1365	Hosp+Pall Care Spec Code 17	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1366	Focus On Women'S Health Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1367	Qual Care Ent Disorder Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1368	Prev Trt Inf D/O Hiv/Hep Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1369	Qualcare Mental Hlth/Sud Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1370	Rehab Support Msk Care Mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1371	Mst rec gsa<7	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1372	Mst rec gsa >=7 and<8	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1373	Mst rec gsa >=8 and <=9	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1374	Ra dx enc 90 days dur per pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1375	Ra dx enc 90 days dur per pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1376	Ra dx enc 90 days dur per pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1377	Fu colscop 10 yr doc w/ disc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1381	Pt sec strk wthin 5 days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1382	Enc dur perf pd pos 11	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1383	Acute pvd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1384	Pt died dur perf pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1385	Pt rsn not seen 2nd pam	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1386	Exc sx melmn or mlnm is	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1387	Pt died dur perf pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1388	Pt doc exm rec melmn	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1389	Pt rsn no exm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1390	Pt no doc exm for rec	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1391	All pt dx w/ rec mlnm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1392	Pt rsn no exm or lst to fu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1393	Pr no dx rec mlnm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1394	Stg i-iii br ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1395	Init chemo w/def dur ec grp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1396	Pt ther clin trial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1397	Pt w/ recur/prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1398	Bslne and fu promis doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1399	Pt lve prac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1400	Pt died dur perf pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1401	Stg i-iii br ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1402	Init chemo w/def dur ec grp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1403	Bslne and fu promis doc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1404	Pt ther clin trial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1405	Pt w/ recur/prog	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1406	Pt lve prac	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1407	Pt died dur perf pd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1408	Gmln brca bef dx ca	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1409	Recd gmln brca1/brca2 couns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1410	No gmln brca1/brca2 couns	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1411	1st ln ici no chemo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1412	Met nsclc w/ egfr alk oth ab	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1413	Pos pdl1 bef init ici tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1414	Med rsn no pdl1 bef 1st ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1415	No pos pdl1 bef ici ther	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1416	Pt rec hosp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1417	Pt up to date cov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1418	Med rsn not up to date cov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1419	Pt not up to date cov	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1420	Complete ophthalmologic mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1421	Dermatological care mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
M1422	Gastroenterology care mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1423	Opt care urologic cnd mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1424	Pulmonology care mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
M1425	Surgical care mvp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P2028	Cephalin Floculation Blood	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P2029	Congo Red Blood	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P2031	Hair Analysis	Investigational Denial	Always considered investigational; investigational services are denied member liability.
P2033	Thymol Turbidity Blood	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P2038	Mucoprotein Blood	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P9020	Platelet Rich Plasma Each Unit	HTCC Benefit Denial	Not a covered benefit per HTCC
P9603	Travl 1 Way Nec Lab Spec; Actl Mile	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P9604	Travl 1 Way Nec Lab Spec; Trip Chrg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P9612	Cath Clct Spec 1 Pt All Places Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
P9615	Catheterization Collection Specimen	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q0035	Cardiokymography	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q0091	Scr Pap Smer; Obtain Prep&convy-lab	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q0173	Trimethobenzamide Hcl 250 Mg Oral	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q0174	Thiethylperazine Maleate 10 Mg Oral	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q0181	Uns Oral Anti-emetic Not>48 Hr Dose	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
Q0515	Inj Sermorelin Actate 1 Mcg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
Q2034	Influenza virus vaccine, split virus, for IM use	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q2039	NOS flu vacc, 3 yrs & >, im	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
Q2052	IVIG demo, sevices/supplies	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q3031	Collagen Skin Test	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
Q4050	Cast Spl Unlist Types&matl Casts	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
Q4051	Splint Supplies Miscellaneous	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
Q4082	Drug/bio NOC part B drug CAP	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
Q4103	Skin Substitute, Oasis Burn Matrix, Per Square Cen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4104	Skin Substitute, Integra Bilayer Matrix Wound Dres	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4108	Skin Substitute, Integra Matrix, Per Square Centim	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4110	Skin Substitute, Primatrix, Per Square Centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4111	Skin Substitute, Gammagraft, Per Square Centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4112	Allograft, Cymetra, Injectable, 1cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4113	Allograft, Graftjacket Express, Injectable, 1cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4115	Skin substitute, alloskin, per sq centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4117	Hyalomatrix	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4118	Matristem micromatrix	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4123	Alloskin	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4124	Oasis tri-layer wound matrix	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4125	Arthroflex	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Q4126	Memoderm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4127	Talymed	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4130	Strattice tm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4134	hMatrix	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4135	Mediskin	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4136	EZderm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4137	Amnioexcel or biodexcel, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4138	Biodfence dryflex, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4139	Amnio or biodmatrix, inj 1cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4140	Biodfence 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4141	Alloskin ac, 1 cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4142	Xcm biologic tiss matrix 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4143	Repriza, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4145	Epifix, inj, 1mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4146	Tensix, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4147	Architect ecm, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4148	Neox 1k, 1cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4149	Excellagen, 0.1 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4150	Allowrap ds or dry 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4152	Dermapure 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
Q4153	Dermavest 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4155	Neoxflo or clarixflo 1 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4156	Neox 100 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4157	Revitalon 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4158	Marigen 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4160	Nushield 1 square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4161	Bio-connekt per square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4162	Amnio bio and woundex flow	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4163	Amnio bio and woundex sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4164	Helicoll, per square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4165	Keramatrix, per square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4166	Cytal, per square centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4167	Truskin, per sq centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4168	Amnioband, 1 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4169	Artacent wound, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4170	Cygnus, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4171	Interfyl, 1 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4173	Palingen or palingen xplus	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4174	Palingen or promatrx	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4175	Miroderm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
Q4176	Neopatch, per sq centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4177	Floweramnioflo, 0.1 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4178	Floweramniopatch, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4179	Flowerderm, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4180	Revita, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4181	Amnio wound, per square cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4182	Transcyte, per sq centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4183	Surgigraft, 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4184	Cellesta, 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4185	Cellesta flowab amnion 0.5cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4188	Amnioarmor 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4189	Artacent ac, 1 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4190	Artacent ac 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4191	Restorigin 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4192	Restorigin, 1 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4193	Coll-e-derm 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4194	Novachor 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4195	Puraply 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4196	Puraply am 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4197	Puraply xt 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
Q4198	Genesis amnio membrane 1sqcm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4199	Cygnus Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4200	Skin te 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4201	Matrion 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4202	Keroxx (2.5g/cc), 1cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4203	Derma-gide, 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4204	Xwrap 1 sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4205	Membrane graft or wrap sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4206	Fluid flow or fluid gf 1 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4208	Novafix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4209	Surgraft per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4211	Amnion bio or axobio sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4212	Allogen, per cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4213	Ascent, 0.5 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4214	Cellesta cord per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4215	Axolotl ambient, cryo 0.1 mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4216	Artacent cord per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4217	Woundfix biowound plus xplus	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4218	Surgicord per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4219	Surgigraft dual per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
Q4220	Bellacell HD, Surederm sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4221	Amniowrap2 per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4222	Progenamatrix, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4224	Hhf10-P Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4225	Amniobind, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4226	Myown harv prep proc sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4227	Amniocore per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4229	Cogenex amnio memb per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4230	Cogenex flow amnion 0.5 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4232	Corplex, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4233	Surfactor /nudyn per 0.5 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4234	Xcellerate, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4235	Amniorepair or altiply sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4236	Carepatch per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4237	Cryo-cord, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4238	Derm-maxx, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4239	Amnio-maxx or lite per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4240	Corecyte topical only 0.5 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4241	Polycyte, topical only 0.5cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4242	Amniocyte plus, per 0.5 cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Code	Description	Edit Type	Comment
Q4245	Amniotext, per cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4246	Coretext or protext, per cc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4247	Amniotext patch, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4248	Dermacyte amn mem allo sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4249	Amniply, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4250	Amnioamp-mp per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4251	Vim, Per Square Centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4252	Vendaje, Per Square Centimet	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4253	Zenith Amniotic Membrane Psc	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4254	Novafix dl per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4255	Reguard, topical use per sq	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4256	Mlg Complet, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4257	Relese, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4258	Enverse, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4259	Celera Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4260	Signature Apatch, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4261	Tag, Per Square Centimeter	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4262	Dual Layer Impax, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4263	Surgraft Tl, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4264	Cocoon Membrane, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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Q4265	Neostim Tl Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4266	Neostim Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4267	Neostim Dl Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4268	Surgraft Ft Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4269	Surgraft Xt Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4270	Complete Sl Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4271	Complete Ft Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4272	Esano A, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4273	Esano Aaa, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4274	Esano Ac, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4275	Esano Aca, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4276	Orion, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4278	Epieffect, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4279	Vendaje Ac, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4280	Xcell Amnio Matrix Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4281	Barrera Slor Dl Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4282	Cygnus Dual Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4283	Biovance Tri Or 3L, Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4284	Dermabind Sl, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4285	Nudyn Dl Or Dl Mesh Pr Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
Q4286	Nudyn Sl Or Slw, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4287	Dermabind Dl, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4288	Dermabind Ch, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4289	Revoshield+ Amnio, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4290	Membrane Wrap Hydr Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4291	Lamellas Xt, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4292	Lamellas, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4293	Acesso Dl, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4294	Amnio Quad-Core, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4295	Amnio Tri-Core, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4296	Rebound Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4297	Emerge Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4298	Amnicore Pro, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4299	Amnicore Pro+, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4300	Acesso Tl, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4301	Activate Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4302	Complete Aca, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4303	Complete Aa, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4304	Grafix Plus, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4305	Amer Am Ac Tri-Lay Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4306	Americ Amnion Ac Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4307	American Amnion, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4308	Sanopellis, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4309	Via Matrix, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
Q4310	Procenta, Per 100 Mg	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4311	Acesso, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4312	Acesso Ac, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4313	Dermabind Fm, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4314	Reeva, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4315	Regenelink Amniotic Mem Allo	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4316	Amchoplast, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4317	Vitograft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4318	E-Graft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4319	Sanograft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4320	Pellograft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4321	Renograft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4322	Caregraft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4323	Alloply, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4324	Amniotx, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4325	Acapatch, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4326	Woundplus, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4327	Duoamnion, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4328	Most, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4329	Singlay, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4330	Total, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4331	Axolotl Graft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4332	Axolotl Dualgraft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4333	Ardeograft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4336	Artecent C, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4337	Artecent Trident, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4338	Artacent Velos, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4339	Artacent Vericlen, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4340	Simpligraft, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4341	Simplimax, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.

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****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
Q4342	Theramend, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4343	Dermacyte Ac Matrx Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4344	Tri Membrane Wrap, Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4345	Matrix Hd Allogrft Per Sq Cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4346	Shelter dm matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4347	Rampart dl matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4348	Sentry sl matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4349	Mantle dl matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4350	Palisade dm matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4351	Enclose tl matrix, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4352	Overlay sl matrix, per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q4353	Xceed tl matrix per sq cm	Investigational Denial	Always considered investigational; investigational services are denied member liability.
Q9001	Va chaplain assessment	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9002	Va chaplain counsel individu	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9003	Va chaplain counsel group	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9004	Va Whole Health Partner Serv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9951	Locm 400/> Mg/ml Iodine Conc Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9953	Inj Ironbased Mr Contrast Agent Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9954	Oral Mr Contrast Agent Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9955	Inj Perflexane Lipid Microsphers Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9959	Hocm 150-199 Mg/ml Iodine Conc Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9962	Hocm 300-349 Mg/ml Iodine Conc Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
Q9964	Hocm 400 Or > Mg/ml Iodine Conc Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
R0076	Trans Prtble Ekg Facl/location-pt	Non-Reimbursable Services	CMS Status B, not reimbursed separately.
S0014	Tacrine Hydrochloride 10 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0021	Injection Ceftoperazone Sodium 1 Gm	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0023	Inj Cimetidine Hydrochloride 300 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0034	Injection Ofloxacin 400 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0081	Inj Piperacillin Sodium 500 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0140	Saquinavir 200 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
S0142	Colistmthate Soduim Inhal Conc-mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0177	Levamisole Hydrochloride Oral 50 Mg	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0220	Med Conf Md W/team Hlth Prof;30 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0221	Med Conf Md W/team Hlth Prof;60 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0260	Hx & Phys Related To Surgical Proc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0265	Genetic Cnsl Phys Sup Ea 15 Mins	Benefit	Possibly a benefit exclusion
S0270	Home Std Case Rate 30 Days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0271	Home Hospice Case 30 Days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0272	Home Episodic Case 30 Days	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0273	Md Home Visit Outside Cap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0274	Nurse Practr Visit Outs Cap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0280	Medical home, initial plan	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0281	Medical home, maintenance	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0310	Hospitalist Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0311	Comprehensive management care coord adv ill	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0320	Tel Calls Rn Dz Mgmt Memb Monitr;mo	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0353	Cancer treatment plan initial	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0354	Cancer treatment plan change	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S0601	Screening Proctoscopy	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S0630	Remv Suturs; Md Not Md Who Clos Wnd	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S1015	Iv Tubing Extension Set	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S1035	Artifical pancreas invasive disposable sensor	Medical Necessity	Review for medical necessity
S1036	Arifical pancreas external transmitter	Medical Necessity	Review for medical necessity
S1037	Artifical pancreas external receiver	Medical Necessity	Review for medical necessity
S1091	Stent non-coronary propel	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S2080	Laser-assisted Uvulopalatoplasty	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S2102	Islet Cell Tiss Tplnt Panc; Allogen	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S2103	Adrenal Tissue Transplant To Brain	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S2107	Adoptive Immunotx Course Treatment	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S2117	Arthroereisis Subtalar	Investigational Denial	Always considered investigational; investigational services are denied member liability.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
S2118	Total Hip Resurfacing	HTCC Benefit Denial	Not a covered benefit per HTCC
S2348	Decomp Perq Disc Rf 1/mx Lumb	HTCC Benefit Denial	Not a covered benefit per HTCC
S2900	Surg Tech Rqr Use Robotic Surg Sys	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S3005	Prfrm Msr Eval Pt Self Assess Dprss	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S3600	Stat Laboratory Request	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S3601	Emerg Stat Lab Chrg Pt Hb/nrs Facl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S3650	Saliva Test Hormone Level;menopause	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S3722	Dose optimization auc - 5fu	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S3852	Dna Analy Apoe Epsilon 4 Allele Alz	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S5013	5% Dxtros/45% N/s Kci&mgso4 1000 Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S5014	5% Dxtros/45% N/s Kci&mgso4 1500 Ml	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8096	Portable Peak Flow Meter	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8100	Hold Chamb W/inhal/nebulizr;no Mask	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8101	Hold Chamb W/inhal/nebulizr; W/mask	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8110	Peak Expiratory Flow Rate	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8120	O2 Cntn Gaseous 1 U = 1 Cubic Foot	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8130	Interferential stim 2 chan	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
S8131	Interferential stim 4 chan	Not Medically Necessary	Always considered not medically necessary. Will be denied as a provider write-off
S8185	Flutter Device	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8186	Swivel Adaptor	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8301	Infection Control Supplies Nos	Unlisted Code	Unlisted Code. Submit documentation to describe service. Unlisted codes may be used for potentially investigational or potentially cosmetic services and are subject to review.
S8431	Compression Bandage Roll	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8450	Splint Prefabricated Digit	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8451	Splint Prefabricated Wrist Or Ankle	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8452	Splint Prefabricated Elbow	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S8930	Auricular electrostimulation	HTCC Decision	Possible HTCC decision denial
S8940	Equestrian/hippotherapy Per Session	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S8990	Phys/manip Tx Maint Not Restoration	HTCC Decision	Possible HTCC decision denial
S8999	Resuscitation Bag	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Clinical Edits by Code List
Complete List
Applies to Uniform Medical Plan (UMP)

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

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Code	Description	Edit Type	Comment
S9055	Procuren/oth Growth Factor Prep	HTCC Benefit Denial	Not a covered benefit per HTCC
S9083	Global Fee Urgent Care Centers	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9088	Services Prov An Urgent Care Center	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9090	Vert Axial Decomprs Per Session	Investigational Denial	Always considered investigational; investigational services are denied member liability.
S9145	Insulin Pump Init Instruct Use Pump	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9150	Evaluation By Occularist	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9430	Pharm Compounding & Dispensing Serv	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9475	Amb Set Sbstnc Abs Tx/dtox Srvc Day	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
S9480	Intensive Op Psyc Services Per Diem	Non-Reimbursable Services	Not considered a payable Professional service. Will be denied provider write-off.
S9529	Routine veinpuncture for collection of specimen(s)	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1000	Priv Duty/independent Nrs To 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1001	Nursing Assessment/evaluation	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1002	Rn Services Up To 15 Minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1003	Lpn/lvn Services Up To 15 Minutes	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1004	Srvc Qualified Nrs Aide To 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1005	Srvc Qual Nursing Aide Up To 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1006	Alcohl&/sbstnc Abs Fam/couple Cnsl	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1007	Alcohol&/substance Abuse Services	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1009	Child Sit Ind Alc&/substnc Abs Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1010	Meals Rec Alcohl&/substnc Abs Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1012	Alcohol&/sbstnc Abs Srvc Skl Dvlp	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1013	Sign Lange/oral Intepr Srvc-15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1014	Telehealth Trans Min Prof Srvc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1015	Clinic Vst/encounter All-inclusive	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1016	Case Management Each 15 Mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1017	Targeted Case Management Ea 15 Mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1018	School-basd Ind Ed Prog Serv Bundld	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1019	Personal Care Services Per 15 Mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1020	Personal Care Services Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1021	Home Hlth Aide/cert Nurse Asst Vst	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

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Code	Description	Edit Type	Comment
T1022	Contract Home Health Agcy Srvc Day	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1023	Scr Ind Particip Spec Prog Proj/tx	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1024	Eval&tx Team Mx/sev Handicap Child	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1025	Mxdiscplin Child Cmplx Impair Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1026	Mxdiscplin Child W/cmplx Impair Hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1027	Fam Train & Cnsl Child Dvlp 15 Mins	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1028	Assess Home Physical & Family Envir	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1029	Comp Envir Lead Investigat-dwell	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1030	Nrs Care Home Registered Nurse-diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1031	Nursing Care The Home Lpn Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1032	Sv doula brth wrk per 15 min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1033	Sv doula brth wrk per diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1040	Comm bh clinic svc per diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1041	Comm bh clinic svc per month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1502	Admn Orl Im&/subq Med Hlth Prof	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1503	Med Admin Other Than Oral	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1505	Elec med comp dev, noc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T1999	Misc Tx Items&supplies Retail Noc	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2001	N-emerg Trnsprt; Pt Attendnt/escort	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2002	Non-emerg Transportation; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2003	Non-emerg Trnsprt; Encounter/trip	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2004	N-emerg Trnsprt;commer Carr Mx-pass	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2005	Nonemergency Trnsprt; Stretcher Van	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2007	Trnsprt Wait Time Non-er Veh 1/2 Hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2010	Pasrr Level I Id Screen Per Screen	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2011	Pasrr Level Ii Evaluation Per Eval	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2012	Habilitation Ed Waiver; Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2013	Habilitation Ed Waiver; Hour	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2014	Habilitatn Prevocationl Waivr;diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2015	Habilitation Prevocational Waivr;hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
T2016	Habilitation Res Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2017	Habilitation Res Waiver; Per 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2018	Habilitatn Supp Emplmnt Waivr;diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2019	Habiltatn Supp Emplmnt Waivr;15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2020	Day Habilitation Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2021	Day Habilitation Waiver; Per 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2022	Case Management; Per Month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2023	Targeted Case Management; Per Month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2024	Srvc Assess/plan Care Dvlp Waiver	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2025	Waiver Services; Nos	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2026	Spclized Childcare Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2027	Spclized Childcare Waiver; 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2028	Specialized Supply Nos Waiver	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2029	Specialized Medical Eqp Nos Waiver	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2030	Assisted Living Waiver; Per Month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2031	Assisted Living Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2032	Res Care Nos Waiver; Per Month	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2033	Res Care Nos Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2034	Crisis Interven Waiver; Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2035	Utility Services Med Eqp Waiver	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2036	Tx Camping Ovrngt Waiver; Ea Sess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2037	Tx Camping Da Waiver; Ea Sess	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2038	Cmty Transition Waiver; Per Service	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2039	Vehicle Mod Waiver; Per Service	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2040	Financial Mgmt Waiver; 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2041	Supp Broker Slf-dired Waivr; 15 Min	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2042	Hospice Routine Home Care Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2043	Hospice Continuous Home Care Per Hr	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2044	Hospice Inpat Respite Care Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2045	Hospice General Inpat Care Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.

Based on Medical Policy, potential investigational codes may be denied as Investigational (member liability) or not medically necessary (provider liability).

****In addition, some cosmetic codes may be denied as cosmetic (member liability) or not medically necessary (provider liability).****

Code	Description	Edit Type	Comment
T2046	Hospice Lt Care Rm And Bd Per Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2047	Hab prevo waiver per 15	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2048	Bhval Hlth; Ltc Res W/room&bd-diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2049	Non-emerg Trnsprt; Van Mileage;mile	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2050	Financial Mgt Waiver/Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2051	Support Broker Waiver/Diem	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T2101	Humn Brst Milk Prc Stor&dstrb Only	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T4545	Incon disposable penile wrap	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T5001	Pstn Seat Pers W/spcl Orthoped Need	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
T5999	Supply, Not Otherwise Specified	Non-Reimbursable Services	Not considered a payable service. Will be denied provider write-off.
V5262	Hearing Aid Dispbl Type Monaural	Non-Reimbursable Services	Not considered a payable Professional service. Will be denied provider write-off.
V5263	Hearing Aid Dispbl Type Binaural	Non-Reimbursable Services	Not considered a payable Professional service. Will be denied provider write-off.
V5265	Ear Mold/insert Disposable Any Type	Non-Reimbursable Services	Not considered a payable Professional service. Will be denied provider write-off.

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Behavioral Health Utilization Management
Applied Behavioral Analysis (ABA)
Concurrent Request Form

Please fully complete all sections. Once finished you may fax this form and supporting clinical documents via email: FAXBHRepository@regence.com or Fax: (888) 496-1540.

Member information		
Member Name:		Member ID:
Date of birth:	Age:	Gender: ☐ M ☐ F

Ordering physician	
Physician name:	NPI:
Address:	
Phone #:	Fax #:

Agency Information		
Agency name:		
Tax ID:	NPI:	
Address:		
Phone #:	Fax #:	
Contact person: (if different than BCBA)	Phone #:	Fax #:

BCBA or rendering provider information. ☐ Same as Agency above	
Provider name:	
Tax ID:	NPI:
Address:	
Phone #:	Fax #:

ABA Concurrent Request

Original start date of ABA: _____. Current Authorization Number: _____.

Expedited request ☐
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.
Explanation required:

Note: There is very little evidence to support the efficacy of ABA for people 13 years and older. If you are requesting ABA for someone 13 or older, please provide additional justification for this (e.g., severe risk of injury to self or others related to ASD or self-injurious stereotypical movement disorder).

Clinical updates and progress:

Documentation:

Please include a completed Individualized Treatment Plan (ITP) with your request that includes:

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.

☐ Please include data on targeted behaviors and information regarding how the treatment plan is address these targeted behaviors. Please include details such as most recent treatment plan updates.

☐ Please indicate progress toward each of the defined goals in the ITP. Please document progress as it relates to each of the targeted behaviors on the ITP.

☐ Objective measurements using standardized instruments that include frequency, intensity, and duration and evaluation. Please include details such as dates, measurements used, and scores.

Request Details

Authorization start date: _____.

- Please note that the below CPT codes are the Regence approved CPT codes for ABA services.
- Authorizations are for 6 months (26 weeks).
- Please list requested units for 6 months. Each unit is for 15 minutes.
  Example: Services for 97153 are provided for 10 hours per week. This would total 40 units per week and 1040 units per 6 months (26 weeks).
- Place of Service (i.e.: home, school, specify other setting).

  School is not an approved/eligible POS for Federal Employee Program (FEP) policies.

Adaptive Behavior Treatment	Units: 15 min=unit	CPT Code	Timeframe: 6 Months	Place of Service
Behavioral Identification Assessment		97151		
Observational Behavioral Follow-Up Assessment		97152		
Adaptive Behavior Treatment by Protocol		97153		
Group Adaptive Behavior Treatment w/ protocol		97154		
Adaptive Behavior Treatment w/Protocol Modification		97155		
Family Adaptive Behavior Treatment Guidance		97156		
Multiple-Family Group Adaptive Behavior Treatment Guidance		97157		
Adaptive Behavior Treatment Social Skills Group		97158		
Exposure Behavioral Follow-Up Assessment		0362T		
Exposure Adaptive Behavioral Treatment w/ Protocol Modification (first 60min)		0373T		

Provider name (print):	License information:
Provider signature:	Date:

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Behavioral Health Utilization Management

Concurrent Request Form

This form is used to request continued authorization for inpatient, residential, partial hospitalization program (PHP) or intensive outpatient program (IOP) treatment.

Please submit via email: FAXBHRepository@regence.com or Fax: (888) 496-1540.

Today's Date:	Member ID #:	Current Authorization #:

Request continued authorization:

Mental Health level of care requested

☐ Inpatient hospital (IP) ☐ Residential (RES) ☐ Partial Hospital (PHP) ☐ Intensive Outpatient (IOP)

☐ IP - eating dis. ☐ RES - eating dis. ☐ PHP - eating dis. ☐ IOP - eating dis.

Substance Use Disorder level of care requested

☐ ASAM 4 ☐ ASAM 3.7 ☐ ASAM 3.5 ☐ ASAM 2.5 ☐ ASAM 2.1

For PHP & IOP - specify program frequency (# of days per week):

Start Date:	Days Requested:	Estimated Length of stay:

Member information

Member Name:	Member DOB:

Facility information ☐ **No Change** ☐ **See Changes below**

Facility name:	Tax ID #:

NPI #:	Office Phone #:	Office Fax #:

Mailing Address:

Attending physician first and last name:	Attending physician phone #

Utilization Reviewer Information

UR/Contact Name:	Phone #:	Confidential voicemail ☐ Yes ☐ No	Fax #:

ICD-10 diagnoses update. Please indicate primary.

Primary Diagnosis:

Clinical Update since last review — symptoms, risk factors, functional impairments.

Co-occurring medical / physical illness updates

(Please explain how these are being addressed)

For Eating Disorders: Updated Weight, BMI, Vitals

☐ Not applicable

Updated assessment of American Society of Addiction Medicine (ASAM)
☐ Not applicable

Dimension 1. Acute intoxication and/or withdrawal potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe: (include vitals and withdrawal symptoms):

Dimension 2. Biomedical conditions and complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 3. Emotional, behavioral, or cognitive complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 4. Readiness to change.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 5. Relapse, continued use or continued problem potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 6. Recovery living environment.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

If any ASAM dimensions have moderate or higher risk ratings, how are they being addressed in treatment or discharge planning?

☐ Not applicable

Treatment Plan

Updated treatment goals / Progress toward goals:

Updated treatment interventions:

Updated Medications:

Coordination of care updates: case management, family, community agencies. If case is open with another agency please include name of agency, phone, and case number.

☐ Not applicable

Continued Stay Rationale - be specific about goals to be accomplished.

Discharge Planning

Discharge planner name:	Phone:

Aftercare plan:

Please list any outstanding items needing attention for next review.

Submitted by:	Phone:

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Behavioral Health Utilization Management

Discharge Notification Form

This form is used to confirm discharge from inpatient, residential, partial hospitalization program (PHP) or intensive outpatient program (IOP) treatment.

Note - if seeking a stepdown please complete the Stepdown Request form.

Please submit via email: FAXBHRepository@regence.com or Fax: (888) 496-1540.

Today's Date:	Member ID #:	Current Authorization #:
Admit date:	**Discharge Date**:	Level of care:
Member information		
Member Name:		Member DOB:
Member address:		Member phone #:
Where will member reside and with whom?		
Facility name:		
Discharge Diagnosis:		
Aftercare Appointments - (be specific with names of all provider and dates of appointments)		
Additional Discharge Plans - list all medical, social, and community referrals		
Discharge Medications:		
Discharge planner name:		Discharge planner phone #:

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Extenuating Circumstances

This policy is modeled after the Best Practice Recommendations that support Washington State Senate Bill 5346 and regulatory requirements of WAC 284-43-2060.

This policy and process is applicable to all plans issued or renewed on or after January 1, 2018 by Regence with exception of Extenuating Circumstances Criteria #7 below. *Extenuating Circumstances criteria # 7 is applicable to plans issued on or after January 1, 2018 by Regence in WA State only excluding Medicare Advantage and FEP.

This policy does not apply to prescription drug services.

Overview

Obtaining required pre-authorization prior to service delivery is the optimal practice to mitigate provider and member financial risk, however several extenuating circumstances may make it impossible, before treating the member, to obtain a prior authorization.

Claims will not be administratively denied for lack of prior authorization so long as we are contacted before the claim is submitted, the specific extenuating circumstance is documented (suggested supporting documentation is outlined below) and such circumstance meets at least one of the Extenuating Circumstances criteria outlined below. If we are contacted after the claim is submitted, the administrative denial may be disputed as an extenuating circumstance via the appeal process if the specific extenuating circumstance is documented, as noted above, and such circumstance meets at least one of the Extenuating Circumstances criteria outlined below.

NOTE: If we are contacted after the claim is submitted but still in process, the administrative denial on the claim must be disputed via the appeal process post claim denial. We are unable to stop claims processing.

In addition, even if the service(s) meet the below Extenuating Circumstances criteria, we will still review for appropriateness, level of care, medical necessity and benefit coverage under the criteria for the applicable plan based on the information available to the provider or facility at the time of treatment.

The criteria and procedures that participating providers and facilities must follow to notify Regence of an extenuating circumstance pre-claim submission or to dispute a claim denied for no pre-authorization are outlined below.

Extenuating Circumstances Criteria

The following seven exceptions to obtaining pre-authorization may qualify as an Extenuating Circumstance:

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.

Examples:

- The provider verified that no medical coverage was in place at time of treatment. It was later determined that medical coverage was in place. In some cases, patients prefer to pay out of pocket rather than initiate COBRA coverage and pay the ongoing premium. However, a second care encounter could change the patient's mind and COBRA coverage would be initiated retroactively to the beginning to the month, thus providing coverage for a treatment that has already been delivered.
- The provider asked the patient about current coverage prior to the service, the patient provided current insurance coverage information and the provider verified that the coverage was in force at time of treatment. After the patient was treated, it was discovered that another health plan takes precedent and is responsible for coverage.
- Coverage retrospectively determined to not be related to an accident or work-related injury. During the scheduling process, these patients indicate that their condition is accident related. During or after treatment, the provider discovers that the service is not accident/work related.
- Other primary insurance retrospectively discovered: Coverage for these patients is verified with the health plan of record prior to treatment and any pre-authorization/admission notification requirements are met. After the patient is treated, the provider is notified that another health plan is primary. Two examples: a. Before treatment, Department of Social and Health Services (DSHS) benefits are verified with no other insurance on file at that time. Later, DSHS notifies the provider that commercial coverage was in place. b. Before treatment, the patient's father's health plan verifies eligibility. Later, the health plan notifies the provider that the other parent has coverage and that coverage is primary.

This DOES NOT INCLUDE when the provider could communicate with the member prior to giving treatment, but insurance coverage information was not obtained and/or was not verified prior to the service(s). This situation is not an extenuating circumstance. The normal prior authorization and/or admission notification practices are to be followed.

Note to Providers: Best practice is verifying that current insurance information is on file, which can help reduce the number of 'Unable to Know Coverage' situations. Each time a patient is seen, providers should obtain comprehensive coverage information from the guarantor/member.

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.

Examples:

- Trauma or unresponsive patients: These patients are usually brought in via 911 with no family, no id etc. – may be admitted as Jane/John Doe.

- Psychiatric patients: These patients are admitted through the Emergency Department for clinical conditions related to cognitive impairment.
- Child not attended by parent: These patients are children who need immediate medical attention and are brought in by someone other than their parents, e.g. babysitter, grandparent, etc.
- Non-English speaking patients: These patients don't speak English and a translator cannot be obtained in a timely manner.

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.

Note: A copy of the faxed pre-authorization request showing the information was entered correctly indicating the member health plan information and a fax confirmation from the fax machine showing the fax was successfully sent to the appropriate health plan fax number will be considered compelling evidence.

5. A surgery which requires pre-authorization occurs in an urgent/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.

These are situations where immediate or very-near-term medical services are required that are typically related to a service already being performed, e.g., diagnostic, office visit, surgery. Prior authorization is not completed prior to service delivery. (Note: These situations are only extenuating circumstances related to a prior authorization and do not prevent a provider from notifying the health plan about an admission within the specified time period, e.g., 24 hours.)

Examples:

- Patient is seen in a physician's office and the physician determines there is an acute and immediate need for diagnostic imaging or a hospital admission.
- Patient is undergoing a procedure which may or may not require pre-authorization. Once the procedure begins, it evolves into a different/additional/more complex procedure or identifies the need for an add-on surgery/procedure, which is often scheduled for the same day or late in the afternoon/evening for the next morning.

This DOES NOT INCLUDE when the provider performs a procedure or provides a service that is considered experimental or investigational where a health plan denial of coverage would result in patient financial responsibility.

An extenuating circumstance DOES NOT APPLY when the service or services occur during an office visit solely for the convenience of the provider.

***7. An enrollee is discharged from a facility and insufficient time exists for institutional or home health care services to receive approval prior to delivery of the service. *NOTE: This criteria is only applicable to plans issued on or after January 1, 2018 by Regence in WA State only excluding Medicare Advantage and FEP.**

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Notifying Regence About an Extenuating Circumstance

Pre-Claim Submission

Please note that if you are submitting an extenuating circumstance request for a member who has discharged from your facility that you submit the request with your claim for processing.

Call the **Provider Contact Center** to notify us of an extenuating circumstance

The following may be requested:

Member name, DOB, ID #

Provider name and ID

Date of Service

Description of extenuating circumstance that was present

Supporting documentation of the extenuating circumstance will be requested to be faxed to (866) 273-1820.

Suggested supporting documentation is outlined below.

Notification of an extenuating circumstance may also be faxed directly to (866) 273-1820 and must include ALL the following:

Member Name, DOB and ID

Provider name and ID

Date of Service

CPT codes

Description of extenuating circumstance that was present

Fax cover sheet should include “Extenuating Circumstance” in subject line:

Return Fax #

Supporting documentation (suggested documentation is outlined below)

Note: Claims submitted prior to receiving a written response from Regence regarding the extenuating circumstance request may be subject to the administrative denial.

Post Claim Administrative Denial

Use the adverse determination appeal form (PDF) to dispute a claim that has denied for no pre-authorization. Please complete the form and follow the instructions outlined in the section that applies to ‘Denials for Pre-authorization not obtained’.

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Please fax the completed form and all extenuating circumstance supporting documentation as applicable to: (866) 273-1820.

Suggested supporting documentation is outlined below.

Extenuating Circumstance Supporting Documentation

Submit the following documentation to support an extenuating circumstance as applicable:

Dated documentation, e.g. admission face sheet, obtained at the time of service indicating: The insurance information provided by the patient/representative or the patient's/representative's inability to provide insurance information or the patient's/representative's reporting self-pay.

Verification of no coverage such as Availity screenshot at the time of inquiry (though eligibility at date of service was later confirmed).

Dated documentation obtained at time of service showing eligibility confirmation from another payer, e.g. web eligibility screen shot or copy of electronic eligibility confirmation, AND/OR that payer's EOB denying the service as not eligible for coverage (e.g. denied due to alternate primary coverage).

Applicable office visit chart notes for either the date of service or the referral along with other clinical documentation (as needed), e.g. diagnosis, H & P, failed alternative treatment(s), or interim/alternative treatment(s) as appropriate, indicating the medical necessity for the procedure and the rationale for providing the procedure at that time without prior authorization, i.e. procedure is time sensitive or emergent.

A copy of the faxed pre-authorization request showing the information was entered correctly indicating the member health plan information and a fax confirmation from the fax machine showing the fax was successfully sent to the appropriate health plan fax number.

Any other documentation felt to support an extenuating circumstance was present.

Note: Submission of the above referenced documentation does not guarantee payment. Even if the Extenuating Circumstance criteria applies, the service is subject to benefit coverage and medical necessity under post service review.

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Behavioral Health Utilization Management

Initial Request Form

This form is used to request inpatient, residential, partial hospitalization program (PHP) or intensive outpatient program (IOP) treatment.

Please submit via email: FAXBHRepository@regence.com or Fax: (888) 496-1540.

Expedited request: I attest that this request meets the below definition by checking the expedited request box: ☐

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.

Is this for a Medicare Preservice Benefit Organization Determination Request? ☐ Yes ☐ No

Today's Date:	Member ID #:

Request authorization:

Mental Health level of care requested

☐ Inpatient hospital (IP) ☐ Residential (RES) ☐ Partial Hospital (PHP) ☐ Intensive Outpatient (IOP)

☐ IP - eating dis. ☐ RES - eating dis. ☐ PHP - eating dis. ☐ IOP - eating dis.

Substance Use Disorder level of care requested

☐ ASAM 4 ☐ ASAM 3.7 ☐ ASAM 3.5 ☐ ASAM 2.5 ☐ ASAM 2.1

For PHP & IOP - specify program frequency (# of days per week):

Admit or projected start date: ☐ Voluntary or ☐ Involuntary	Days Requested:	Estimated Length of stay:

Member information

Member Name:	Member DOB:
Member address:	Member phone #:

Name of parent/guardian if minor:	Member email:	Primary language:

Provider information			
Please check one: ☐ Requesting / Prescribing Provider ☐ Rendering / Treating Provider			
Provider name:		Tax ID #:	
NPI #:	Office Phone #:		Office Fax #:
Mailing Address		Provider Specialty:	
Attending physician first and last name:		Attending physician phone #:	

Facility information ☐ **Same as above**			
Facility name:		Tax ID #:	
NPI #:	Office Phone #:		Office Fax #:
Mailing Address:			
Attending physician first and last name:		Attending physician phone #:	

Utilization Reviewer Information			
UR/Contact Name:	Phone #:	Confidential voicemail ☐ Yes ☐ No	Fax #:

ICD-10 diagnoses. Please indicate primary.

Primary Diagnosis:

Precipitant to Admission

Patient Treatment History

Current Outpatient Providers or Facility care: (please include dates & contact information).

Past Outpatient Providers or Facility Care: (please include dates & contact information).

Risk Assessment / Functional Impairments

Co-occurring medical / physical illness

(Please explain how these are being addressed)

For Eating Disorders: Weight, BMI, Vitals

☐ Not applicable

Current assessment of American Society of Addiction Medicine (ASAM)
For substance use disorders, please complete the following information. ☐ Not applicable

Dimension 1. Acute intoxication and/or withdrawal potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe: (include vitals and withdrawal symptoms):

Dimension 2. Biomedical conditions and complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 3. Emotional, behavioral, or cognitive complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 4. Readiness to change.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 5. Relapse, continued use or continued problem potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 6. Recovery living environment.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Treatment Plan

Treatment goals:

Treatment interventions: (include family treatment and community referrals)

Medications:

Coordination of care — Include coordination activities with case managers, family, community agencies, etc. If case is open with another agency, name the agency, phone, and case number

☐ Not applicable

Discharge Planning

Discharge planner name:	Phone:

Aftercare plan:

Please list any outstanding items needing attention for next review.

Submitted by:	Phone:

HEALTH TECHNOLOGY CLINICAL COMMITTEE (HTCC) ASSESSMENTS AVAILABE FOR ELECTRONIC AUTHORIZATION AND ROUTING TO THE CITE AUTO AUTHORIZATION TOOL

For UMP members, the electronic authorization tool will automatically route you to the Cite Auto Authorization tool for select CPT codes and allow documentation of specific clinical criteria for your patient. If all criteria are met, you will be able to see the approval on the Auth/Referral Dashboard soon after you click submit.

The HTCC Assessments listed below are available when routed to the Cite Auto Authorization tool:

HTCC Assessment Title Link to Washington State Health Care Authority Health Technology Reviews Website: https://www.hca.wa.gov/about-hca/health-technology-assessment/health-technology-reviews	HTCC Number	Codes
Artificial disc replacement	20170120B	22856, 22858, 22861, 0095T, 0098T
Cardiac Stents	20160115B	92928, 92933, 92937, 92941, 92943
Catheter Ablation Procedures for Supraventricular Tachyarrhythmias (SVTA) Including Atrial Flutter, Atrial Fibrillation	20130517B	93653, 93655, 93656, 93657
Cervical Spinal Fusion for Degenerative Disc Disease	20130322B	22551, 22552, 22554, 22853, 22854, 22859, 22600
Discography	20080215B	62290 72295
Genomic Microarray Testing	20180119A	81228, 81229, 81349, S3870, 0156U, 0209U
Pharmacogenomic testing for selected conditions (including Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing)	20170120A	81225, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U
Pharmacogenomic testing for selected conditions and Laboratory and Genetic Testing for use of Thiopurines	20170120A	81225, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U
Spinal Injections	20160318B	62320, 62321, 62322, 62323, 64479, 64480, 64483, 64484, 64490, 64491, 64492, 64493, 64494, 64495
Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) and Gastrointestinal (GI) Symptoms	20120518A	43200, 43202, 43235, 43237, 43238, 43239, 43242, 43259
Vagal Nerve Stimulation for Epilepsy and Depression	20200515B	K1020, 61885, 61886, 64553, 64568, C1822, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688

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.

Regence

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Pre-authorization Request Form
DME
Commercial, Individual, Medicare, BCBS FEP members:
Fax: 1 (855) 207-1209
Administrative Services Only (ASO) members:
Fax: 1 (844) 679-7763
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

Requesting/Prescribing 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:

DME Company Name			Tax ID #	NPI #
Mailing Address			**Fax #**	
City	**State**	**ZIP Code**	**Phone # Ext.**	**Confidential Voice Mail** ☐ Yes ☐ No
Email Address			Signed copy of prescription attached: ☐ Yes ☐ No Invoice attached: ☐ Yes ☐ No	

SECTION 3 – PREAUTHORIZATION REQUEST

Date of Service _____

Please check one: ☐ Outpatient Hospital ☐ Inpatient ☐ ASC ☐ Office ☐ Home
☐ Other _____

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

Submit the following documentation, as appropriate, with this request:

- Signed copy of prescription
- Invoice with pricing

  AND
- Specific clinical documentation as outlined in the associated Regence Medical Policy, Policy Guidelines section

  OR
- Specific clinical information documenting the applicable Medicare, or BCBS FEP medical necessity criteria, **including:**
  - History and physical
  - Lab/Radiology/Testing results
  - Current symptoms and functional impairment
  - Treatment history and any other information such as chart notes that support medical necessity for the request

Any other supporting documents you would like considered, such as letters from outpatient providers, etc.

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
Medical Services
Commercial, Individual, Medicare, BCBS FEP members:
Fax: 1 (855) 207-1209
Administrative Services Only (ASO) members:
Fax: 1 (844) 679-7763
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 or Independent Laboratory Name			Tax ID #	NPI #
Mailing Address			Fax #	
City	State	ZIP Code	Phone # Ext.	Confidential Voice Mail ☐ Yes ☐ No

SECTION 3 – PREAUTHORIZATION REQUEST

Date of Service/Anticipated Admission _____

Please check one: ☐ Outpatient Hospital ☐ Inpatient ☐ ASC ☐ Office
☐ Other _____

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

Submit the following documentation, as appropriate, with this request:

- Specific clinical documentation as outlined in the associated Regence Medical Policy, Policy Guidelines section

  OR
- Specific clinical information documenting the applicable Medicare, or BCBS FEP medical necessity criteria, **including:**
  - History and physical
  - Lab/Radiology/Testing results
  - Current symptoms and functional impairment
  - Treatment history and any other information such as chart notes that support medical necessity for the request

Any other supporting documents you would like considered, such as letters from outpatient providers, etc.

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
Skilled nursing (SNF), Long Term Acute Care (LTAC), Inpatient Rehabilitation (IP Rehab)
Fax: 1 (855) 848-8220
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.

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

Requesting/Prescribing 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
Email Address			**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.	

SECTION 3 – PREAUTHORIZATION REQUEST

Date of Admission _____

Transfer from another facility? ☐ Yes ☐ No If Yes, Facility Name: _____

Skilled Services Needed:	
Level of Function/Cognition:	Current:
	Prior:
Ambulatory Ability:	
Social Support: Lives	☐ Alone ☐ w/son/daughter ☐ w/ spouse ☐ w/ other _____

Please provide all diagnosis and their descriptions.

Diagnosis code(s) and description(s)	
Primary:	
Second:	
Third:	

SECTION 4 – DOCUMENTATION SUBMISSION

Submit the following documentation, as appropriate, with this request:

Specific clinical information documenting the applicable MCG™, Medicare, or BCBS FEP medical necessity criteria, **including:**

- History and physical
- PT/OT/SLP assessment and current notes within past 48 hours, as applicable
- Current symptoms and functional impairments
- Treatment history and any other information, such as chart notes that support medical necessity for the request.
- Physician Progress Notes from the past 48 hours

Any other supporting documents you would like considered, such as letters from outpatient providers, etc.

Sample Non-Covered Services Member Consent Form

This sample may be used as a guideline when developing a member consent form. Please consult with your legal counsel before adopting this format.

NON-COVERED SERVICES MEMBER CONSENT FORM

I, _____
(list patient name and member number), understand that the services and/or supplies listed below may not be considered eligible for benefits (e.g., services and/or supplies may be determined to be not medically necessary, non-covered or investigational) by _____ _____ (health insurer). I understand that my health insurance coverage has certain restrictions and limitations, such as authorization requirements, and non-covered services and/or supplies. Since I have chosen to obtain the services and/or supplies listed below, I agree to be financially responsible for any and all related charges, if they are not covered by my insurance.

_____
Services/Supplies Requested

_____

_____
Condition/Diagnosis

_____
Approximate Cost of Service

_____
Date of Service

_____
Member or Legal Guardian Signature Member Identification Number Date

_____
Witness Signature Date

_____

Regence

Regence BlueShield serves select counties in the state of Washington and is an Independent Licensee of the Blue Cross and Blue Shield Association

Behavioral Health Utilization Management

Stepdown Request Form

This form is used to request immediate stepdown authorization from a higher level of care to a lower level of care.

Please submit via email: FAXBHRepository@regence.com or Fax: (888) 496-1540

Expedited request: I attest that this request meets the below definition by checking the expedited request box: ☐

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.

Is this for a Medicare Preservice Benefit Organization Determination Request? ☐ Yes ☐ No

Today's Date:	Member ID #:	Current Authorization #:
Current Level of Care:	Discharge Date:	

Request stepdown authorization:

Mental Health level of care requested

☐ Residential (RES) ☐ Partial Hospital (PHP) ☐ Intensive Outpatient (IOP)

☐ RES - eating dis. ☐ PHP - eating dis. ☐ IOP - eating dis.

Substance Use Disorder level of care requested

☐ ASAM 3.7 ☐ ASAM 3.5 ☐ ASAM 2.5 ☐ ASAM 2.1

For PHP & IOP - specify program frequency (# of days per week):

Member information

Member Name:	Member DOB:

Facility information ☐ **Same Facility / No Change** ☐ **See Changes below**

Facility name:	Tax ID #:	
NPI #:	Office Phone #:	Office Fax #:
Mailing Address:		
Attending physician first and last name:		Attending physician phone #

Utilization Reviewer Information			
UR/Contact Name:	Phone #:	Confidential voicemail ☐ Yes ☐ No	Fax #:

ICD-10 diagnoses. Please indicate primary.

Primary Diagnosis:

Clinical Update since last review — symptoms, risk factors, functional impairments.

Co-occurring medical / physical illness updates

(Please explain how these are being addressed)

For Eating Disorders: Updated Weight, BMI, Vitals

☐ Not applicable

Updated assessment of American Society of Addiction Medicine (ASAM)
☐ Not applicable

Dimension 1. Acute intoxication and/or withdrawal potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe: (include vitals and withdrawal symptoms):

Dimension 2. Biomedical conditions and complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 3. Emotional, behavioral, or cognitive complications.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 4. Readiness to change.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 5. Relapse, continued use or continued problem potential.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

Dimension 6. Recovery living environment.

Risk rating: ☐ Minimal/none. ☐ Mild. ☐ Moderate. ☐ Significant. ☐ Severe.

Describe:

If any ASAM dimensions have moderate or higher risk ratings, how are they being addressed in treatment or discharge planning?

☐ Not applicable

Discharge Planning

Discharge planner name:	Phone:

Aftercare plan:

Please list any outstanding items needing attention for next review.

Treatment Plan

Updated treatment goals / Progress toward goals:

Updated treatment interventions:

Updated / Current Medications:

Coordination of care updates: case management, family, community agencies. If case is open with another agency please include name of agency, phone, and case number.

☐ Not applicable

Submitted by:	Phone:

Regence

Medical Policy Manual Genetic Testing, Policy No. 01

Genetic Testing for Alzheimer's Disease

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

Genetic testing has been investigated as an aid in the diagnosis of patients presenting with symptoms suggestive of Alzheimer's disease (AD), or as a technique for risk assessment in asymptomatic patients with a family history of AD.

MEDICAL POLICY CRITERIA

I. Genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein gene (*APP*) associated with autosomal dominant Alzheimer's disease may be considered **medically necessary** for an asymptomatic individual when either of the following criteria are met:

   A. Targeted genetic testing for a known familial variant when the individual has a first- or second-degree relative (see Policy Guidelines) with a known familial variant AND the results of testing will be used to inform reproductive decision-making; OR

   B. The individual has a family history of dementia consistent with autosomal dominant Alzheimer's disease (three or more affected members in two generations) for whom the genetic status of the affected family members is unavailable, AND the results of testing will be used to inform reproductive decision-making.

II. Genetic testing for risk assessment or in the evaluation of dementia or Alzheimer's disease is considered **investigational** for all other indications and when Criterion I is not met**.** Genetic testing includes, but is not limited to, testing for the apolipoprotein E (*APOE*) epsilon 4 allele, presenilin (*PSEN*) genes, amyloid precursor protein (*APP*) gene, or triggering receptor expressed on myeloid cells 2 (*TREM2*) gene.

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

LIST OF INFORMATION NEEDED FOR REVIEW

First-degree relatives are parents, siblings, and children of an individual; second-degree *relatives* are grandparents, aunts, uncles, nieces, nephews, grandchildren.

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No.81
3. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
4. Aduhelm, aducanumab, Medication Policy No. dru740

BACKGROUND

Alzheimer's disease (AD) is the most common form of dementia. In 2020, as many as 5.8 million Americans were living with AD, and by 2060 this number is projected to rise to 14 million.[1] Although scientist don't fully understand the cause of AD, it is diagnosed based on a clinical-neuropathologic assessment, and age and a family history are the best known risk factors. The symptoms of AD most commonly appear after the age of 60, known as late-onset AD; however, AD can be found in younger people, known as early-onset AD. Researchers believe genetics may play a role in the development of AD in patients who have a family history, or in the risk assessment or management of asymptomatic patients with a family history of AD.

GENETIC VARIANTS

Individuals with early onset familial AD (i.e., before age 65, but as early as 30 years) form a small subset of AD patients. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic mutations in three genes have been identified in affected families: amyloid-beta precursor protein gene (*APP*), presenilin 1 (*PSEN1*) gene, and presenilin 2 (*PSEN*2) gene. *APP* and *PSEN1* pathogenic variants have 100% penetrance absent death from other causes, while *PSEN*2 has 95% penetrance. A variety of variants within these genes has been associated with AD; variants in *PSEN1* appear to be the most common. While only 3%–5% of all patients with AD have early onset disease, pathogenic variants have been identified in up to 70% or more of these patients. Identifiable genetic variants are, therefore, rare causes of AD.

Testing for the apolipoprotein E (*APOE*) 4 allele among patients with late-onset AD and for *APP*, *PSEN1*, or *PSEN*2 variants in the rare patient with early onset AD have been investigated as an aid in diagnosis in patients presenting with symptoms suggestive of AD, or a technique for risk assessment in asymptomatic patients with a family history of AD. Pathogenic variants in *PSEN1* and *PSEN*2 are specific for AD; *APP* variants are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon

The apolipoprotein E (*APOE*) lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The *APOE* gene has three alleles—ε2, 3, and 4—with the ε3 allele being the most common. Individuals carry two *APOE* alleles. The presence of at least one ε4 allele is associated with a 1.2- to 3-fold increased risk of AD depending on the ethnic group. The correlation between *APOE* and AD in African-American, Hispanic populations is not as strong as is seen in white populations, despite higher rates of AD than white populations in both groups.[2] Among those homozygous for ε4 (about 2% of the population), the risk of AD is higher than for those heterozygous for ε4. The mean age of onset of AD is about 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of patients with sporadic AD carry an ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease-causing variant. In the absence of *APOE* testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a two- to four-fold greater risk of developing AD than the general population.[3] There is evidence of possible interactions between ε4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, and diabetes[4]), and a higher risk of developing AD. However, it is not clear that all risk factors have been taken into account in such studies, including the presence of polymorphisms in other genes that may increase the risk of AD.

Studies have also identified rs75932628-T, a rare functional substitution for R47H of *TREM2*, as a heterozygous risk variant for late-onset AD.[5, 6] On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628 encodes a histidine substitute for arginine in the gene that encodes *TREM2*.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. *TREM2* may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids and toxic products. A decrease in the function of *TREM2* would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the *TREM2* variant confers a risk of AD that is similar to the *APOE* ε4 allele, although it occurs less frequently.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.[7] Other proposed diagnostic tests for AD include cerebrospinal (CSF) fluid levels of Tau protein or beta-amyloid precursor protein. These CSF tests are addressed in a separate medical policy (see Cross References).

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The FDA has not regulated these tests to date. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[8] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review focuses on clinical validity and utility.

GENETIC TESTING FOR LATE-ONSET ALZHEIMER DISEASE

Clinical Validity

The advances in genetic understanding of AD have been considerable, with associations between late-onset AD and more than 20 non-*APOE* genes suggested.[9]

Naj (2014) published a genome-wide association study of multiple genetic loci in late-onset AD.[10] Genetic data from 9,162 Caucasian participants with AD from the Alzheimer Disease Genetics Consortium were assessed for polymorphisms at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association of *APOE* with an earlier age of onset and found significant associations for *CR1*, *BIN1*, and *PICALM*. *APOE* contributed 3.7% of the variation in age of onset and the other nine loci combined contributed 2.2% of the variation. Each additional copy of the *APOE* ε4 allele reduced age of onset by 2.45 years.

Lambert (2013) published a large meta-analysis of GWAS of susceptibility loci for late-onset AD in 17,008 AD cases and 37,154 controls of European ancestry.[11] Nineteen loci had genome-wide significance in addition to the *APOE* locus. The researchers confirmed several genes already reported to be associated with AD (*ABCA7*, *BIN1*, *CD33*, *CLU*, *CR1*, *CD2AP*, *EPHA1*, *MS4A6A–MS4A4E*, *PICALM*). New loci located included *HLA-DRB5–HLA-DRB1*, *PTK2B*, *SORL1*, and *SLC24A4-RIN3*.

Susceptibility Testing at the Apolipoprotein E Gene

Many studies have examined the association between the apolipoprotein ε4 allele (*APOE*E4*) and AD. The Rotterdam and Framingham studies are both examples of large observational studies demonstrating the association. The Rotterdam Study was a prospective cohort study in the city of Rotterdam, the Netherlands, with main objectives of investigating risk factors of cardiovascular, neurologic, ophthalmologic, and endocrine diseases in the elderly.[12] In a sample of 6,852 participants, carriers of a single ε4 allele had a relative risk (RR) of developing AD approximately double that of ε3/ε3 carriers. Carriers of the two ε4 alleles had a relative risk of developing dementia approximately eight times that of ε3/ε3 carriers. The Framingham Heart Study was a longitudinal cohort study initiated in 1948 in Framingham, Massachusetts, to identify common risk factors for cardiovascular disease.[13] In 1,030 participants, the relative risk for developing AD was 3.7 (95% confidence interval [CI] 1.9 to 7.5) for carriers of a single ε4 allele and 30.1 (95% CI 10.7 to 84.4) for carriers with two ε4 alleles compared to those without an ε4 allele. The association of the *APOE* ε4 allele with AD is significant; however, *APOE* genotyping does not have high specificity or sensitivity, and is of little value in the predictive testing of asymptomatic individuals.[14]

The American College of Medical Genetics and Genomics has concluded that *APOE* genotyping for AD risk prediction has limited clinical utility and poor predictive value.[15]

The association of *APOE* genotype with response to AD therapy has been examined. Exploratory analyses of pooled safety data from two phase 3 trials of the FDA-approved amyloid-beta targeting therapy aducanumab indicate that APOE ε4 carrier status is associated with a higher incidence of amyloid-related imaging abnormalities (ARIA).[16-18] Specifically, the incidence of ARIA-edema was 43% versus 20%, in APOE ε4 carriers and non-carriers receiving a 10 mg/kg dose of aducanumab, respectively. The overall incidence of any ARIA ranged from 36-41% in the treatment group compared to 10.3% in the placebo group. The clinical effects of ARIA range from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA compared to 0.6% in the placebo arm.

The majority of ARIA-edema radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of aducanumab 10 mg/kg who had ARIA-edema, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients (refer to prescribing label for classification of severity of ARIA). Resolution occurred in 68% of ARIA-edema patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. Ten percent of all patients who received aducanumab 10 mg/kg had more than 1 episode of ARIA-edema. Radiographic severity and symptomatic status were similar for APOE ε4 carriers and non-carriers.

Aducanumab dosing management decisions in the trials were based on clinical symptom severity and ARIA severity on MRI.[17] After radiographic resolution of ARIA-edema or stabilization of ARIA-hemorrhage and resolution of symptoms (if present), participants could resume dosing at the same dose and titration schedule. Limited follow-up data are available for the safety analysis because the phase 3 trials were stopped prematurely for futility.

The USA-1 Study group found *APOE* genotype did not predict therapeutic response.[19] Rigaud (2002) followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial.[20] They found no statistically significant effect of *APOE* genotype on change in cognition (assessed by Cognitive subscale of the Alzheimer's Disease Assessment Scale). However, the study was not designed to examine predictive therapeutic response, and there were baseline cognitive differences according to *APOE* genotype. There is currently insufficient information to make treatment decisions based on *APOE* subtype.

Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*) Gene

Korvatska (2015) published results from a retrospective study of genetic and pathologic studies that included 131 families (751 individuals) with late-onset AD (LOAD) between 1985 and 2014.[21] The authors found 12 of the 16 patients with AD in the LOAD123 family carried R47H. Eleven patients with dementia had apolipoprotein ε 4 (*APOE4*) and *R47H* genotypes. R47H carriers demonstrated a shortened disease duration (mean [SD] 6.7 [2.8] vs. 11.1 [6.6] years, two-tailed t test; p =0.04) and more frequent α-synucleinopathy. The panmicroglial marker ionized calcium-binding adapter molecule 1 was decreased in all AD cases and the decrease was most pronounced in *R47H* carriers (mean [SD] in the hilus 0.114 [0.13] for R47H_AD vs. 0.574 [0.26] for control individuals, two-tailed t test p=0.005 and vs. 0.465 [0.32] for AD, p=0.02; in frontal cortex gray matter: 0.006 [0.004] for *R47H*_AD vs. 0.016 [0.01] for AD, p=0.04, and vs. 0.033 [0.013] for control individuals, p<0.001). Major histocompatibility complex class II, a marker of microglial activation, was increased in all patients with AD (AD: 2.5, R47H_AD: 2.7, and control: 1.0, p < 0.01).

Jonsson (2013) evaluated 3,550 subjects with AD and found a genome-wide association with only one marker, the T allele of rs75932628 (excluding the *APOE* locus and the *A673T* variant in *APP*).[5] The frequency of *TREM2* rs75932628 was then tested in a general population of 110,050 Icelanders of all ages and was found to confer a risk of AD of 0.63% (odds ratio [OR] 2.26, 95% confidence interval [CI] 1.71 to 2.98, $p=1.13x10^{-8}$). In the control population of 8,888 patients 85 years of age or older without a diagnosis of AD, *TREM2* frequency was 0.46% (OR 2.92, 95% CI 2.09 to 4.09, $p=3.42x10^{-10}$). In 1,236 cognitively intact controls age 85 or older, the frequency of *TREM2* decreased even further to 0.31% (OR 4.66, 95% CI 2.38 to 9.14, $p=7.39x10^{-6}$). The decrease in *TREM2* frequency in elderly patients who are cognitively intact supports the findings associating *TREM2* with increasing risk of AD.

Guerriero (2013) also found a strong association of the *R47H TREM2* variant with AD (p=0.001).[6] Using three imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association with the variant and disease (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, and found a highly significant association with AD (OR 5.05, 95% CI 2.77 to 9.16, $p=9.0x10^{-9}$).

Clinical Utility

Chao (2008) published results from the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study, which was designed to examine consequences of AD risk assessment by

APOE genotyping.[22] Of 289 eligible participants, 162 were randomized (mean age, 52.8 years; 73% female; average education, 16.7 years) to either risk assessment based on *APOE* testing and family history (n=111) or family history alone (n=51). During a one-year follow-up, those undergoing *APOE* testing with a high-risk genotype were more likely than low-risk or untested individuals to take more vitamins (40% vs. 24% and 30%, respectively), change diet (20% vs. 11% and 7%, respectively), or change exercise behaviors (8% vs. 4% and 5%, respectively). There is insufficient evidence to conclude that these short-term behavioral changes would alter clinical outcomes. Green (2009) examined anxiety, depression, and test-related distress at six weeks, six months, and one year in the 162 participants randomized in REVEAL.[23] There were no significant differences between the group that received the results of *APOE* testing and the group that did not in changes in anxiety or depression overall or in the subgroup of participants with the *APOE* ε4 allele. However, the ε4 negative participants had significantly lower test-related distress than ε4 positive participants (p=0.01).

Christensen (2016) examined disclosing associations between *APOE* genotype and AD risk alone versus AD and coronary artery disease (CAD) risk in an equivalence trial from the REVEAL group.[24] Two hundred ninety participants were randomized to receive AD risk disclosure alone or AD+CAD risk disclosure. The 257 participants who received their genetic information were included in analyses. Mean anxiety, depression, and test-related distress scores were below cutoffs for mood disorders at all time points in both disclosure groups and were similar to baseline levels. At the 12-month follow-up, both anxiety (measured by the Beck Anxiety Index) and depression (measured by the Center for Epidemiologic Studies Depression Scale) fell within the equivalence margin indicating no difference between disclosure groups. Among participants with an ε4 allele, distress (measured by Impact of Event Scale) was lower at 12 months in AD+CAD group than in the AD-only group (difference -4.8, 95% CI -8.6 to -1.0, p=0.031). AD+CAD participants also reported more health behavior changes than AD-alone participants, regardless of APOE genotype.

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic variant carriers can delay or mitigate future disease. Furthermore, there are many actions patients may take following knowledge of a pathogenic variant. Changes in lifestyle factors (e.g., diet, exercise) or the incorporation of “brain training” exercises can be made, but there is no evidence that these interventions impact clinical disease.

Section Summary

Both the *APOE* gene and the triggering receptor gene have shown strong statistical associations with AD, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of *APOE* ε4 is poor, and there is a lack of evidence on the clinical sensitivity and specificity of the triggering receptor gene. Furthermore, no studies were identified that address how the use of the *APOE* or other AD-associated variants might be incorporated into clinical practice, and it is not clear how management of patients with these genes would change in a way that improves outcomes. The REVEAL studies have found short-term changes in behaviors following disclosure of *APOE* genetic testing results in high-risk adults with little increase in anxiety or depression overall, although with possible increase in distress among ε4 allele carriers. It is unclear whether these changes in behaviors would improve clinical outcomes or whether there are long-term effects on psychological outcomes among ε4 carriers. Therefore, clinical utility has not been demonstrated for these tests.

GENETIC TESTING FOR EARLY-ONSET FAMILIAL ALZHEIMER'S DISEASE

Clinical Validity

In the scenario of targeted testing of individuals with a known familial pathogenic variant, due to nearly complete penetrance of pathogenic variants, an identified carrier will almost certainly develop the disease unless dying at an age preceding disease onset. Therefore, the clinical validity is nearly certain.

In the scenario of genetic testing of individuals with a family history consistent with autosomal dominant early-onset AD but in whom a pathogenic variant has not been found, the testing yield is less certain. Genetic testing for presenilin 1 (*PSEN1*) is estimated to detect disease-causing variants in 30% to 60% of individuals with familial early-onset AD,[25, 26] although estimates vary A number of variants scattered throughout the *PSEN1* gene have been reported, requiring sequencing of the entire gene when the first affected member of a family with an autosomal dominant pattern of AD inheritance is tested. Variants in amyloid-beta precursor protein (*APP*) and presenilin 2 (*PSEN2*) genes account for another 10% to 20% of cases.

Genetic yields may vary by population. Giau (2019) reported on 200 patients with clinically diagnosed early-onset AD from Thailand, Malaysia, the Philippines, and Korea who were genetically screened between 2009 and 2018.[27] Thirty-two (16%) patients carried pathogenic *APP* (8/32 [25%]), *PSEN1* (19/32 [59%]), or *PSEN2* (5/32 [16%]) variants. However, this analysis included possible and probable pathogenic variants in addition to those classified as definite. Overall, approximately 84% (p=0.01) of autosomal dominant pedigrees in the tested Asian population were genetically unexplained. Clinical and phenotypic expressivity is variable. A report by Ryan (2016) indicates that individuals with a *PSEN1* variants may have a significantly younger age of onset than individuals with an *APP* variant (mean age [SD] 43.6 years [7.2] vs. 50.4 years [5.2], respectively, p<0.0001).[28] However, the presence of *PSEN1*, *PSEN2*, or *APP* variants is not useful in predicting age of onset (although age of onset is usually similar in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals.

A study by Cochran (2019) confirmed a high diagnostic yield in early-onset or atypical dementia.[29] Fifty percent (16/32) of patients tested harbored one or more genetic variants capable of explaining symptoms, including variants in *APP*. Nine of 32 patients (28%) had a variant defined as pathogenic or likely pathogenic whereas six had one or more variants with moderate penetrance. The authors noted this supports a potential oligogenic model for early-onset dementia.

Clinical Utility

The potential clinical utility of testing is in early identification of asymptomatic patients who are at risk for developing early-onset AD. Genetic testing, will in most cases, lead to better risk stratification, distinguishing patients who will develop the disease from those who will not. If early identification of patients at risk leads to interventions to delay or mitigate clinical disease, then clinical utility would be established. Identification of asymptomatic, young adult carriers could impact reproductive planning. And clinical utility may be demonstrated if testing leads to informed reproductive planning that improves outcomes. However, there is no evidence that early intervention for asymptomatic variant carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a pathogenic variant: changes in

lifestyle factors (e.g., diet, exercise) and incorporation of “brain training” exercises; but there is no evidence that these interventions impact clinical disease.

Alternatively, clinical utility could be demonstrated if knowledge of variant status leads to beneficial changes in psychological outcomes. However, a systematic review on the psychological and behavioral impact of genetic testing for AD found few studies on the impact of testing for early-onset familial AD. The existing studies generally have small sample sizes and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.[30]

When a known pathogenic variant is identified in a prospective parent, with reasonable certainty, disease will develop and there is a 50% risk of an affected offspring. When a pathogenic variant is detected in a prospective parent, the prospective parent can choose to refrain from having children or choose medically assisted reproduction during which preimplantation testing would allow a choice to avoid an affecting offspring. Identification of a pathogenic variant by genetic testing is more accurate than the alternative of obtaining a family history alone. Therefore, testing in the reproductive setting can improve health outcomes.

Section Summary

For those individuals who do have a family member with early-onset, familial AD, with a known pathogenic familial variant or a family pedigree consistent with autosomal dominant AD, testing a prospective parent when performed in conjunction with genetic counseling provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. There are currently no known preventive measures or treatments that can mitigate the effect of AD. It is not clear how change in the management of asymptomatic patients with these genes would improve outcomes. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS

The American College of Medical Genetics and Genomics lists genetic testing for *APOE* alleles as one of five recommendations in the Choosing Wisely initiative.[15] The recommendation is “Don’t order *APOE* genetic testing as a predictive test for Alzheimer disease.” The stated rationale is that *APOE* is a susceptibility gene for later-onset AD, the most common cause of dementia. These recommendations stated that “The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity, and the *APOE* genotyping for AD risk prediction has limited clinical utility and poor predictive value.”

AMERICAN COLLEGE OF GENETICS AND NATIONAL SOCIETY OF GENETIC COUNSELORS

The American College of Genetics and the National Society of Genetic Counselors issued the following joint practice guidelines in 2011, which were reaffirmed in 2019:[3, 31]

- Pediatric testing for AD should not occur.

- Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for AD should only occur in the context of genetic counseling (in person or through videoconference) and support by someone with expertise in this area.
    - Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member.
    - Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended.
- Direct-to-consumer *APOE* testing is not advised.
- A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.
- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD [late-onset AD] and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
    - The lifetime risk of AD in the general population is approximately 10–12% in a 75–80 year lifespan.
    - The effect(s) of ethnicity on risk is still unclear.
    - Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown.

For families in which an autosomal dominant AD gene mutation is a possibility:

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- Testing for genes associated with early onset autosomal dominant AD should be offered in the following situations:
    - A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption).
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a mutation consistent with EOAD (currently *PSEN1*/2 or *APP*).
- The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted (available online at: www.molgen.ua.ac.be/ADMutations/) before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing.
    - Discuss the likelihood of identifying a mutation in *PSEN1*, *PSEN*2, or *APP*, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
    - Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains

interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed.

SUMMARY

There is enough research to show that *PSEN* and *APP* genetic testing for autosomal dominant Alzheimer's disease can help individuals at risk for this disorder to make reproductive decisions. Therefore, this genetic testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing for late- or early-onset Alzheimer's disease can improve health outcomes, including for those with a family history of Alzheimer's disease. Therefore, genetic testing when policy criteria are not met, including risk assessment or to aid in the diagnosis of Alzheimer's disease, is considered investigational.

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CODES

Codes	Number	Description
CPT	81401	Molecular pathology procedure, Level 1
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
HCPCS	S3852	DNA analysis for *APOE* epsilon 4 allele for susceptibility to Alzheimer’s disease

Date of Origin: *January 2011*

Regence

Medical Policy Manual Genetic Testing, Policy No. 02

Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome

Effective: January 1, 2025

Next Review: February 2025
Last Review: December 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

Familial cancer syndromes, including hereditary breast and ovarian cancer (HBOC) syndrome are related to variants in the *BRCA* genes (*BRCA1* and *BRCA2*). Variants in several other genes, including *PALB2* and *STK11*, are also associated with increased risk of breast, ovarian, and other cancers. Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated a high lifetime cumulative risk of cancer and a tendency for multiple cancers in affected individuals. LFS is related to variants in the *TP53* gene. Identification of patients with variants in *BRCA1/2, TP53,* or other genes may lead to enhanced screening and/or surveillance that could lead to improved outcomes.

MEDICAL POLICY CRITERIA

Note: Both maternal and paternal family histories are important in identifying families with a high risk of genetic variant and therefore, each lineage must be considered separately. For PTEN single-gene testing, see Cross References below.

I. **Family with a Known Pathogenic Variant**: Genetic testing for a known familial pathogenic variant in *BRCA1*, *BRCA2, BRIP1*, *CDH1*, *PALB2, PTEN, RAD51C*, *RAD51D, STK11* or *TP53* may be considered **medically necessary**.

II. **Individuals with Active Cancer or a Personal History of Cancer**: Genetic testing (including panel testing) for *BRCA1*, *BRCA2, CDH1*, *PALB2, PTEN, STK11* and/or *TP53* variants in cancer-affected individuals may be considered **medically necessary** when one or more of the following criteria are met:

A. Personal history of breast, pancreatic, ovarian (See Policy Guidelines), fallopian tube, and/or peritoneal cancer; or

B. Personal history of prostate cancer (Gleason score ≥ 7) *and* one or more of the following:

1. Metastatic prostate cancer; or
2. High-risk prostate cancer, defined as any of the following:
    a. Gleason score ≥ 8; or
    b. T stage of T3a, T3b, or T4; or
    c. PSA > 20 ng/mL; or
    d. Gleason pattern 5 histology
3. Intraductal/cribriform histology; or
4. Ashkenazi Jewish ancestry; or
5. One or more close blood relatives with any of the following: breast, ovarian, fallopian tube, peritoneal, pancreatic, and/or prostate cancer (Gleason score ≥ 7) (see Policy Guidelines).

C. *BRCA1* and *BRCA2* germline (blood-based) testing when tumor genetic testing has been performed and the results indicate that a *BRCA1* or *BRCA2* variant is present in tumor tissue.

D. The treating provider has documented that the individual is at increased risk for a *BRCA* variant based on one of the following seven risk-stratification tools endorsed by the USPSTF (See Policy Guidelines) and the documentation indicates which tool was used: the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen 7 (FHS-7), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), BRCAPro (brief versions).

III. **Individuals without Active Cancer and Without History of Cancer**: Genetic testing (including panel testing) for *BRCA1*, *BRCA2, CDH1*, *PALB2, PTEN, STK11,* and/or *TP53* variants in cancer-unaffected individuals (no personal history of the following: breast cancer, ovarian cancer, fallopian tube, peritoneal cancer, pancreatic cancer, or prostate cancer [Gleason score ≥ 7]) with unknown variant status, may be considered **medically necessary** when one or more of the following criteria are met:

A. Individual is at increased risk when one or more of the following family history criteria are met:

1. A first-degree relative has been diagnosed with breast or ovarian cancer; or
2. Two or more close blood relatives (see Policy Guidelines) have been diagnosed with breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, diffuse gastric cancer, and/or colorectal cancer; or

3. A close blood relative (see Policy Guidelines) has been diagnosed with any of the following:
    a. Bilateral breast cancer; or
    b. Male breast cancer; or
    c. Breast cancer before age 50; or
    d. Both breast and ovarian cancer.

B. The treating provider has documented that the individual is at increased risk for a *BRCA* variant based on one of the following seven risk-stratification tools endorsed by the USPSTF (See Policy Guidelines) and the documentation indicates which tool was used: the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen 7 (FHS-7), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), BRCAPro (brief versions); or

C. Confirmatory *BRCA1* or *BRCA2* testing when the treating provider has documented that direct-to-consumer DNA testing (such as ancestry testing) indicates a pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant.

IV. Genetic testing for *TP53* may be considered **medically necessary** when the treating provider has documented a concern that the patient is at increased risk for a *TP53* variant, including in the evaluation of possible Li-Fraumeni syndrome.

V. Genetic testing for *BRIP1*, *RAD51C*, and/or *RAD51D* may be considered **medically necessary** when any of the following criteria are met:

A. Personal history of ovarian cancer; or

B. A first- or second-degree blood relative with ovarian cancer.

VI. Genetic testing for *BRCA1*, *BRCA2, BRIP1*, *CDH1*, *PALB2, PTEN, RAD51C*, *RAD51D, STK11* and/or *TP53* variants for hereditary breast/ovarian cancer risk is considered **investigational** in patients who do not meet Criteria I., II., III., IV., or V.

VII. Single gene or panel testing for any other gene not listed in the criteria above (including but not limited to *ATM*, *BARD1*, and *CHEK2*) is considered **investigational** for hereditary breast and/or ovarian cancer.

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

POLICY GUIDELINES

DEFINITIONS

Close blood relatives include 1st-, 2nd-, and 3rd-degree relatives from the same lineage as follows:

- *1st-degree relatives* are parents, siblings, and children of an individual;
- *2nd-degree relatives* are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual; and
- *3rd-degree relatives* are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Ovarian cancer is a type of cancer that starts in the ovaries and can spread into the pelvis and abdomen. For the purposes of this policy, fallopian tube and peritoneal cancers are also included in the definition of ovarian cancer.

Invasive and stage 0 (including ductal and lobular carcinoma in situ) are considered breast cancer for the purposes of this policy.

RISK STRATIFICATION TOOLS FOR IDENTIFYING AN INCREASED RISK OF *BRCA* VARIANTS

The thresholds for referral for genetic counseling for the USPSTF-endorsed screening tools are listed below. Most of these tools are accessible from the USPSTF website at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing

- Ontario Family History Assessment Tool (FHAT): Score of ≥ 10
- Manchester Scoring System: Score of 10 in either column or combined score of 15 for both columns
- Referral Screening Tool (RST): Presence of ≥ 2 items
- Pedigree Assessment Tool (PAT): Score of ≥ 8
- Family History Screen 7 (FHS-7): ≥ 1 positive response
- International Breast Cancer Intervention Study instrument (Tyrer-Cuzick): risk level ≥ 10%
- BRCAPro (brief versions): risk level ≥ 10%

TESTING AFFECTED FAMILY MEMBERS

Initial testing of an affected family member is strongly recommended whenever possible. Should a *BRCA* variant be found in the affected family member(s), unaffected family member DNA can be tested specifically for the same variant without having to sequence the entire gene.

BRCA TESTING FOR TREATMENT WITH LYNPARZA™ (OLAPARIB)

For individuals who have had a previous *BRCA* test other than BRACAnalysis CDx (Myriad Genetics), repeat *BRCA* variant testing with BRACAnalysis CDx may be necessary when treatment with Lynparza™ (olaparib) is being considered.

BRCA TESTING FOR TREATMENT WITH RUBRACA™ (RUCAPARIB)

For individuals who have had a previous *BRCA* test other than FoundationFocus CDxBRCA (Foundation Medicine), repeat *BRCA* variant testing with FoundationFocus CDxBRCA may be necessary when treatment with Rubraca™ (rucaparib) is being considered.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF GENETIC TESTING DOCUMENTATION

All of the following information must be submitted for review prior to the genetic testing:

1. Name of genetic test(s) and/or panel test
2. The exact gene(s) and/or variants being tested

3. Name of performing laboratory and/or genetic testing organization (more than one may be listed)
4. Relevant billing codes
5. Date of sample collection/blood draw
6. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
7. Clinical documentation by the provider (e.g., primary care physician, family practitioner, gynecologist) of family history and supporting rationale for the requested test(s)

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, Genetic Testing, Policy No. 42
3. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
4. Genetic Testing for PTEN Hamartoma Tumor Syndrome, Genetic Testing, Policy No. 63
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
6. Lynparza™ (olaparib), Medication Policy Manual, Policy No. dru389

BACKGROUND

BRCA1 AND *BRCA2*

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC), and some cases of hereditary site-specific breast cancer have causative variants in *BRCA* genes in common. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for cancer susceptibility in the majority of HBOC families, especially if ovarian cancer is a feature. However, in site-specific breast cancer, *BRCA* variants are responsible for only a proportion of affected families, and research to date has not yet identified other moderate or high-penetrance gene variants that account for disease in these families. *BRCA* gene variants are inherited in an autosomal dominant fashion through either the maternal or paternal lineage (each lineage must be considered separately). It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality. Genetic counseling is highly recommended when genetic testing is offered and when the genetic test results are disclosed. Please see Appendix 1 for a recommended testing strategy.

BRIP1

BRIP1 (BRCA1 interacting protein C-terminal helicase 1) encodes a protein that interacts with BRCA1 to function in DNA repair. Heterozygous pathogenic *BRIP1* variants increase the risk

of ovarian cancer, while homozygous pathogenic *BRIP1* variants are associated with Fanconi anemia. The prevalence of *BRIP1* variants in women with ovarian cancer appears to be approximately 1% and the lifetime risk associated with a pathogenic variant is estimated to be 5.8%.[1]

PALB2

PALB2 (partner and localizer of BRCA2) encodes a protein that assists BRCA2 in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. Women with a pathogenic *PALB2* variant have a 14% lifetime risk of breast cancer by age 50, which increases to 35% by age 70.[2]

PTEN

PTEN (phosphatase and tensin homolog) encodes a tumor suppressor that antagonizes the PI3K signaling pathway through its lipid phosphatase activity and negatively regulates the MAPK pathway through its protein phosphatase activity.[3] *PTEN* variants are inherited in an autosomal dominant manner. There is a spectrum is disorders that result from germline variants in *PTEN* referred to as *PTEN* hamartoma tumor syndrome / Cowden syndrome. These syndromes are associated with multiple tumors, including a lifetime risk of breast cancer of up to 50%.[1]

STK11

STK11 (serine/threonine kinase 11) encodes a tumor suppressor that controls the activity of AMP-activated protein kinase (AMPK) family members, thereby playing a role in cell metabolism, apoptosis and DNA damage response. *STK11* variants are associated with Peutz-Jeghers syndrome, an autosomal dominant syndrome characterized by the gastrointestinal polyps, breast cancer, non-epithelial ovarian cancer, and other neoplasms.[1]

RAD51C and *RAD51D*

RAD51 genes encode tumor suppressors that are involved in DNA repair. Heterozygous pathogenic variants in these genes are associated with ovarian cancer. The cumulative risk of ovarian cancer for an individual with such a variant approaches 2.6% (the risk for women with a family history of ovarian cancer without a BRCA variant) between the ages of 50 to 54 for *RAD51D* and 60 to 64 for *RAD51C*.[1]

TP53

The *TP53* gene contains the genetic instructions for the production of tumor protein p53 (or p53). The p53 protein is a tumor suppressor that functions as a cell cycle regulator to prevent cells from uncontrolled growth and division when there is DNA damage. Somatic (acquired) pathogenic variants are one of the most frequent alterations found in human cancers. Germline (inherited) pathogenic variants in *TP53* are associated with Li-Fraumeni syndrome (LFS).

ATM

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia syndrome. This condition is characterized

by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Females with a heterozygous *ATM* variant have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

BARD1

The *BARD1* (BRCA1-associated RING domain) gene is located on chromosome 2 (sequence 2q34-q35). *BARD1* encodes a protein which interacts with the N-terminal region of *BRCA1*, and *BARD1* and *BRCA1* can form a heterodimer by their N-terminal RING finger domains which form a stable complex.[4] *BARD1* variants have been associated with an increased risk of estrogen-receptor (ER) negative breast cancer, triple-negative breast cancer, and with breast cancer at a younger age (under age 50 years) in some studies, but do not appear to increase risk of ovarian cancer.[5, 6]

CHEK2

CHEK2 (cell cycle checkpoint kinase 2) is involved with DNA repair and human cancer predisposition like BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of BRCA1 protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The *CHEK2* variant, *1100delC* in exon 10 has been associated with familial breast cancers.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[7] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The clinical utility of testing for variants in the *BRCA1* and *BRCA2* genes to inform surveillance, prognosis and treatment of patients with hereditary breast cancer has been unequivocally demonstrated. Therefore, the scientific evidence will no longer be reviewed for the clinical utility of *BRCA1* and *BRCA2* testing, as they may be considered medically necessary.

In addition, there are several genes: *PTEN, STK11*, *CDH1*, and *TP53*; which are the causative factors in rare, but highly penetrant cancer syndromes that substantially increase the risk of breast cancer. Although rare, when taken together, variants in these genes are thought to account for at least 5% to 10% of breast cancer diagnoses. Since the clinical utility of testing for variants in these genes to inform surveillance, prognosis and treatment of patients with hereditary breast cancer has been demonstrated, they will not be reviewed extensively in the evidence section below.

The focus of the scientific evidence review below is on the investigational indications only, such as *CHEK2* testing. The evidence review is related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and

- Improve health outcomes as a result of those decisions.

CHEK2 TESTING

Systematic Reviews on Breast Cancer Association

A number of systematic reviews have described the association of cell cycle checkpoint kinase 2 (*CHEK2*) variants with hereditary breast cancer. The prevalence of this finding varies greatly by geographic region, being most common in Northern and Eastern Europe. In the US, *CHEK2* variants are much less common than *BRCA* variants and *BRCA* rearrangements. For example, in the study by Walsh (2006), 14 (4.7%) of the 300 patients with a positive family history of breast cancer (four affected relatives) who were negative by standard *BRCA* testing, were positive for *CHEK2* variants.[8]

A systematic review and meta-analysis by Suszynska (2019) included association estimates for *CHEK2* variants.[9] The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. The studies of panel results were used to calculate variant frequencies by the gene. As a control, population variant frequencies were extracted from the Genome Aggregation Database. In the 43 breast cancer studies included in the review, 94,845 patients contributed to the meta-analysis of *CHEK2* in breast cancer patients. The odds ratio (OR) of breast cancer for *CHEK2* variants including variants c.470T>C and c.1283C>T was 0.96 (95% confidence interval [CI] 0.90 to 1.03); after excluding variants c.470T>C and c.1283C>T, the remaining *CHEK2* variants had an OR for breast cancer of 1.73 (95% 1.58 to 1.89).

Liang (2018) conducted a meta-analysis to investigate the link between *CHEK2* and breast cancer.[10] Two researchers independently searched seven online databases and selected for analysis 26 published studies representing a pooled sample of 118,735 cancer patients and 195,807 controls, all case-control studies conducted in Europe or the Americas. Meta-analysis revealed that *CHEK2* variants are more common in patients with breast cancer (OR 2.89; 95% CI 2.63 to 3.16), with variants 5.9% more likely in female patients with breast cancer than in male patients with breast cancer. Limitations of the study included a study population that might not represent the general population, inaccurate control sampling methods in some original studies, selection biases, and unclear criteria for breast-cancer diagnoses.

A meta-analysis by Schmidt (2016) evaluated data on *CHEK2* variant status and breast cancer risk from the Breast Cancer Association Consortium.[11] The analysis included 44,777 breast cancer patients and 42,997 controls from 33 studies in which individuals were genotyped for *CHEK2* variants. The estimated odds for invasive breast cancer in patients with and without the *CHEK2 1100delC* variant was 2.26 (95% CI 1.90 to 3.10).

In a meta-analysis by Yang (2012), the link between *CHEK2 1100delC* heterozygote and breast cancer risk was investigated.[12] A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. A significant association was found between *CHEK2 1100delC* heterozygote and breast cancer risk. Authors concluded that the *CHEK2 1100delC* variant could be a potential factor for increased breast cancer risk in Caucasians; however, they suggested that more consideration is needed in order to apply it to allele screening or other clinical work.

In a systematic review and meta-analysis by Liu (2012), authors identified fifteen case-control studies with 19,621 cases and 27,001 controls that were included in their analysis.[13] Authors reported a significant association found between the *CHEK2 I157T* variant and increased risk of unselected breast cancer, and early-onset breast cancer. In addition, an even stronger significant association was found between the *CHEK2 I157T* variant and increased risk of lobular type breast tumors. Authors concluded the *CHEK2 I157T* variant may be another important genetic variant which increases risk of breast cancer, especially the lobular type. The methodological quality of this review was limited; the evidence was not quality appraised for risk of bias.

A meta-analysis by Han (2013) investigated the relationship of the *CHEK2 I157T* variant and the incidence of cancer.[14] In total, 26,336 cases and 44,219 controls from 18 case-control studies were used in the meta-analysis. Authors concluded that the *CHEK2 I157T* variant was an important cancer gene, which increases cancer risk, especially for breast and colorectal cancer.

Zhang (2011) performed a systematic review of candidate-gene association studies of breast cancer risk, identifying more than 1,000 published articles. Meta-analysis was performed for a total of 279 genetic variants in 128 genes that were identified by at least three different researchers. Significant associations with the risk of breast cancer were found for 29 variants in 20 genes. The association was strong for ten variants in six genes, four of which were located in the *CHEK2* gene.[15]

Peng (2011) identified 87 meta-analyses and pooled analyses which examined the association of 145 candidate gene variants and breast cancer. They found significant association for 46 variants, with ORs ranging from 0.66 to 3.13. The further analysis of ORs (using the method of false-positive report probability) identified ten noteworthy associations, including *CHEK2* (**1100delC*).[16]

Weischer (2008) performed a meta-analysis of studies on *CHEK2 1100delC* heterozygosity and the risk of breast cancer among patients with unselected (including the general population), early-onset (<51 years of age) and familial breast cancer.[17] The analysis identified prospective cohort and case-control studies on *CHEK2* 1100delC and the risk of breast cancer published before March 2007. Inclusion criteria were women with unilateral breast cancer who did not have a known multicancer syndrome, Northern or Eastern European descent, availability for *CHEK2* genotyping, *BRCA1* and *BRCA2* variant-negative or unknown status, and breast cancer-free women as controls. The meta-analysis included 16 studies with 26,488 patient cases and 27,402 controls. Using fixed-effect models, for *CHEK2 1100delC* heterozygotes versus those without a variant, the aggregated OR for breast cancer was 2.7 (95% CI 2.1 to 3.4) and 2.4 (95% CI 1.8 to 3.2), respectively, for *CHEK2 1100delC* heterozygotes versus those without a variant in studies of patients with unselected breast cancer, 2.6% (95% CI 1.3 to 5.5) versus 2.7 (95% CI 1.3 to 5.6), respectively, for early-onset breast cancer, and 4.8 (95% CI 3.3 to 7.2) versus 4.6 (95% CI 3.1 to 6.8), respectively, for familial breast cancer. The cumulative risk at age 70 years for *CHEK2*1100delC* variant was 37% (confidence interval 26% to 56%). This risk is lower than cumulative risk at age 70 of 57% for *BRCA1* and 49% for *BRCA2*.

CHEK2 and Breast Cancer Prognosis

A study by Huzarski (2014) estimated the 10-year survival rate for patients with early-onset breast cancer, with and without *CHEK2* variants.[18] Patients were consecutively identified

women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for four founder variants in the *CHEK2* gene after diagnosis, and their medical records were used to retrieve tumor characteristics and treatments received. Dates of death were retrieved from a national registry. A total of 3,592 women were eligible for the study, of whom 487 (13.6%) carried a *CHEK2* variant (140 with truncating variants, 347 with missense variants). Mean follow-up was 8.9 years. Ten-year survival for individuals with a *CHEK2* variant was similar to that of individuals without a variant, at 78.8% (95% CI 74.6% to 83.2%) and 80.1% (95% CI 78.5% to 81.8%), respectively. After adjusting for other prognostic features, the hazard ratio comparing those with and without the missense variant was similar, as for those with and without a truncating variant.

A study by Kriege (2014) compared breast cancer outcomes in patients with and without *CHEK2* variants.[19] Different study cohorts were combined to compare 193 individuals with *CHEK2* variants with 4,529 controls. Distant disease-free survival and breast cancer-specific survival were similar in the first six years after diagnosis. After six years, both distant disease-free survival (multivariate HR 2.65, 95% CI 1.79 to 3.93) and breast cancer-specific survival (multivariate HR 2.05, 95% C, 1.41 to 2.99) were worse in those *CHEK2* variants. No interaction between *CHEK2* status and adjuvant chemotherapy was observed.

Weischer (2012) reported on breast cancer associated with early death, breast cancer–specific death, and the increased risk of a second breast cancer (defined as a contralateral tumor) in patients with and without a *CHEK2* variant.[20] The study included 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, with data from 22 studies participating in the Breast Cancer Association Consortium conducted in 12 countries. The 22 studies included 30,056 controls. Data were reported on early death in 25,571 women, breast cancer–specific death in 24,345 and a diagnosis of a second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2 1100delC* heterozygous and 25,112 (98.2%) did not have a *CHEK2* variant. Median follow-up was 6.6 years, over which time 124 (27%) deaths, 100 (22%) breast cancer–specific deaths, and 40 (9%) second breast cancers among those with a *CHEK2 1100delC* variant were observed. Corresponding numbers among those without this variant were 4,864 (19%), 2,732 (11%), and 607 (2%), respectively. At the time of diagnosis, those with a *CHEK2* variant versus those without were on average four years younger ($p<0.001$) and more often had a positive family history ($p<0.001$).

CHEK2 Evidence Summary

The evidence for testing for *CHEK2* variants in individuals who are undergoing risk assessment for breast cancer includes population and family-based case control studies. Relevant outcomes are overall survival, test accuracy, test validity, morbid events, resource utilization, and treatment-related morbidity. Studies have shown that a *CHEK2* variant is of moderate penetrance and confers a risk of breast cancer of two to four times that of the general population; this risk appears to be higher in patients who also have a strong family history of breast cancer, however, risk estimates are subject to bias and overestimation. Several studies have suggested that individuals with *CHEK2* variants with breast cancer may have worse breast cancer-specific survival and distant-recurrence free survival, with about twice the risk of early death.

Further studies are needed to determine whether some patients with a *CHEK2* variant have a risk that is similar to the risk with a high-penetrance variant and identify those that would be

best managed according to the well-established guidelines for high-risk patients. Clinical management recommendations for inherited conditions associated with moderate penetrance variants, such as *CHEK2*, are not standardized, nor is it known if testing for *CHEK2* variants will lead to changes in patient management or improved health outcomes. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

ATM TESTING

Systematic Reviews on Breast Cancer Association

A systematic review conducted by Moslemi (2021) included 24 cross-sectional studies reporting on the prevalence of *ATM* variants in individuals with breast cancer.[21] The review found a pooled prevalence of 7% (95% CI 6% to 9%) based on 21 studies included in the meta-analysis with high heterogeneity (I^2=93%). In individuals with and *ATM* and *BRCA1* or *BRCA2* variant, prevalence was 11% (95% CI 7% to 11%, I^2=99%), in those with an ATM variant but without a *BRCA1/2* variant, the prevalence was 3% (95% CI 2% to 4%, I^2=85%). Meta-regression found age did not have a significant effect on prevalence of ATM in individuals with breast cancer, and Egger's test did not reveal evidence of publication bias (p=0.98).

The Suszynska (2019) systematic review described previously also included association estimates for *ATM* variants.[9] In the 43 breast cancer studies included in the review, 94,787 patients contributed to the meta-analysis of *ATM* in breast cancer patients. The OR of breast cancer for *ATM* variants was 2.42 (95% CI 2.16 to 2.71).

Marabelli (2016) reported on a meta-analysis of the penetrance of *ATM* variants in breast cancer, which used a model allowing the integration of different types of cancer risk estimates to generate a single estimate associated with heterozygous *ATM* gene variants.[22] The meta-analysis included 19 studies, which were heterogeneous in terms of population, study designs, and baseline breast cancer risk. The estimated cumulative absolute risk of breast cancer in those with a heterozygous *ATM* variant was 6.02% by age 50 (95% credible interval 4.58% to 7.42%) and 32.83% by age 80 (95% credible interval 24.55% to 40.43%).

ATM Evidence Summary

For individuals with risk of HBOC who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance; moreover, *ATM* variants confer a risk of breast cancer two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of HBOC was not identified. It is unclear that the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance variant such as *ATM*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

BARD1 TESTING

Systematic Reviews on Breast Cancer Association

Two systematic reviews conducted by Suszynska (2019)[9] and (2020)[23] reported estimates on the association of *BARD1* variants with risk of breast cancer. The prevalence of *BARD1* variants was 0.22% to 0.25% in individuals with breast cancer; prevalence in controls was about 0.09%. The reviews found presence of a *BARD1* variant was associated with approximately a two- to three-fold increased risk of breast cancer. The 2020 review identified 60 distinct pathogenic variants among individuals with breast cancer, 21 of which were present in controls. In individuals with a recurrent pathogenic variant (defined as occurring in three or more cases), risk was elevated among those with the c.334C>T (R112*), c.1652C>G (S551*), c.1690C>T (Q564*) variants, but prevalence was very low (≤0.03% among cases and ≤0.004% among controls) and these estimates were imprecise.

BARD1 Evidence Summary

For individuals with risk of HBOC who receive genetic testing for a *BARD1* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *BARD1* variants are of low to moderate penetrance; *BARD1* variants confer a risk of breast cancer about two to three times that of the general population. Direct evidence for the clinical utility of genetic testing for *BARD1* variants in individuals with risk of HBOC was not identified. It is unclear that the relative risk associated with the low- to moderate-penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a low- to moderate-penetrance variant such as *BARD1*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES (NCCN)

Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic Cancer[1]

High-Penetrance Genes: *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53*

- The NCCN Guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer (v.3.2024) recommend testing for high-penetrance breast and/or ovarian cancer susceptibility genes, including *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* testing, in select individuals.
- In patients with a known familial pathogenic or likely-pathogenic variant, targeted testing for the specific variant is recommended.
- In patients with no known familial variant, multi-gene testing of the patient or, if the patient is unaffected, testing of the family member with the highest likelihood of a pathogenic/likely pathogenic variant is recommended prior to testing the patient, if possible; if the affected individual is of Ashkenazi Jewish descent, testing for the three known founder variants is recommended.

Additional Genes

The NCCN guidelines include a table listing *BRCA1*, *BRCA2*, *TP53* and a number of other genes associated with increased risks of breast, ovarian, and/or pancreatic cancer, along with cancer risk management for these genes. The authors note that the inclusion of a gene in the

table “does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.”

Regarding moderate penetrance genes and multigene testing, the guidelines state:

> “Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of the genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of P/LP [pathogenic/likely pathogenic] variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history.”

Prostate Cancer[24]

The NCCN guidelines for prostate cancer (v.2.2024) include recommendations for germline testing for genes related to hereditary breast and ovarian cancers in patients with prostate cancer, including *BRCA1* and *BRCA2*. Germline testing is recommended for patients with high-risk, very-high-risk, regional, or metastatic prostate cancer prostate cancer patients and those with any of the following:

- Ashkenazi Jewish ancestry
- A family history of a familial cancer risk mutation
- A positive family history of certain types of cancer
- A personal history of breast cancer

US PREVENTIVE SERVICES TASK FORCE (USPSTF)

The 2019 USPSTF guideline titled *Risk Assessment, Genetic Counseing, and Genetic Testing for BRCA-Related Cancer* recommends the following:[25]

- The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (Grade B recommendation).
- The USPSTF recommends against routine risk assessment, genetic counseling or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations (Grade D recommendation).

SOCIETY OF GYNECOLOGIC ONCOLOGY (SGO)

In 2014, the SGO[26] published a consensus statement that was evidence informed for inherited gynecologic cancer. SGO recommends genetic assessment (counseling with or without testing) for patients genetically predisposed to breast or ovarian cancer. The SGO and NCCN guidelines generally align with some slight variations. Specifically, SGO recommends that other individuals may benefit from genetic assessment (e.g., unaffected women with a male relative with breast cancer, few female relatives, hysterectomy or oophorectomy at a young age in multiple family members, or adoption in the lineage).

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The American Society of Clinical Oncology (ASCO) 2015 policy statement update on genetic and genomic testing for cancer susceptibility states that testing for high-penetrance variants in appropriate populations has clinical utility in that the variants inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes.[27] Regarding moderate-penetrance genes, the update stated, “Clinical utility remains the fundamental issue with respect to testing for mutations in moderate-penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate penetrance variants, and no guidelines exist to assist oncology providers."

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, AMERICAN SOCIETY FOR RADIATION ONCOLOGY, AND SOCIETY OF SURGICAL ONCOLOGY

ASCO and the Society of Surgical Oncology (SSO) published consensus guidelines for germline testing in patients with breast cancer in 2024, which included the following recommendations:[28]

- “All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are 65 years or younger at diagnosis should be offered *BRCA1*/*2* testing.
- All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are older than age 65 should be offered *BRCA1*/*2* testing if:
    - they are candidates for poly(ADP–ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease,
    - they have triple-negative breast cancer,
    - their personal or family history suggests the possibility of a pathogenic variant,
    - they were assigned male sex at birth,
    - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations.
- Patients undergoing *BRCA1/2* testing should also be offered testing for other cancer predisposition genes as suggested by their personal or family history. Consultation with a provider experienced in clinical cancer genetics can help guide this decision-making and should be made available to patients when possible.
- All patients with recurrent breast cancer (local or metastatic) who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing regardless of family history.
- *BRCA1/2* testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast.
- All patients with a personal history of breast cancer diagnosed ≤65 years who are without active disease should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment.
- All patients with a personal history of breast cancer diagnosed over age 65 with no active disease, who meet one of the following criteria, should be

offered *BRCA1*/*2* testing if the result will inform personal risk management or family risk assessment:

  - their personal or family history suggests the possibility of a pathogenic variant,
  - they were assigned male sex at birth,
  - they had triple-negative breast cancer,
  - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations.

- Testing for high penetrance genes beyond *BRCA1*/*2*, including *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients.

- Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing *BRCA1/2* testing.

- If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. Consultation with a provider experienced in clinical cancer genetics can be helpful in selecting a specific multi-gene panel or interpreting its results and should be made available to patients when possible."

Consensus guidelines for the management of hereditary breast cancer published in 2020 by the ASCO, the SSO, and the American Society for Radiation Oncology include a number of recommendations related to surgery, radiation, and therapy, including the following:[29]

- "Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast-conserving therapy (BCT) from receiving BCT. (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate)

- Surgical management of the index malignancy (BCT v ipsilateral therapeutic and contralateral risk-reducing mastectomy [CRRM]) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers. (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Strong)

- The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers: age at diagnosis (the strongest predictor of future CBC; refer to Table 1 in the original guideline), family history of breast cancer, overall prognosis from this or other cancers (e.g., ovarian), ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI]), comorbidities, and life expectancy. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

- *BRCA1/2* mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

- For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT should be offered to those for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- The evidence regarding CBC risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data on *CHEK2* 1100delC. Information about the specific gene and what is known about the risk of CBC should be discussed in the context of shared decision making. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
- Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI. (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)"

SUMMARY

BRCA1, BRCA2, TP53, PALB2*, *PTEN*, *STK11,* and/or *CDH1

There is enough research to show that testing for variants in certain genes can guide treatment decisions and improve health outcomes for people suspected of having hereditary breast or ovarian cancer. In addition, clinical guidelines based on research from the National Comprehensive Cancer Network (NCCN) recommend genetic testing of these genes for certain people. Therefore, testing for variants in *BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, and/or CDH1* may be considered medically necessary when criteria are met.

There is not enough research to show that testing for variants in *BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, and/or CDH1* can improve health outcomes for individuals who do not meet the policy criteria. Therefore, this testing is considered investigational.

Other Genes

There is not enough research to show that testing for genes other than *BRCA1*, *BRCA2*, *BRIP1, RAD51C, RAD51D, PALB2*, *PTEN*, *STK11, CDH1,* and/or *TP53*, including but not limited to *ATM, BARD1,* and *CHEK2* testing, can improve health outcomes for people suspected of having a hereditary breast and ovarian cancer syndrome. While there are a number of genes that are associated with increased risk of breast and/or ovarian cancer, it is not clear that changing patient management based on the results of testing these moderate-penetrance genes will lead to better health outcomes compared to management based on other risk factors such as family history. Therefore, testing for any other genes, including panel testing of *BRCA1*, *BRCA2*, *BRIP1, RAD51C, RAD51D, PALB2*, *PTEN*, *STK11, CDH1,*

and/or *TP53* done in combination with other genes, is considered investigational for determining risk of hereditary breast or ovarian cancer.

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CODES

Codes	Number	Description
		Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated
	0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)]
	0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0131U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)
	0132U	Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)
	0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81162	BRCA1, (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangement)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

Codes	Number	Description
	81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
	81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
	81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
	81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants; genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	~~81433~~	~~Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11~~ (Deleted 01/01/2025)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Appendix 1 Recommended Testing Strategy

- Individuals meeting the criteria above should be tested for *BRCA1* and *BRCA2* variants
- Individuals with a known familial BRCA variant
    - Targeted testing for the specific variant is recommended

Appendix 1 Recommended Testing Strategy

- Individuals with unknown familial BRCA variant
  - Non-Ashkenazi Jewish descent
    - If no familial variant can be identified, two possible testing strategies are:
      - Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no variant (negative result).
      - Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing) may be performed.
    - If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART) may be done.
      - Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.
  - Ashkenazi Jewish descent
    - NCCN recommends testing for the three known founder variants first (i.e., 185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*).
    - If testing is negative for the founder variants, comprehensive genetic testing may be considered.

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. Prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing before this time may consider repeat testing for the rearrangements.

Date of Origin: *January 2011*

Regence

Medical Policy Manual Genetic Testing, Policy No. 05

Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease

Effective: March 1, 2025

Next Review: December 2025
Last Review: January 2025

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

Apolipoprotein E (apo E) genotype has been associated with risk for coronary artery disease (CAD) and may affect responses to lipid-lowering medications. Genetic testing of apo E has been proposed for individual CAD risk assessment and to predict the response to statin therapy.

MEDICAL POLICY CRITERIA

Apolipoprotein E genetic testing is considered **investigational** for the risk assessment and management of cardiovascular disease.

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

CROSS REFERENCES

1. Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, Laboratory, No. 63

BACKGROUND

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with 'normal' levels of total and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Apolipoprotein E (apo E) is the primary apolipoprotein found in very-low-density lipoproteins (VLDLs) and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The apo E gene is polymorphic, consisting of three alleles (e2, e3, and e4) that code for three protein isoforms, known as E2, E3, and E4, which differ from one another by one amino acid. These molecules mediate lipid metabolism through their different interactions with the LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the apo E phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various apo E genotypes are more atherogenic than others and that apo E measurement may provide information on risk of CAD above traditional risk factor measurement. It has also been proposed that the apo E genotype may be useful in the selection of specific components of lipid-lowering therapy such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. Apo E genotype may be one factor that determines an individual's degree of response to interventions such as statin therapy.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

A 2002 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment[2] summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor […] independently contributes to risk assessment compared to established risk factors.

- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Similarly, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) noted that emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:[3]

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

The focus of the following literature appraisal is on evidence related to the clinical utility of testing or the ability of apo E testing to:

- Provide clinically relevant information beyond that provided by traditional lipid measures, and
- Improve health outcomes as a result of patient management decisions that would not otherwise have been made in the absence of apo E testing.

APO E AS A PREDICTOR OF CARDIOVASCULAR DISEASE

A large body of research has established a correlation between lipid levels and the underlying apo E genotype. Numerous studies have focused on the relationship between genotype and physiologic markers of atherosclerotic disease. A number of small- to medium-sized cross-sectional and case-control studies have correlated apo E with surrogate outcomes such as cholesterol levels, markers of inflammation, or carotid intima-media thickness.[4-10] These studies have generally shown a relationship between apo E and these surrogate outcomes. For example, in population studies, the presence of an apo e2 allele was associated with the lowest cholesterol levels and the apo e4 allele was associated with the highest levels.[11, 12] Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of total and LDL-cholesterol levels.[13-16]

Some larger observational studies have correlated apo E genotype with clinical disease. For example, the Atherosclerosis Risk in Communities (ARIC) study followed 12,000 middle-aged individuals free of coronary artery disease (CAD) at baseline for 10 years.[17] This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik (2006) reported that apo E polymorphisms were associated with LDL levels and carotid intima-media thickness but were not predictive of incident CAD.[18] A British birth cohort study found apo e2 genotypes to be associated with both deep and lobar intracerebral hemorrhage (ICH). APO e4 and apo e2/4 genotypes had selective associations with ICH in case-control and age-adjusted analyses.[19] However, Ajnakina (2023) published a study using data from the English Longitudinal Study of Aging (ELSA) that did not find an association between *APO-ε4* status and cardiovascular disease deaths in 7,131 adults aged ≥50 years with 10 years of follow-up.[20]

Shao (2022) conducted a meta-analysis of 32 studies to analyze the correlation between APOE polymorphisms and risk of myocardial infarction (MI).[21] The studies included 13,706 cases of MI and 14,817 controls. Pooled analysis using the random-effects model found the apo e4 genotypes were associated with the highest risk of MI (OR 1.24, 95% CI 1.09-1.42) and MI frequency was lowest in people with apo e2 genotypes (OR 0.74, 95% CI 0.64-0.86).

Sofat (2016) published a meta-analysis of three studies of circulating apo E and CVD events.[22] The method for selecting the studies was not described. The three studies included 9,587 participants and 1,413 CVD events. In the pooled analysis, there was no association of apo E with CVD events. The unadjusted odds ratio (OR) for CVD events for a standard deviation increase in apo E concentration was 1.02 (95% CI, 0.96 to 1.09). After adjustment for other cardiovascular risk factors, the OR for CVD for a standard deviation increase in apo E concentration was 0.97 (95% CI 0.82 to 1.15).

A systematic review by Zhao (2017) assessed the link between apo E polymorphisms and premature CAD.[23] Premature CAD (PAD) was defined as CAD in males below age 55 and females below age 65. The review included 18 research reports with a low to moderate risk of bias, for a total of 2,361 cases of PCAD and 2,811 controls. Overall, the e2 allele was not significantly associated with PCAD. However, when results were stratified by race, the e2 allele appeared to increase the risk of PCAD in Asians (OR 1.54, 95% CI 1.09 to 2.17, as compared to the e3 allele), while a protective effect was seen in Caucasians (OR 0.77, 95% CI 0.62 to 0.95, as compared to the e3 allele). Subgroup analysis showed a decreased risk of myocardial infarction associated with e2 compared to e3 (OR 0.70, 95% CI 0.49 to 0.98). Overall, the e4 allele was associated with greater risk of PCAD (OR 1.62, 95% CI 1.27 to 2.06). This increased risk was seen for all racial groups.

An earlier meta-analysis published by Bennet (2007) summarized the evidence from 147 studies on the association of apo E genotypes with lipid levels and cardiac risk.[24] Eighty-two studies included data on the association of apo E with lipid levels, and 121 studies reported the association with clinical outcomes. The authors reported that patients with the apo e2 allele had LDL levels that were approximately 31% less compared with patients with the apo e4 allele. Patients with the apo e3 allele had an approximately 20% decreased risk for coronary events compared with patients with apo e2 (OR 0.80, 95% CI 0.70 to 0.90), and patients with the apo e4 had an estimated 6% higher risk of coronary events that was not statistically significant (OR 1.06, 95% CI 0.99 to 1.13).

No studies were identified that compared the health outcomes of patient management based on apo E genotypes compared with patient management based on conventional risk assessment measures such as LDL. Therefore, it is unclear how the associations reported above can be used to improve health outcomes over current patient management procedures.

APO E AS A PREDICTOR OF RESPONSE TO THERAPY

Apo E has been investigated as a predictor of response to therapy by examining apo E alleles in the intervention arm(s) of lipid-lowering trials. Some data have suggested that patients with an apo e4 allele may respond better to diet-modification strategies.[25-27] King (2022) found that people who were given nutritional advice tailored to their apo e4 genotype modified their diet.[28] Subjects with apo e4 genotypes associated with increased CVD risk who ate higher than recommended levels of saturated fat reduced their fat intake (p=0.012) to recommended levels after hearing genotype-specific dietary advice (p=0.409). Participants with non-risk apo e4 genotypes who ate higher than recommended levels of saturated fat also reduced their fat

intake (p=0.001) after nutritional advice but continued to consume significantly higher than recommended levels of saturated fat (p=0.007). However, the number of participants who had both the risk-associated genotype and the risk-associated diet at baseline was small (n=9). Other studies have suggested that response to statin therapy may vary with apo E genotype and that the e2 allele indicates greater responsiveness to statins.[25, 27, 29-32] There is also evidence that apo e2 correlates with superior response to long-term aspirin therapy in people with existing cardiovascular disease.[33]

No studies were identified that directly compared the health outcomes of patient management that was based on apo E status with those based on conventional measures.

PRACTICE GUIDELINE SUMMARY

No clinical practice guidelines or position statements from U.S. professional associations were identified that recommended the use of apo E in cardiovascular risk assessment, including but not limited to the following:

- The 2021 National Lipid Association (NLA) scientific statement on lipid measurements in cardiovascular disease.[34]
- The 2020 National Lipid Association (NLA) scientific statement on genetic testing in dyslipidemia[35]
- The 2013 American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk in asymptomatic patients.[36]
- The 2019 U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease.
- The American Diabetes Association and the American College of Cardiology Foundation consensus conference publication.[37]

SUMMARY

APO E AS A PREDICTOR OF CARDIOVASCULAR DISEASE

There is some research that shows that apolipoprotein E (apo E) genotype may have an effect on cholesterol levels and risk for coronary artery disease (CAD). However, there is not enough research to show that testing for apo E genotype helps to improve health outcomes for people at risk for CAD. There are no clinical guidelines based on research that recommend testing apo E genotype for cardiovascular risk. Therefore, the use of apo E measurements in the risk assessment and management of cardiovascular disease is considered investigational.

APO E AS A PREDICTOR OF RESPONSE TO THERAPY

There is not enough research to show that genetic testing of apolipoprotein E (apo E) can improve health outcomes for people that are considering starting a statin medication to reduce their cardiovascular risk. Therefore, apo E testing to predict response to lipid-lowering therapy is considered investigational.

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CODES

Codes	Number	Description
CPT	81401	Molecular pathology procedure, Tier 2, Level 2
HCPCS	None	

Date of Origin: *January 2013*

Regence

Medical Policy Manual Genetic Testing, Policy No. 06

Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes

Effective: January 1, 2025

Next Review: October 2025
Last Review: January 2025

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

There are hereditary conditions that predispose affected individuals to colorectal cancer (CRC), including MUTYH-associated polyposis (MAP), familial adenomatous polyposis (FAP) with associated variants (collectively referred to as APC-associated polyposis), and Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer, or HNPCC).

MEDICAL POLICY CRITERIA

Note: This policy only addresses testing for Lynch syndrome and APC-associated and MUTYH-associated polyposis syndromes.

I. Genetic testing for *APC*, *MUTYH*, mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and/or *EPCAM* gene variants may be considered **medically necessary** when any one of the following criteria is met:

   A. At-risk relatives (see Policy Guidelines) of patients with either of the following:

      1. Familial adenomatous polyposis (FAP); or

      2. A known *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and/or *EPCAM* disease-

associated variant.

B. Patients with a differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome

C. Lynch syndrome is suspected in patients with colorectal cancer or endometrial cancer

D. Lynch syndrome is suspected in patients *without* colorectal or endometrial cancer (including both cancer-free individuals and individuals with a Lynch-associated cancer other than colorectal or endometrial cancer, see below), when no affected family members have been tested for MMR or *EPCAM* variants, and one or more of the following is met:

1. A first-degree relative with a colorectal or endometrial cancer diagnosed before age 50
2. A first-degree relative with both of the following (a. and b.):
   a. Colorectal or endometrial cancer; and
   b. A second Lynch syndrome-associated cancer (cancer of the colon/rectum, endometrium, stomach, ovary, pancreas, bladder, ureter, renal pelvis, biliary tract, brain [usually glioblastomas], or small intestine, or a sebaceous adenoma, sebaceous carcinoma, or keratoacanthomas)
3. Two or more first- or second-degree relatives (from the same side of the family) with Lynch syndrome-associated cancers, including one diagnosed before age 50
4. Three or more first- or second-degree relatives (from the same side of the family) with Lynch syndrome-associated cancers
5. Two colorectal cancers in first-degree relatives involving at least two generations, with at least one individual diagnosed by age 55
6. Documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, such as MMRpro, PREMM5, or MMRpredict

II. Genetic testing for *BRAF* variants or *MLH1* promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when MLH1 protein is not expressed on immunohistochemical (IHC) analysis.

III. Genetic testing for Lynch, APC-associated, and MUTYH-associated polyposis syndromes that does not meet the medical necessity criteria (I or II) is considered **investigational**, including but not limited to panel tests that include genes other than *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM*.

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

POLICY GUIDELINES

Genes Associated with Lynch and Polyposis Syndromes: Genes associated with Lynch and polyposis syndromes include the following: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2* and *EPCAM* genes.

Definition of At-risk Relatives: *At-risk relatives* refers to first- and second-degree relatives of the patient. First-degree relatives include an individual's parents, siblings, and children.

Lynch-Associated Cancers: Lynch-associated cancers include cancers of the colon/rectum, endometrium, stomach, ovary, pancreas, bladder, ureter, renal pelvis, biliary tract, brain (usually glioblastomas), and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas.

Patients with Colorectal or Endometrial Cancer: When tumor tissue is available for testing either the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test with or without *BRAF* gene variant testing should be used as an initial evaluation of tumor tissue prior to MMR gene analysis.

Risk Prediction Models: Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available, such as MMRpro[1], PREMM$_5$[2], or MMRpredict[3].

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. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided, if any

CROSS REFERENCES

1. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
2. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. BRAF Genetic Testing To Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

BACKGROUND

APC-ASSOCIATED POLYPOSIS

Recommendations for patient surveillance and cancer prevention vary according to the syndrome, therefore it is important to distinguish among classical FAP, attenuated FAP, and MUTYH-associated polyposis (MAP [mono- or biallelic]) by genetic analysis.

Familial Adenomatous Polyposis (FAP) (also known as Classical FAP)

FAP is characterized by the presence of hundreds to thousands of precancerous colon polyps, appearing on average at 16 years of age. If left untreated, all affected individuals eventually develop CRC. The mean age of CRC diagnosis in untreated individuals is 39 years.

Germline variants in the adenomatous polyposis coli (*APC*) gene, located on chromosome five, are responsible for FAP and are inherited in an autosomal dominant manner.

Gardner Syndrome

FAP may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE). These collective extraintestinal manifestations of FAP are referred to as Gardner Syndrome.

Turcot Syndrome

When associated with central nervous system (CNS) tumors, FAP is referred to as Turcot syndrome.

Attenuated FAP (AFAP)

Like FAP, AFAP is characterized by a significant risk for CRC as well, but there are fewer precancerous colonic polyps (10-99, 30 on average). The average age of CRC diagnosis in AFAP patients is 50-55 years. The disorder is associated with fewer extraintestinal cancers than FAP but with a significantly higher risk compared to the general population. The lifetime risk of CRC in individuals with AFAP is about 70% by the age of 80.

AFAP is inherited in an autosomal dominant manner and explained by germline variants in the *APC* gene as well. However, fewer than 30% of AFAP patients have *APC* variants and may have variants in the MUTYH gene instead (see below).

MUTYH-Associated Polyposis (MAP) (formerly MYH-associated polyposis)

MAP occurs with a similar frequency to FAP. While MAP also has clinical features similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. In contrast to FAP and AFAP, MAP is explained by variants in the *MUTYH* gene and is inherited in an autosomal recessive manner. Biallelic *MUTYH* variants are associated with a cumulative CRC risk of about 80% by age 70. Monoallelic *MUTYH* variant-associated risk of CRC appears to be relatively minimal, although the risk is still under debate.

LYNCH SYNDROME

Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC) is a hereditary disorder characterized by a high predisposition to colon cancer (27-45% for men and 22-38% for women by age 70) and cancers of the endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain (usually glioblastomas), sebaceous gland adenomas and keratoacanthomas, and small intestine.[4, 5] These cancers are sometimes

collectively referred to as HNPCC- or Lynch syndrome-associated cancers. The syndrome is estimated to account for approximately 3% of colorectal and endometrial cancers.[6] Lynch syndrome is also estimated to account for 2% of all endometrial cancers in women and 10% of endometrial cancer in women under 50 years of age. Female carriers of the germline variants *MLH1*, *MSH2*, *MSH6* and *PMS2* have an estimated 40%-62% lifetime risk of developing endometrial cancer, as well as a 4%-12% lifetime risk of ovarian cancer.

Lynch Syndrome and Variants in Mismatch Repair (MMR) Genes

Lynch syndrome is inherited in an autosomal dominant manner and may be caused by any of a large number of possible variants in one of the several mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and rarely *MLH3*, *PSM1* and *EXO1*). Variants in MMR genes prevent normal DNA repair in the repetitive DNA sequences called microsatellites. This results in microsatellite instability (MSI) and ultimately leads to an increased risk for malignancy.

A majority (70%) of Lynch syndrome patients have variants in either *MLH1* or *MSH2*, and testing for MMR gene variants is often limited to these two genes. If results are negative, *MSH6* and *PMS2* genes may be tested for variants next. Large gene sizes and the difficulty of detecting variants in these genes make direct sequencing a time- and cost- consuming process. Therefore, additional indirect screening methods are needed to determine which patients should proceed to direct sequencing for MMR gene variants. Available tumor screening methods include MSI testing and immunohistochemical (IHC) testing.

BRAF V600E testing is an optional screening method that may be used in conjunction with IHC testing for *MLH1* to improve efficiency. A methylation analysis of the *MLH1* gene can largely substitute for *BRAF* testing or be used in combination to slightly improve efficiency. *MLH1* gene methylation largely correlates with the presence of *BRAF*-V600E and in combination with BRAF testing can accurately separate Lynch from sporadic CRC in IHC *MLH1*-negative cases.[7] Therefore, *BRAF*-positive samples need not be further tested by MLH1 sequencing.

Lynch Syndrome and Variants in Non-Mismatch Repair (non-MMR) Genes

Deletions in the non-MMR *EPCAM* (epithelial cell adhesion molecule) gene may result in inactivation of the non-mutated *MSH2* gene, thereby causing Lynch syndrome. *EPCAM* testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and IHC shows a lack of *MSH2* expression, but no *MSH2* variant is found by sequencing.

AMSTERDAM AND BETHESDA CRITERIA

The objective of the Amsterdam I and revised Amsterdam II criteria is to define families that are very likely to have Lynch syndrome.[6] In another words, these criteria aim to “establish the diagnosis of Lynch syndrome based upon familial clustering of HNPCC-related tumors.”[8] The revised Amsterdam II criteria are broader than Amsterdam I as they consider both colorectal *and* HNPCC-associated cancers in the assessment.[6] The Amsterdam criteria were originally developed by the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) in order to standardize family selection criteria for collaborative research on Lynch syndrome. Consequently, these criteria are not without limitations when applied to clinical diagnosis. In recent years, “family history is considered less useful as the first step in identifying Lynch syndrome in individuals *with* newly diagnosed CRC than strategies involving

the analysis of tumor samples (e.g., MSI, IHC)."[9, 10] However, family history is still considered "an important component of cancer risk assessment in the general population"[10]

The Bethesda criteria were developed with a different purpose than the Amsterdam criteria.[4, 11] They were designed to "help predict which patients *with* colorectal cancer are likely to have a mismatch-repair variant and should thus undergo further testing."[8]

REGULATORY STATUS

The majority of genetic tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Labs are subject to Clinical Laboratory Improvement Amendment (CLIA) regulations that monitor high-complexity testing.

Genetic Testing Panels

Sequencing of FAP, AFAP, MUTYH or Lynch syndrome variants may be offered in combination with other gene or chromosomal microarray tests that are not associated with Lynch syndrome or FAP. Medical necessity must be established for each genetic test included in a panel. When FAP, AFAP, MUTYH or Lynch syndrome analysis is bundled with any other genetic test, additional Medical Policies may apply.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

FAP GENETIC TESTING

The initial policy evidence for FAP genetic testing was based on a 1998 TEC Assessment[13], which offered the following conclusions:

- Genetic testing for familial adenomatous polyposis (FAP) may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 adenomatous polyps; or close relatives of patients with clinically diagnosed FAP or of patients with an identified *APC* variant.
- The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

The additional policy information on attenuated FAP and on MUTYH-associated polyposis diagnostic criteria and genetic testing is based on information from GeneReviews[14] and from several publications[15-19] that build on prior, cited research.

LYNCH SYNDROME AND COLORECTAL CANCER GENETIC TESTING

MISMATCH REPAIR (MMR) GENETIC TESTING

Agency for Healthcare Research and Quality (AHRQ) / Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Evidence Assessment

The policy evidence for Lynch syndrome genetic testing in CRC patients was initially based on an evidence report published by the AHRQ[20], a supplemental assessment to that report contracted by the EGAPP Working Group[9], and an EGAPP recommendation for genetic testing in CRC.[10] Based on the AHRQ report and supplemental assessment, the EGAPP report came to the following conclusions regarding genetic testing for MMR variants in patients already diagnosed with CRC:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR mutation testing and should not be used as a sole determinant or screening test.
- MSI and IHC screening tests for MMR mutations have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for *MLH1* and *MSH2* and 77% for *MSH6*, and a specificity of about 90% for all. It is likely that, using high quality MSI testing methods, these parameters can be improved. IHC screening has a sensitivity for *MLH1*, *MSH2*, and *MSH6* of about 83% and a specificity of about 90% for all.
- Optional BRAF testing can be used to reduce the number of patients, who are negative for *MLH1* expression by IHC, needing *MLH1* gene sequencing, thus improving efficiency without reducing sensitivity for MMR mutations.
- A chain of indirect evidence can be constructed for the clinical utility of testing all patients with CRC for MMR mutations.
    - The chain of indirect evidence from well-designed experimental nonrandomized studies (as noted below) is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR mutation.
    - Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose MMR gene mutation testing. Among those positive for MMR gene mutations, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.
        - One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs. those who did not.
        - Surveillance, prevention for other Lynch syndrome cancers (for detail, refer to last outline bullet)
    - The chain of evidence from descriptive studies and expert opinion (as noted below) is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., cancer index patient).
        - Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies
        - Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.

- Surveillance, prevention for other Lynch syndrome cancers:
  - While invasive and not recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In one retrospective study, women who chose this option had no gynecologic cancer over 10 years whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer
  - In one study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome but results were not statistically significant and a survival benefit has yet to be shown.[21] Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.
  - Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

Based on an indirect chain of evidence with adequate evidence of benefit to unaffected family members found to have Lynch syndrome, the EGAPP working group recommended testing all patients with CRC for MMR gene variants. Although MMR gene sequencing of all patients is the most sensitive strategy, it is highly inefficient and cost-ineffective and not recommended. Rather, a screening strategy of MSI or IHC testing (with or without optional *BRAF* testing) is recommended and retains a relatively high sensitivity. Although a particular strategy was not recommended by the EGAPP Working Group, several are potentially effective; efficiency and cost-effectiveness may depend upon local factors.

American Society of Clinical Oncology (ASCO)/ Society of Surgical Oncology (SSO) Recommendations

As the EGAPP recommendations have noted, the evidence to date is limited regarding benefits derived from patients with CRC who undergo testing and are found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with CRC and Lynch syndrome who choose prophylactic surgical treatment.

Early documentation of the natural history of CRC in highly selected families with a strong history of hereditary CRC indicated risks of synchronous and metachronous cancers as high as 18% and 24%[22] in patients who already had CRC. As a result, in 1996, the Cancer Genetic Studies Consortium, a temporary NIH-appointed body, recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis (IRA) should be considered in preference to segmental resection.[23] Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and CRC, effective prevention measures remain imperative. One study suggested that subtotal colectomy with IRA markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance.[24] A mathematical model comparing total colectomy and IRA to hemicolectomy resulted in increased life expectancies of 2.3, 1, and 0.3 years for ages 27, 47, and 67,

respectively; for Duke's A, life expectancies for the same ages are 3.4, 1.5, and 0.4, respectively.[25] Based on this work, the joint ASCO and SSO review of risk-reducing surgery in hereditary cancers recommends offering both options to the patient with Lynch syndrome and CRC, especially those who are younger.[26] This ASCO/SSO review also recommends offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

Vos (2020) evaluated the yield to detect Lynch syndrome in a prospective cohort of 3,602 newly diagnosed CRC cases below age 70.[27] The standard testing protocol included IHC or MSI testing, followed by *MLH1* hypermethylation testing. Testing identified *MLH1* hypermethylation in a majority of cases tested (66% of 264). The percentage of MMR deficient CRC explained by hypermethylation increased with age, while the percentage of patients with hereditary CRC decreased with age. Of the 47 patients who underwent genetic testing, 55% (26/47) were determined to have Lynch syndrome. The authors estimated that only 78% of these cases would have been identified by the revised Bethesda guidelines. The percentage by age was 86% (6/7) in those under 40 years, 57% (17/29) in patients aged 40 to 64 years, and 30% (3/10) in patients 65 to 69 years of age and the number needed to test to identify one case of Lynch syndrome after prescreening was 1.2 (95% confidence interval [CI] 1.0 to 2.0) in patients under 40 years, 4.1 (95% CI 3.1 to 5.5) in patients 40 to 64 years of age, and 21 (95% CI 11 to 43) in CRC patients aged 65 to 69.

EPCAM TESTING

Several studies characterized *EPCAM* deletions and established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently non-functional) and with the presence of *MSH2* promoter hypermethylation, and, most importantly, have shown the co-segregation of these *EPCAM* variants with Lynch-like disease in families.[28-33] Because studies differ slightly in how patients were selected, prevalence of these *EPCAM* variants is difficult to estimate, but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have a MMR variant, but have MSI-high tumor tissue. Kempers (2011) reported that carriers of an *EPCAM* deletion had a 75% (95% CI 65 to 85) cumulative risk of CRC by age 70, not significantly different from that of carriers of an *MSH2* deletion (77%, 95% CI 64 to 90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI 0 to 27) by age 70, compared to carriers of a variant in *MSH2* (51%, 95% CI 33 to 69, p=0.0006).[34]

BRAF TESTING

BRAF V600E or *MLH1* promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH1 protein expression by IHC testing for *MLH1*. The presence of *BRAF* V600E or absence of MLH1 protein expression rarely occurs in Lynch syndrome and would eliminate the need for further germline variant analysis for a Lynch syndrome diagnosis.[7, 35, 36]

Capper (2013) reported on a technique of *BRAF* V600E-specific (VE1) IHC testing for *BRAF* variants on a series of 91 MSI-H CRC patients.[37] The authors detected *BRAF*-mutated CRC with 100% sensitivity and 98.8% specificity. VE1 positive lesions were detected in 21% of *MLH1*-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Although additional studies are needed to confirm the efficacy of this technique,

VE1 IHC testing for *BRAF* may be an alternative to *MLH1* promoter methylation analysis and a method for avoiding further MMR testing.

LYNCH SYNDROME AND ENDOMETRIAL CANCER GENETIC TESTING

The ASCO/SSO review discussed above also recommends offering prophylactic total abdominal hysterectomy to female patients with CRC who have completed childbearing or to women undergoing abdominal surgery for other conditions, especially when there is a family history of endometrial cancer.[26] This recommendation is based on the high rate of endometrial cancer in variant-positive individuals (30 to 64% in studies that may be biased by strong family history; overall, possibly as low as 20 to 25%[11]) and the lack of efficacy of screening.

The estimated the risk of endometrial cancer in variant carriers is 34% by age 70 (95% CI 17 to 60%), and of ovarian cancer is 8% by age 70 (95% CI 2 to 39%).[38] Risks do not appear to appreciably increase until after age 40. When surgery is chosen, oophorectomy should also be performed because of the high incidence of ovarian cancer in Lynch syndrome (12%).[24] As already noted, in one retrospective study, women who chose this option had no gynecologic cancer over 10 years whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.[9]

In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.[39] This study estimated that for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on variant-specific risks suggests that prophylactic gynecological surgery benefits for carriers of *MSH6* variants may offer less obvious benefits compared to harms as lifetime risk of endometrial cancer is lower than for carriers of *MLH1* or *MSH2* variants, and lifetime risk of ovarian cancer is similar to the risk for the general population.[38] An alternative to prophylactic surgery is surveillance for endometrial cancer using transvaginal ultrasound and endometrial biopsy. Evidence indicates that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

Several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using MMR-IH.[40] Clarke and Cooper (2012) noted that Sloan Kettering Cancer Center screens all patients less than 50 years of age with endometrial cancer using MMR-IHC, as well as patients older than 50 with suggestive tumor morphology, lower uterine segment (LUS) location, personal/family history, or synchronous cell carcinoma of the ovary.[41] Kwon (2011) recommended MMR-IHC screening of women with endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome associated cancer.[42]

However, in the case of *EPCAM* deletion carriers, three studies found three cases of endometrial cancer in 103 female carriers who did not undergo preventive hysterectomy.[34, 43, 44] Women with *EPCAM* deletions consequently have a life-time risk of developing endometrial cancer decreased by 10-fold when compared with MMR gene variant carriers. This might support a clinical management scenario rather than prophylactic surgery.[43]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)[45]

Lynch Syndrome

The NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (v.3.2024) recommend that all colorectal and endometrial cancers should undergo tumor testing with MSI and/or IHC for the four MMR genes and *EPCAM*.

The guidelines state that direct referral for germline genetic testing to rule out Lynch syndrome may be preferred in patients with a strong family history or if diagnosed before age 50.

Criteria that may justify Lynch syndrome testing according to this guideline are:

- A known Lynch syndrome variant in the family
- MMR deficiency on tumor testing
- Diagnosis of a Lynch syndrome-related cancer, and:
    - Cancer diagnosis prior to age 50, or
    - A synchronous or metachronous Lynch syndrome-related cancer, or
    - One first- or second-degree relative with a Lynch syndrome-related cancer diagnosed before age 50, or
    - Two or more first- or second-degree relatives with a Lynch syndrome-related cancer, regardless of age
- A family history of any of the following (on the same side of the family):
    - One or more first-degree relatives with colorectal or endometrial cancer diagnosed before age 50
    - One or more first-degree relatives with a colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer
    - Two or more first- or second-degree relatives with Lynch syndrome-related cancers, including at least one diagnosed before age 50
    - Three or more first- or second-degree relatives with Lynch syndrome-related cancers, regardless of age
- A >5% risk based on predictive models (e.g., MMRpro, PREMM$_5$, or MMRpredict

The guideline also indicated that abnormal *MLH1* expression by IHC in colorectal or endometrial cancers should be followed by tumor *MLH1* promoter methylation testing, or, for CRCs, testing for a *BRAF* V600E variant prior to genetic testing to exclude a diagnosis of Lynch syndrome. However, the guideline notes, “the absence of a *BRAF* V600E [pathogenic variant] does not rule out *MLH1* methylation.”

Polyposis Syndrome

The NCCN guidelines also address familial adenomatous polyposis (classical and attenuated) and *MUTYH*-associated polyposis, and they recommend genetic testing for patients with a personal history of 20 or more adenomas, known familial pathogenic variants in adenomatous polyposis genes, or multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE). Additionally, they recommend considering genetic testing for those with a personal history of 10 to 19 adenomas, unilateral CHRPE, some adenomas and clinical indications of serrated polyposis syndrome, a personal history of other APC-associated cancers (desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer), or to differentiate AFAP from MAP or other types of colonic polyposis.

AMERICAN COLLEGE OF GASTROENTEROLOGY

The American College of Gastroenterology (ACG) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.[46]

Lynch Syndrome

ACG recommends that all newly diagnosed CRCs should be evaluated for mismatch repair deficiency, and that analysis may be done by immunohistochemical (IHC) testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or testing for microsatellite instability; tumors that demonstrate loss of *MLH1* should undergo *BRAF* testing or analysis for *MLH1* promoter hypermethylation. Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated *BRAF* variant or hypermethylation of *MLH1*), a known family variant associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS. Genetic testing of patients with suspected LS should include germline variant genetic testing for the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* genes or the altered gene(s) indicated by IHC testing.

Adenomatous polyposis syndromes

Individuals who have a personal history of more than 10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes. Genetic testing of patients with suspected adenomatous polyposis syndromes should include *APC* and *MUTYH* gene variant analysis.

U.S. MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER

In 2014, the Multi-Society Task Force published guidelines regarding Lynch syndrome testing and indicated, “the use of genetic panels might uncover patients and families with forms of attenuated polyposis, such as *MYH*-associated polyposis, attenuated familial adenomatous polyposis, and polymerase proofreading polyposis; there is often blurring of the clinical presentations of these syndromes and LS (Lynch Syndrome).”[47]

SUMMARY

There is enough research to show that genetic testing for *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* can improve health outcomes for some cancer patients and their families. There are many clinical practice guidelines that recommend genetic testing for certain people at high risk for these colorectal cancer syndromes. Therefore, genetic testing for any combination of these genes variants may be considered medically necessary when policy criteria are met.

There is enough research to show that tumor testing for a *BRAF* variant can help to diagnose Lynch syndrome in patients with a particular type of colorectal tumor, which can improve health outcomes for patients and their families. Therefore, testing for *BRAF* variants or *MLH1* promoter methylation may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing for Lynch, APC-associated, and MUTYH-associated polyposis syndromes can improve risk assessment and lead to better health outcomes for patients when policy criteria are not met. This includes testing with panel tests that contains genes other than *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Therefore, genetic testing that does not meet the policy criteria, such as panel testing that includes testing for genes other than *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM,* is considered investigational.

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CODES

Codes	Number	Description
CPT	0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
	0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) (Use 0130U in conjunction with 81435, 0101U)
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81210	BRAF *(*B-Raf proto-oncogene, serine/threonine kinase*)* (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	;known familial variants
	81294	;duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	;known familial variants
	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary duplication/deletion variants duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	;known familial variants
	81300	;duplication/deletion variants
	81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

Codes	Number	Description
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	;known familial variants
	81319	;duplication/deletion variants
	81401	Molecular pathology procedure, Level 2
	81406	Molecular pathology procedure, Level 7
	81435	Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants; genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	~~81436~~	~~;duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11~~ (Deleted 01/01/2025)
HCPCS	None	

Date of Origin: *January 2012*

Genetic Testing for Cutaneous Malignant Melanoma

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

Genetic markers for cutaneous malignant melanoma (CMM) are being evaluated in those with a family history of the disease and to estimate risk for those who do not have family history of CMM.

MEDICAL POLICY CRITERIA

Genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered **investigational**.

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

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Gene Expression Profiling for Melanoma, Genetic Testing, Policy No. 29

BACKGROUND

GENETICS OF CUTANEOUS MALIGNANT MELANOMA

A genetic predisposition to cutaneous malignant melanoma (CMM) is suspected in specific clinical situations:

- Melanoma has been diagnosed in multiple close blood relatives;
- Multiple primary melanomas are identified in a single patient; and
- In the case of early age of onset.

A positive family history of melanoma is the most significant risk factor; it is estimated that approximately 10% of melanoma cases report a first- or second-degree relative with melanoma. Hereditary melanoma, caused by single gene disorder accounts for about half of these.[1]

Multiple genes associated with high risk for melanoma have been identified:

- *CDKN2A*, located on chromosome 9p21, encodes proteins that act as tumor suppressors. Mutations at this site can alter the tumor suppressor function.
- *CDK4* is an oncogene located on chromosome 12q13. CDK4 is a rare cause of hereditary melanoma than CDKN2A and is phenotypically similar.
- *BAP1*, which is located on 3p21, encodes a protein that acts as a tumor suppressor, and is associated with both cutaneous and uveal melanoma.
- *POT1*, located on 7q31.33 is associated with cutaneous melanoma and other cancers. Germline *POT1* variants have been identified in fewer than 100 families.

Additional genes that may be associated with CMM include genes involved in defined tumor syndromes in which melanoma risk may be increased (e.g., *PTEN*), and variants that suggest increased risk, but low-to-intermediate melanoma penetrance (e.g., *MITF, MC1R*).[1-3]

The incidence of *CDKN2A* disease-associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a *CDKN2A* disease-associated variants. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas.[4] However, the incidence of *CDKN2A* mutations increases with a positive family history; *CDKN2A* disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20–40% in kindreds with three or more affected first-degree relatives.[5] Variant detection rates in the *CDKN2A* gene are generally estimated as 20–25% in hereditary CMM but can vary between 2% and 50%, depending on the family history and population studied.

Hereditary CMM has been described as a family in which either two first-degree relatives are diagnosed with melanoma or a family with three melanoma patients, irrespective of the degree of relationship.[6] Others have defined hereditary CMM as having at least three (first-, second-, or third-degree) affected members or two affected family members in which at least one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative, or one member had multiple primary melanomas.[7]

Other malignancies are associated with hereditary CMM. Pathogenic *CDKN2A* variants in particular are associated with an increased risk for pancreatic cancer. Uveal melanoma is the most common cancer associated with *BAP1* tumor predisposition syndrome (TPD). *BAP1* variants are also associated with cutaneous melanoma, renal cell carcinoma and mesothelioma. The incidence of de novo *BAP1* variants is not known, penetrance is incomplete, and manifestations vary within affected families.[2] Core cancers associated with

POT1-TPD are cutaneous melanoma, chronic lymphocytic leukemia, angiosarcoma and glioma. The penetrance and complete phenotype of *POT1* pathogenic variants are not well understood.[3]

Hereditary forms of CMM can occur either with or without a family history of multiple dysplastic nevi. Families with both CMM and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome (FAMMM). This syndrome is difficult to define since there is no agreement on a standard phenotype, and dysplastic nevi occur in up to 50% of the general population. Atypical or dysplastic nevi are associated with an increased risk for CMM. Initially, the phenotypes of atypical nevi and CMM were thought to co-segregate in FAMMM families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that in families with *CDKN2A* variants, there were family members with multiple atypical nevi who were non-carriers of the *CDKN2A* familial variant. *CDK4* variants are detected in fewer than one percent of patients with FAMMM syndrome.[8] Thus, the nevus phenotype cannot be used to distinguish carriers from non-carriers of CMM susceptibility in these families.

MANAGEMENT

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.[9] Badenas (2012) suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with two cases of melanoma or to an individual with two primary melanomas (the rule of two); in countries with high incidence of melanoma, genetic testing should be offered to families with three cases of melanoma, or to an individual with three primary melanomas (the rule of three).[10] Delaunay (2017) suggested a modification to the recommendations by Badenas. In countries with a low to medium incidence of melanoma, Delaunay propose that the rule of two should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of three should apply.[11]

In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and

- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

ANALYTIC VALIDITY

No published data on the analytic validity of genetic testing for variants associated with cutaneous malignant melanoma were identified.

CLINICAL VALIDITY

Clinical validity is related to interpretation of the results of genetic analysis for the individual patient. One issue common to genetic testing for any type of cancer susceptibility, is determining the clinical significance of individual variants. For example, variants in the *CDKN2A* gene can occur along its entire length, and some of these variants represent benign variants. Interpretation will improve as more data accumulate regarding the clinical significance of individual variants in families with a known hereditary pattern of melanoma. However, the penetrance of a given variant will also affect its clinical significance, particularly because the penetrance of *CDKN2A* variants may vary with ethnicity and geographic location.[4, 5] For example, exposure to sun and other environmental factors, as well as behavior and ethnicity may contribute to penetrance. Bishop estimated that the calculated risk of developing melanoma before age 80 years in carriers of *CDKN2A* variants ranged from 58% in Europe to 91% in Australia.[13]

Interpretation of a negative test is another issue. Melanoma incidence has steadily increased since 1975. Potential reasons include increased exposure to ultraviolet radiation, increased skin cancer detection, and increased longevity.[14] *CDKN2A* and other germline variants associated with high risk for melanoma are relatively uncommon. Family history of melanoma can be associated with other shared heritable traits (e.g., fair skin, red hair), as well as shared environmental exposures. Therefore, patients with a strong family history and normal genetic test results must not be falsely reassured that they are not at increased risk.[4]

Simonin-Wilmer (2023) published a population-based study comparing *POT1* assessment of 2928 melanoma cases to 3298 controls, all of European ancestry.[15] Forty-three *POT1* protein-altering variants were identified. The variants were divided into three groups. Group 1 included 14/43 variants deemed pathogenic. Group 2 included 4/43 variants that were possibly pathogenic, and the remaining 25/43 variants were in Group 3. In the study, 126 cases and 149 controls had a Group 3 variant (p=0.66), indicating no increased risk for melanoma. For Groups 1 and 2 combined, nearly twice as many cases as controls had Group 1 or 2 variants, but the difference was not statistically significant (p=0.096). The authors concluded that about 0.5% of melanoma cases have a pathogenic *POT1* variant.

Bruno (2022) published a prospective study of multi-gene panel testing related to melanoma involving 940 cutaneous melanoma index cases from 1044 Italian families.[16] The panel included the *CDKN2A*, *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, *MITF*, and *ATM* genes. The panel test revealed 89 variants, with 52 occurring on the *CDKN2A* gene. Intermediate risk *MITF* (18) or *ATM* (10) variants were detected in 28 tests. Other gene variants the panel test detected were *CDK4* (1), *BAP1* (5), and *POT1* (4). The presence of pancreatic cancer in the proband and/or family increased the likelihood of detecting a variant, especially in *CDKN2A* (15/52) and *ATM* (4/10). Participants older than 60 years at melanoma diagnosis had fewer detectable variants [odds ratio (OR)=0.13, p=0.008].

De Simone (2020) conducted a retrospective review of melanoma predisposition variants (e.g., *CDKN2A*, *CDK4*) in 888 patients with melanoma from central Italy.[17] Overall, the study included 309 patients with multiple primary melanomas, 435 patients with familial melanoma, and 144 cases with both multiple primary melanomas and familial melanoma. Patients were divided in two clinical categories: "low significance" and "high significance" based on personal and family history. In the sample, 128 patients (72% belonging to the "high significance" category, 28% belonging to the "low significance" category) were found to carry a DNA change defined as pathogenic, likely pathogenic, variant of unknown significance (VUS)-favoring pathogenic or VUS.

Cust (2018) used data from two large case-control studies to assess the incremental contribution of gene variants to risk prediction models using traditional phenotype and environmental factors.[18] Data from 1035 cases and controls from an Australian study and 1460 cases and controls from a United Kingdom study were used in the analyses. The logistic regression models contained the following variables: presence of 45 single nucleotide polymorphisms (among 21 genes); family history of melanoma; hair color; nevus density; nonmelanoma skin cancer; blistering sunburn as a child; sunbed use; freckling as an adult; eye color; and sun exposure hours on weekends and vacation. When polygenic risk scores were added to the model with traditional risk factors, the area under the receiving operator curve (AUC) increased by 2.3% for the Australia population and 2.8% for the United Kingdom population. The *MC1R* gene variants, which are related to pigmentation, were responsible for most of the incremental improvement in the risk prediction models.

Gironi (2018) conducted genetic testing in Italian families prone to cutaneous melanoma to elucidate distinctive clinical and histological features of melanomas in *CDKN2A* mutation carriers.[19] Three hundred patients with cutaneous melanoma (CM) were enrolled and interviewed about their personal and family history of CM and other cancers. Specifically, patients were eligible for genotyping if they had a histologically proven diagnosis of one or more CM and met at least one of the following inclusion criteria: 1) CM diagnosis at less than or equal to 40 years of age; 2) MPM; 3) family history of CM; and/or 4) Personal and/or family history of non-cutaneous cancers suggestive of familial cancer syndrome related to germline mutations of *CDKN2A*, *CDK4, MITF*, and *BAP1* genes. Genotyping revealed 100 patients with wildtype (WT) *CDKN2A* genes and 32 patients with *CDKN2A* variants that were subsequently analyzed according to histological and clinical features. The WT group did not significantly differ from the *CDKN2A* mutation-positive group with respect to phototype (p=0.759) or number of total common melanocytic nevi (p=0.131). However, a personal history of previously excised dysplastic nevi was more frequent among *CDKN2A* variant-positive patients compared to WT (62.5% vs. 26%; p<0.001). A positive family history of CM and/or pancreatic cancer was detected in 90.6% of mutation-positive patients compared to 37% of the WT group (p<0.001). This significance was maintained for CM or pancreatic cancer, individually (78.1% vs. 29%; p<0.001 and 34.4% vs. 10%; p<0.001). There were 54 (41%) patients in this study with at least 1 family member with a history of CM. Among these patients, 25/54 (46.3%) carried a *CDKN2A* germline mutation. There were 21 (16%) of patients with a family history of pancreatic cancer. Among these patients, 11/21 (52.4%) carried a *CDKN2A* germline mutation. Patients with a *CDKN2A* germline mutation developed a statistically significant higher number of MPMs compared to the WT group (mean, 1.88 vs. 1.18; p<0.001). However, while most patients in both genotype groups developed 2 primary melanomas (61% *CDKN2A*, 87.5% WT), 3 or 4 MPMs were observed more frequently in patients with a *CDKN2A* mutation. All *CDKN2A* carriers were found to develop superficial spreading melanomas whereas WT patients generated mostly nodular melanomas (NMs) or lentigo maligna and lentigo maligna

melanomas (LM-LMMs) (p=0.006). There was no significant difference in *CDKN2A* status with respect to meeting inclusion criteria for sentinel node biopsy (15.6% *CDKN2A*, 22% WT; p=0.302). Additionally, 0/5 (0%) patients who underwent the procedure with a *CDKN2A* variant showed metastases compared to 4/22 (18.2%) of WT patients.

Artomov (2017) assessed the rate of rare genetic variants including *CDKN2A* among patients with familial cutaneous melanoma (CM, n=273) in the United States and Greece.[20] Eleven genes that exhibited borderline association (p<0.0001) were independently validated using The Cancer Genome Atlas melanoma cohort (n=379) and a matched set of 3563 European controls with *CDKN2A* (p=0.009), *BAP1* (p=0.03), and *EBF3* (p<0.001), a candidate risk locus, all showing evidence of replication. *EBF3* was then evaluated using germline data from a set of 132 familial melanoma cases and 4769 controls of UK origin (joint p<0.0001). Somatically, loss of *EBF3* expression correlated with progression, poorer outcome, and high *MITF* tumors.

In 2017, Borroni published an Italian case series of 92 consecutive, unrelated patients with familial atypical mole/multiple melanoma syndrome (FAMMM) that were offered genetic counseling and testing for *CDKN2A* and *CDK4* variants.[21] FAMMM is characterized by primary cutaneous melanoma in at least two relatives and/or two or more primary cutaneous melanomas in the same patient. Genetic testing was extended to family members of patients with identified variants. *CDKN2A* variants were found in 19 of the 92 unrelated patients (20.6%) and in 14 healthy relatives. Of these relatives with variants, 11 later underwent excision of dysplastic nevi.

In 2016, Di Lorenzo published a study of 400 patients with cutaneous melanoma who were observed in a six-year period at an Italian university.[22] Forty-eight patients have met the criteria of the Italian Society of Human Genetics (SIGU) for the diagnosis of familial melanoma and were screened for *CDKN2A* and *CDK4* variants. Genetic testing revealed that none of the families carried variants in the *CDK4* gene and only one patient harbored the rare *CDKN2A* p.R87W variant. The study did not identify a high variant rate of *CDKN2A* in patients affected by familial melanoma or multiple melanomas. This difference could be attributed to different factors, including the genetic heterogeneity of the Sicilian population. It is likely that, as in the Australian people, the inheritance of familial melanoma in this island of the Mediterranean Sea is due to intermediate/low-penetrance susceptibility genes, which, together with environmental factors (as latitude and sun exposure), could determine the occurrence of melanoma.

Bruno (2016) reported on the multiMEL study, in which genetic testing for *CDKN2A* and *CDK4* variants were performed on 587 consecutive patients with MPM and 587 consecutive patients with single primary melanoma (SPM).[23] Rates of the variants were 19.1% and 4.4% in patients with multiple primary versus single primary melanoma. Subgroup analyses by familial versus sporadic melanoma showed that among patients with familial MPM and familial SPM, the mutation rates were 44.4% and 24.6%, respectively, compared with sporadic MPM and sporadic SPM variant rates of 10.8% and 2.1%, respectively.

Mangas (2016) measured the rate of *CDKN2A* variants among individuals considered high risk for melanoma, defined as families with at least two cases of melanoma or individuals with multiple melanomas.[24] A total of 57 individuals were tested, 41 of which were considered the index cases. Of the 41, *a CDKN2A* variant was identified in four index cases.

Puig (2016) conducted genetic testing for *CDKN2A* variants among patients with melanoma in Latin America and Spain.[25] The variant rates among patients with familial melanoma were 23.9% and 14.1% in Latin America and Spain, respectively. The *CDKN2A* variant rates were

lower among patients in Latin America and Spain with sporadic MPM, 10.0% and 8.5%, respectively.

A 2016 study by Wendt evaluated *MC1R* variants and melanoma risk in a hospital-based case-control study that included 991 melanoma patients and 800 controls.[26] *MC1R* variants were associated with a higher risk of melanoma after adjustment for age, sex, and ultraviolet radiation exposure (≥2 variants, OR, 2.13 [95% confidence interval [CI], 1.66-2.75], P < .001; P for trend <.001).

Harland (2014) conducted a case control study on patients with melanoma from Australia, Spain, and United Kingdom.[27] *CDKN2A* variant rates for each of the populations were similar (2.3%, 2.5%, and 2.0% in patients from Australia, Spain, and United Kingdom, respectively). Case-control analyses showed that the strongest predictor of carrying a variant was having multiple primaries odds ratio [OR] = 5.4, 95% CI = 2.5 to 11.6; and having three primaries, OR=32.4, 95% CI=14.7 to 71.2). Another predictor of carrying a variant is having a strong family history of melanoma: having 1 relative, OR = 3.8, 95% CI = 1.9 to 7.5; and having two or more relatives, OR = 23.2, 95% CI = 11.3 to 47.6).

Potrony (2014) measured the rate of *CDKN2A* variants among patients in Spain with sporadic multiple primary melanoma (MPM) and familial melanoma.[28] Variant rates were 14.1% in patients with familial melanoma and 8.5% in patients with sporadic multiple primary melanoma.

In 2013, Puntervoll published a description of the phenotype of individuals with *CDK4* variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls).[29] The incidence of atypical nevi was higher in those with *CDK4* variants (70% in melanoma patients; 75% in unaffected individuals) than in those without *CDK4* variants (27%; p<0.001). The distribution of eye color or hair color was not statistically different between *CDK4* variant-positive individuals (with or without melanoma) and variant-negative family members. The authors concluded that “it is not possible to distinguish *CDK4* melanoma families from those with *CDKN2A* variant based on phenotype.” Therefore, the clinical significance of this genetic distinction is currently unclear.

In 2012, Cust classified 565 patients with invasive cutaneous melanoma diagnosed between 18 to 39 years of age, 518 sibling controls, and 409 unrelated controls into *MC1R* categories defined by presence of high risk or other alleles.[30] Compared with sibling controls, two *MC1R* high-risk alleles (R151C, R160W) were associated with increased odds of developing melanoma (OR=1.7; 95% CI, 1.1 to 2.6; OR=2.0; 95% CI, 1.2 to 3.2, respectively), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared with unrelated controls, only the R151C high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other *MC1R* alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty published an article on identifying individuals at high risk for melanoma and emphasized the use of family history.[31]

In 2012, two studies further examined the association of *MC1R* variants and melanoma in southern European populations.[32, 33] Ibarrola-Villava conducted a case-control study in three sample populations from France, Italy, and Spain.[32] Susceptibility genotypes in three genes involved in pigmentation processes were examined in 1639 melanoma patients (15% familial) and 1342 controls. *MC1R* variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. Two other genes not associated with familial cutaneous

melanoma—TYR, which encodes a tyrosinase, and SLC45 A2, which encodes a melanosome enzyme were also were studied. In univariate logistic regression analysis, *MC1R* red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: OR for one allele: 2.2 (95% CI, 1.9 to 2.6); OR for two alleles: 5.0 (95% CI, 2.8 to 8.9). In analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair and skin color) but also in those with dark/olive phenotype. The authors suggested that *MC1R* genotyping to identify elevated risk in Southern European patients considered not at risk based on phenotype alone warranted further investigation. Effects on health outcomes are unknown.

Ghiorzo (2012) studied 49 *CDKN2A*- variant positive and 390 *CDKN2A*- variant negative Italian patients with cutaneous melanoma.[33] *MC1R* variants were associated with increased odds of melanoma only in *CDKN2A*- variant-negative patients in a dose-dependent fashion: OR for one high-risk allele: 1.5 (95% CI, 1.1 to 2.0); OR for two high-risk alleles, 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, effects of *MC1R* variants were statistically significant in most *CDKN2A* variant-negative subgroups and few variant-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, and total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both variant-positive (OR=71.2; 95% CI, 23.0 to 221.0) and variant-negative (OR=5.3; 95% CI, 2.0 to 14.3) patients, although uncertainty in the estimates of association was considerable. Family history of cutaneous nevi (at least 1=one first-degree relative with >10 nevi and /or atypical nevi) increased the odds of melanoma in variant-positive cases only (OR=2.44; 95% CI, 1.3 to 4.5). This finding underscores the significance of nongenetic factors (e.g., sun exposure, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

In 2010, Kanetsky conducted a study to describe associations of *MC1R* (melanocortin one receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure.[34] The study population included melanoma patients (n=960) and controls (n=396) who self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations of high- and low-risk *MC1R* variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of two low-risk, or any high-risk *MC1R* variant was associated with increased risk of melanoma (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.0 to 2.8; OR=2.2; 95% CI, 1.5 to 3.0, respectively). However, risk was noted to be stronger in or limited to people with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR=2.4), had dark hair (OR=2.4), or had dark eyes (OR=3.2). The authors concluded that these findings indicate *MC1R* genotypes provide information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposures alone. However, how this information impacts patient care and clinical outcomes is unknown.

In 2009, Yang conducted a study to identify modifier genes for CMM in CMM-prone families with or without *CDKN2A* variants.[35] Investigators genotyped 537 individuals (107 CMM) from 28 families (19 *CDKN2A*-positive, nine *CDKN2A*-negative) for genes involved in DNA repair, apoptosis, and immune response. Their analyses identified some candidate genes, such as *FAS, BCL7A, CASP14, TRAF6, WRN, IL9, IL10RB, TNFSF8, TNFRSF9*, and *JAK3*, that were associated with CMM risk; after correction for multiple comparisons, *IL9* remained significant.

The effects of some genes were stronger in *CDKN2A* variant-positive families (*BCL7A, IL9*), and some were stronger in CDKN2A-negative families (*BCL2L1*). The authors considered these findings supportive of the hypothesis that common genetic polymorphisms in DNA repair, apoptosis, and immune response pathways may modify the risk of CMM in CMM-prone families, with or without *CDKN2A* variants.

CLINICAL UTILITY

Although genetic testing for *CDKN2A* variants is recognized as an important research tool, its clinical use will depend on how results of genetic analysis can be used to improve patient management. Currently, management of patients considered high risk for malignant melanoma focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. Presently, it is unclear how genetic testing for *CDKN2A* would alter these management recommendations. The following clinical situations can be considered.

Affected Individual with a Positive Family History

If an affected individual has a *CDKN2A* or other germline gene variant associated with high risk for melanoma, they may be at increased risk for being diagnosed at an advanced stage and for having poorer survival than people without detectable gene variants.

Pissa (2023) compared melanoma survival rates before and after initiation in 1987 into a familial dermatologic surveillance program for Swedish families with *CDKN2A* pathologic variants.[36] The study included 473 people with melanoma from 261 families who were diagnosed between 1958 and 2009, with follow-up through 2011. Of the melanoma cases, 96 belonged to 31 families that harbored a *CDKN2A* variant; and 377 were from 230 families that did not have a *CDKN2A* variant. Four cohorts were compared:

1. MUT-pre (n=53): *CDKN2A* carriers (MUT), or relative of a carrier, with first invasive melanoma before inclusion in the surveillance program.
2. MUT-post (n=43): *CDKN2A* carriers (or relative of a carrier) with first invasive melanoma after inclusion in the surveillance program.
3. WT-pre (n=255): *CDKN2A*-negative participants, i.e., wild type (WT), or relative of participant with negative *CDKN2A* test, with first invasive melanoma before inclusion in the surveillance program.
4. WT-post (n=122): *CDKN2A*-negative participants (or relative of participant with negative *CDKN2A* test) with first invasive melanoma after inclusion in the surveillance program.

Overall, worse melanoma-specific survival was associated with tumor T-stage 2-4 (hazard ratio [HR] 5.45, 95%, CI 3.15-9.43, p=0.023), male sex (HR 1.80, 95% CI 1.15-2.83, p=0.011), and diagnosis at >50 years (HR 1.69, 95% CI 1.08-2.64, p=0.023). Survival was not significantly different in the MUT-pre cohort compared to the MUT-post cases, both when unadjusted for age, sex, and T-stage (HR 2.16, 95% CI 0.79-5.94, p=0.134) and after adjusting for factors associated with worse survival (HR 1.17, 95% CI 0.77-2.15, p=0.344). Survival was also similar in the WT-pre compared to the WT-post cohort, using both unadjusted (p=0.444) and adjusted (p=0.781) models. Survival was worse in the MUT-pre cohort compared to the WT-pre cases using both the unadjusted (HR 2.33, 95% CI 1.33-4.08, p=0.003) and adjusted (HR 2.70, 95% CI 1.46-5.00, p=0.001) models. Survival was not significantly different between the MUT-post and WT-post cases in either the unadjusted (HR 0.81, 95% CI 0.30-2.20, p=0.678) or adjusted (HR 1.57, 95% CI 0.6-4.20, p=0.300) models. A secondary analysis was performed

to assess whether worse survival in the MUT-pre cohort was associated with second invasive melanoma, but the survival difference between the two cohorts persisted (HR 2.83, 95%, CI 1.23-6.52, p=0.015).

The authors suggest that inclusion in the surveillance program benefited the families with *CDKN2A* variants because the MUT-pre cohort had worse survival than the WT-pre cohort, and the survival rates were similar in the post-surveillance cohorts. However, neither of the post-surveillance cohorts had significantly different survival when compared to the pre-surveillance cohorts. Importantly, the study does not address whether the difference in survival could be due to other factors, such as treatment differences over the study period. Genetic testing for *CDKN2A* was performed for at least one member of each family, but the genetic status was not known for all study participants and there was no randomization of the surveillance intervention or genetic testing. Therefore, conclusions about the benefit of genetic testing for hereditary melanoma in the study population cannot be drawn.

The National Cancer Institute familial melanoma study compared trends in melanoma thickness in high-risk families to trends in the general U.S. population using Surveillance, Epidemiology, and End Results (SEER) data. Sargen (2021) followed 293 melanoma cases from 56 families. Of 274 melanoma cases with genetic test information, 160 had either a *CDKN2A* or *CDK4* variant, and 114 had neither gene variant. The study found smaller thickness ($p<0.001$) and earlier stage diagnosis ($p<0.001$) of invasive melanoma in people from melanoma-prone families in the surveillance program compared to tumors that were diagnosed before study involvement. However, changes in tumor thickness and stage were similar in families with and without *CDKN2A* or *CDK4* variants ($p<0.05$). During the course of the study reductions in tumor thickness and disease stage in the high-risk study participants generally paralleled reductions seen in the general population obtained from SEER data. While a trend was seen for lower thickness in the study population compared to SEER data, the difference was not significant in the high risk cases pre-study ($p=0.922$) or after study enrollment when assessed for mean thickness ($p=0.20$) and changes over time ($p=0.198$).[8]

People with hereditary melanoma may also be at increased risk for a second primary melanoma compared with the general population. However, limited and protected sun exposure and increased surveillance would be recommended to any patient with a history of malignant melanoma, regardless of the presence of a *CDKN2A* or pathogenic variant. A positive result will establish a familial variant, thus permitting targeted testing for the rest of the family. Additionally, a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member; but, as described earlier, a negative test result is not interpretable.

Unaffected Individual in a High-Risk Family

If the unaffected individual is the first to be tested in the family (i.e., no affected relative has been previously tested to define the target variant), it is very difficult to interpret the clinical significance of a variant, as described. The likelihood of clinical significance is increased if the identified variant is the same as one reported in other families, although the issue of penetrance is a confounding factor. If the unaffected individual has the same variant as an affected relative, then the patient is at high risk for melanoma. However, again it is unclear how this would affect the management of the patient. Even patients who have a genetic test result that rules out a known familial variant associated with melanoma (i.e., “true negatives”) may

still be considered at increased risk for melanoma.[8] Increased sun protection and surveillance are recommended for any patient in a high-risk family.

Published data on genetic testing of the *CDKN2A* and *CDK4* genes focus on the underlying genetics of hereditary melanoma, identification of variants in families at high risk of melanoma, and risk of melanoma in those harboring these variants. Other studies have focused on the association between *CDKN2A* and pancreatic cancer.[37-39] One publication added the caution that differences in melanoma risk across geographic regions justify the need for studies in individual countries before counseling should be considered.[40]

Stump (2020) investigated whether genetic counseling and test reporting for *CDKN2A* carrier status promoted objective reductions in sun exposure.[41] Participants were recruited from two types of pedigrees: families with an identified *CDKN2A* mutation and families with a similar melanoma history but no identified *CDKN2A* mutation. Subjects from *CDKN2A*-positive families were derived from three kindreds and accounted for 32 carriers and 46 noncarriers. No-test control subjects (n=50) were derived from nine *CDKN2A*-negative families. The daily standard erythemal dose (SED; J/m2) of ultraviolet radiation (UVR) exposure was measured with a wrist-worn, battery-powered dosimeter over three 27-day periods. Complete dosimetry data was available for 75.8% of participants, with missing data due to technical issues, device loss, or device damage. The average number of days coded as "not worn" ranged from 7 to 10 days in each assessment period. Both carriers and no-test controls exhibited a significant decrease in UVR dose at one year compared to baseline ($p < 0.01$). No change from baseline was noted for noncarriers at any timepoint. However, these outcomes do not account for the use of sunscreen or sun-protective clothing. Skin pigmentation was assessed via reflectance spectroscopy, yielding a Melanin Index (MI) score in which higher scores represent greater melanin content. Measurements from the face and wrist were standardized to measurements obtained from non-exposed sites to account for differences in skin tone. Data from patients using artificial tanning products within a week of testing were excluded. Only carriers exhibited a significant decrease in skin pigmentation at the wrist at one year ($p < 0.001$). However, no corresponding changes in facial pigmentation were detected for any group. Both carriers and no-test controls self-reported fewer sunburns than non-carriers ($p < 0.05$). Noncarriers did not demonstrate changes in any measure of UVR exposure, however, daily UVR exposure was higher among noncarriers compared to no-test controls at baseline ($p = 0.03$). Despite the incorporation of propensity score matching in their statistical methods, the authors acknowledge that they cannot exclude yet-to-be identified confounding factors driving between-group differences in their non-equivalent control study design. The study did not assess key health outcomes such as melanoma incidence.

Aspinwall (2018) compared potential informational and motivational benefits from genetic testing for melanoma among individuals from high risk families who were variant-positive (n=28), variant-negative (n=41), and unknown carrier status (n=45).[42] High risk individuals were defined as those related to a patient with a known *CDKN2A* variant or those with a significant family history of melanoma (>3 cases) but no identified variant. All participants received genetic counseling, which included a risk estimate of developing melanoma during their lifetime. Outcomes, measured after one month and one year followup, included: feeling informed and prepared to manage risk; motivation to reduce sun exposure; motivation to perform screening; and negative/positive emotions about melanoma risk. Individuals who were tested (both variant-positive and variant negative) reported feeling significantly more informed and prepared to manage risk compared to those not tested. All participants had low negative emotions concerning melanoma risk.

Dalmasso (2018) conducted a retrospective case-control study to determine if there was an association between *CDKN2A* variants and survival among patients with melanoma.[43] From consecutive patients with the diagnosis of melanoma and genetic testing data from a single hospital, 106 variant-positive cases and 199 variant-negative controls, matched by age and sex, were included in the analyses. The overall rate of deaths in both groups was 17%. Melanoma-specific mortality was 10.8% in the variant-positive group and 7.8% in the variant-negative group. There were no statistically significant differences in overall or melanoma-specific survival between the two groups.

In 2018, Stump reported changes in sun protection and stress levels following genetic counseling and test reporting for the *CDKN2A/p16* variant.[44] Participants included 18 minors from melanoma-prone families, with a mean age of 12.4. Nine were carriers and nine were noncarriers. Compared to baseline, at one-year post-disclosure, all subjects self-reported significantly fewer sunburns. In addition, a greater proportion reported sun protection adherence. There were no significant differences between genotypes. Depressive symptoms and cancer worry declined and anxiety symptoms, which began low, remained unchanged post-disclosure. In interviews, all mothers of the subjects indicated that genetic testing was beneficial. Reasons included that it promoted risk awareness (90.9%) and sun protection (81.8%) without making their children scared (89.9%). Independent practice of sun protection by their children was reported by 45.4% of mothers.

Two behavioral studies were published in 2016. Levin examined behavior patterns in families in Norway in which a *CDKN2A* variant was identified.[45] The authors reported that 66 % (95/144) of carriers' first-degree relatives contacted the researchers within the study period, 98% (126/128) of all relatives who came for genetic counseling requested genetic testing, and 93 % (66/71) of those with variants wanted referral for yearly skin examinations. Wu studied the impact of melanoma genetic test reporting and counseling on the frequency of discussion about preventive behaviors between 24 counseled adults and their children and grandchildren.[46] Conversations about preventive behaviors were assessed before testing and at one and six months after testing, using open-ended questions. The authors reported that these discussions declined after test reporting, with a faster decline in variant non-carriers, and that there was a large gap between the number of participants who intended to have preventive behavior discussions and the number that reported having had such discussions at follow-up.

In 2013, Aspinwall reported outcomes for 37 patients (62%) of this cohort who were available for two-year follow-up.[47, 48] Anxiety, depression, and cancer-specific worry declined over two years, although baseline values were low and the declines are of uncertain clinical significance. Adherence to annual total body skin examinations and monthly skin self-examinations varied by carrier status; however, without a comparison group, it is not possible to attribute any change in adherence to knowledge of test results.

In 2012, Branstrom examined a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma.[49] Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

In a 2011 retrospective case-control study, van der Rhee sought to determine whether a surveillance program of families with a Dutch founder variant in *CDKN2A* (the p16-Leiden

variant) allowed for earlier identification of melanomas.[50] Characteristics of 40 melanomas identified in 35 unscreened patients (before heredity was diagnosed) were compared with 226 melanomas identified in 92 relatives of those 35 unscreened melanoma patients who were found to have the *CDKN2A* variant and participated in a surveillance program over a 25-year period. Surveillance comprised a minimum of an annual total skin evaluation, which became more frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow thickness (median thickness, 0.50 mm) than melanomas identified in unscreened patients (median thickness, 0.98 mm), signifying earlier identification with surveillance. However, only 53% of melanomas identified in the surveillance group were detected on regular screening appointments. Additionally, there was no correlation between length of screening intervals (for intervals <24 months) and melanoma tumor thickness at the time of diagnosis. The authors also noted that despite understanding the importance of surveillance, patient noncompliance was still observed in the surveillance program, and almost half of patients were noncompliant when first diagnosed with melanoma.

In a 2008 study, Aspinwall found short-term change in behavior among a small group of patients without melanoma who were positive for the *CDKN2A* variant.[51] In this prospective study of 59 members of a *CDKN2A* variant-positive pedigree, behavioral assessments were made at baseline, immediately after *CDKN2A* test reporting and counseling, and at one month follow-up (42 participants). Across multiple measures, test reporting caused *CDKN2A* disease-associated variant carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history. *CDKN2A*-positive participants without a melanoma history reported greater intention to obtain total body skin examinations, increased intentions and adherence to skin self-examination recommendations, and increased number of body sites examined at one month.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The current (v1.2024) National Comprehensive Cancer Network (NCCN) clinical guidelines on melanoma state:[52]

- Follow-up recommendations for all patients with cutaneous melanoma:
    - Consider genetic counseling referral for *p16/CDKN2A* testing in the presence of three or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family.
    - Multigene panel testing that includes *CDKN2A* is also recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer.
    - Testing for other genes that can harbor melanoma-predisposing mutations may be warranted.
- Risk Factors for Development of Single or Multiple Primary Melanomas:
    - Genetic predisposition: Presence of germline mutations or polymorphisms predisposing to melanoma (e.g. *CDKN2a*, *CDK4*, *MC1R*, *BAP1* [especially for uveal melanoma], *TERT*, *MITF*, *PTEN* and potential other genes).
    - Family history of cutaneous melanoma (especially if multiple); pancreatic, renal, and/or breast cancer; astrocytoma; uveal melanoma; and/or mesothelioma.

AMERICAN CANCER SOCIETY

According to the American Cancer Society, genetic testing for *CDKN2A* and other genes associated with melanoma is available, but “doctors aren’t sure how useful they are at this time.”[53]

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2010, the American Society of Clinical Oncology (ASCO) updated its policy statement on genetic and genomic testing for cancer susceptibility.[54] ASCO recommends that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

In 2014, the ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility.[55] The ASCO "affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."

AMERICAN ACADEMY OF DERMATOLOGY

In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma.[56] Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma was recommended for consideration with a level IIIC grade of evidence. The Work Group explained that "there is no strong evidence that genetic evaluation is either harmful or helpful."

SUMMARY

There is not enough research to show that genetic testing for cutaneous melanoma can improve health outcomes, including for people with melanoma or a family history of melanoma. There are no clinical guidelines based on research that specifically recommend this type of testing. Therefore, genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

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CODES

Codes	Number	Description
CPT	81404	Molecular pathology procedure, Level 5
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *January 2011*

Regence

Medical Policy Manual Genetic Testing, Policy No. 10

Cytochrome p450 and VKORC1 Genotyping for Treatment Selection and Dosing

Effective: April 1, 2025

Next Review: February 2025
Last Review: March 2025

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

CYP450 and *VKORC1* genotyping may help to tailor drug selection and dosing to individual patients based on their predicted drug metabolism. The goal of this testing it to lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

MEDICAL POLICY CRITERIA

Note: For panel testing related to behavioral health disorders, including medication selection, please refer to Genetic Testing Policy No. 53, Genetic Testing for Diagnosis and Management of Behavioral Health Conditions.

I. *CYP2C19* genotyping may be considered **medically necessary** for the following indications:

   A. To aid in the choice of clopidogrel (Plavix®) versus alternative anti-platelet agents; or

   B. To guide decisions on the optimal dosing for clopidogrel.

II. *CYP2D6* genotyping to determine drug metabolizer status may be considered **medically necessary** for patients with:

   A. Gaucher disease type I being considered for treatment with eliglustat (Cerdelga™); or

   B. Huntington disease being considered for treatment with tetrabenazine (Xenazine ®) in a dosage greater than 50mg per day.

III. *CYP2C9* genotyping to determine drug metabolizer status may be considered **medically necessary** for patients with relapsing forms of multiple sclerosis (i.e., clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) being considered for treatment with siponimod (Mayzent®).

IV. Except as defined in Criteria I, II, or III above, *CYP450 (*including *CYP2C9, CYP2C19, CYP2D6, and CYP4F2)* and *VKORC1* genotyping is considered **investigational** for medication selection and dose management, including but not limited to:

   A. Panels that include testing for more than one *CYP450* gene

   B. Testing for the following: anti-tuberculosis medications, atomoxetine HCl, beta blockers, codeine, efavirenz, H. pylori infection, immunosuppressant for organ transplantation, tamoxifen, and warfarin.

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

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Date of blood draw
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Genetic Testing for Diagnosis and Management of Behavioral Health Conditions, Medical Policy Manual, Genetic Testing, Policy No. 53
3. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80
4. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation (polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA polymorphisms (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

CYP450

The cytochrome p450 family (CYP450) is a major subset of drug-metabolizing enzymes. The CYP450 family of enzymes includes but is not limited to:

- CYP2D6 which metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, beta-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including many of the most prescribed drugs.
- CYP2C19 which metabolizes several important types of drugs, including proton-pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

Some *CYP450* genes are highly polymorphic, resulting in enzyme variants that may have variable drug-metabolizing capacities among individuals. The *CYP450* metabolic capacities may be described as follows:

- Extensive metabolizers (EM)
  - Have two active *CYP450* enzyme gene alleles, resulting in an active enzyme molecule
- Poor metabolizers (PMs)
  - Lack active *CYP450* enzyme gene alleles
  - May suffer more adverse events at usual doses of active drugs due to reduced metabolism and increased concentrations
  - May not respond to administered prodrugs that must be converted by CYP450 enzymes into active metabolites
- Intermediate metabolizers (IMs)
  - Have one active and one inactive *CYP450* enzyme gene allele
- Ultrarapid metabolizers (UMs)
  - Have more than two active *CYP450* gene alleles
  - May not reach therapeutic concentrations at usual, recommended doses of active drugs
  - May suffer adverse events from prodrugs that must be converted by CYP450 enzymes into active metabolites

It is important to note that many drugs are metabolized by more than one enzyme, either within or outside of the CYP450 family. Reduced activity in a particular CYP450 enzyme because of genotype may not affect outcomes when other metabolic pathways are available and when other confounders influence drug metabolism, such as interactions between different metabolizing genes, interactions of genes and environment, and interactions among different non-genetic factors.

CYP450 GENOTYPING

The purpose of *CYP450* genotyping is to tailor drug selection and dosing to individual patients based on their gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

Diagnostic genotyping tests for certain CYP450 enzymes are now available:

- The AmpliChip® (Roche Molecular Systems, Inc.) is an U.S. Food and Drug Administration (FDA)-approved, microarray-based pharmacogenomic test. The assay distinguishes 29 known polymorphisms in the *CYP2D6* gene and two major polymorphisms in the *CYP2C19* gene.[1]
- The INFINITI *CYP2C19* Assay (AutoGenomics, Inc.) was cleared for marketing in October 2010 based on substantial equivalence to the AmpliChip *CYP450* test. It is designed to identify variants within the *CYP2C19* gene (*2, *3, and *17).
- The Spartan RX *CYP2C19* Test System (Spartan Bioscience), designed to identify variants in the *CYP2C19* gene (*2, *3, and *17 alleles), was cleared for marketing in August 2013 based on substantial equivalence to the INFINITI *CYP2C19* Assay.
- Verigene *CYP2C19* Nucleic Acid Test (Nanosphere Inc.), designed to identify variants within the *CYP2C19* gene, was cleared for marketing in November 2013 based on substantial equivalence to the INFINITI *CYP2C19* Assay.
- The xTAG® *CYP2D6* Kit (Luminex Molecular Diagnostics) was cleared for marketing in August 2010 based on substantial equivalence to the AmpliChip *CYP450* test. It is designed to identify a panel of nucleotide variants within the polymorphic *CYP2D6* gene on chromosome 22.
- The xTAG® *CYP2C19* Kit v3 (Luminex Molecular Diagnostics), designed to identify variants in the *CYP2C19* gene (*2, *3, and *17 alleles) was cleared for marketing in September 2013 based on substantial equivalence to the INFINITI *CYP2C19* Assay.
- Some tests are offered as in-house laboratory-developed test services. These tests do not require FDA approval.
- Several manufacturers market panels of diagnostic genotyping tests for *CYP450* genes, such as the YouScript Panel (Genelex Corp.), which includes *CYP2D6, CYP2C19, CYP2C9, VKORC1*, *CYP3A4* and *CYP3A5*. Other panel tests include both *CYP450* genes and other non-*CYP450* genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health Inc.).

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used

terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Following is a summary of the key literature. The following limitations in the current evidence for therapeutic agents other than clopidogrel and eliglustat were noted:

- The available evidence is not sufficient to establish how *CYP450* genotyping improves patient management with respect to drug selection and dosing compared to standard treatment without genotyping.
- It is not known if genotyping improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate.
- In general, most published *CYP450* pharmacogenomic studies are retrospective evaluations of *CYP450* genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse events or efficacy). Studies are mostly small and under-powered.
- There is a lack of randomized, prospective studies evaluating the clinical utility of *CYP450* genotyping for any of the indications discussed below.

ANTI-TUBERCULOSIS MEDICATIONS

A number of studies have reported an association between *CYP2E1* status and the risk of liver toxicity from antituberculosis medications.

Systematic Reviews

Wang (2016) reported a meta-analysis of 26 studies with a total of 7,423 participants, evaluating the association of *CYP2E1* variants and susceptibility to antituberculosis drug-induced hepatotoxicity. The overall odds ratios of relevant studies demonstrated that the *CYP2E1 RsaI/PstI C1/C1* genotype was associated with an elevated risk of liver toxicity (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.03 to 1.69, p=0.027), but for the *DraI* variant there was no increase in risk (OR 1.05, 95% CI 0.80 to 1.37, p=0.748).

In a meta-analysis, Sheng (2014) investigated the potential association between cytochrome P450 2E1 (*CYP2E1*) polymorphisms and the risk of anti-tuberculosis drug-induced hepatotoxicity (ATDH).[3] Compared with the wild genotype (*C1/C1*), the OR of ATDH was 1.41 (95% CI 1.1 to 1.82, p=0.007) for the *PstI/RsaI* polymorphism, and 0.78 (95% CI 0.51 to 1.18, p=0.23) for the *DraI* polymorphism. Compared with individuals with N-acetyltransferase 2 (NAT2) fast or intermediate acetylator genotype and *C1/C1* genotype patients who were NAT2 slow acetylators and carried the high activity *CYP2E1 C1/C1* genotype had higher risk for ATDH (OR 3.10, p<0.0001). Authors concluded the meta-analysis indicated that the *CYP2E1 C1/C1* genotype may be a risk factor for ATDH.

A meta-analysis of available trials was reported by Deng (2013).[4] Compared with wild type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR 1.36, 95% CI 1.09 to 1.69). Patients who were slow metabolizers had the highest risk of toxicity (OR 1.88, 95% CI 1.14 to 3.09), and this overall risk was also increased in Asian patients. This study does not address the question of whether genetic testing can reduce liver damage from anti-tuberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels.

Randomized Controlled Trials

No randomized controlled trials (RCTs) evaluating the clinical utility of *CYP450* testing for use in prescribing anti-tuberculosis medications were identified.

Nonrandomized Studies

Evidence of the relationship between *CYP450* genotype and ATDH is limited to small observational studies.[5-7]

Section Summary

The clinical utility of testing for *CYP450* genotyping is uncertain, since management changes for anti-tuberculosis medications based on genotyping results has not been evaluated.

BETA BLOCKER SELECTION AND DOSING

Systematic Reviews

A systematic review by Mottet (2016) examined the influence of pharmacogenetics on heart failure treatment.[8] The authors noted that while studies indicate that *CYP2D6* variants affect the pharmacokinetics of metoprolol, there is limited evidence on the topic and the clinical impact of the relationship has not been established.

Randomized Controlled Trials

No prospective randomized controlled trials of genotype-directed beta blocker selection and dosing have been reported.

Nonrandomized Studies

Existing studies have reported contradictory findings concerning the association of the *CYP2D6* genotype and the response to beta blockers. Some have reported that *CYP2D6* variants are associated with altered responses to these medications,[9, 10] with a few studies indicating that lipophilic beta selective adrenergic receptor antagonists, such as metoprolol used in treating hypertension, may exhibit impaired elimination in patients with *CYP2D6* polymorphisms.[11-15] In addition, increased risk of bradycardia was observed in patients found to be PMs (*CYP2D6 *4/*4*), although the clinical significance of this observation remains to be defined.[11, 16, 17]

In contrast, it has also been reported that no difference in response to metoprolol or carvedilol was observed according to genotype.[18-20]

Section Summary

CYP2D6 genetic variants may be associated with response to beta-blocker treatment, but little evidence currently exists on the clinical utility of testing for *CYP2D6* variants in improving outcomes from beta-blocker treatment.

CLOPIDOGREL: DETERMINING RISK OF ATHEROTHROMBOTIC EVENTS AFTER AN ACUTE CORONARY SYNDROME OR A PERCUTANEOUS CORONARY INTERVENTION

Dual antiplatelet therapy with aspirin and clopidogrel is currently recommended for the prevention of atherothrombotic events after acute myocardial infarction. However, a substantial number of subsequent ischemic events still occur, which may be at least partly due to interindividual variability in the response to clopidogrel. Clopidogrel, a prodrug, is converted by several CYP450 enzymes, including the enzyme coded by *CYP2C19*, to an active metabolite. However, variation in clopidogrel response is an extremely complicated process impacted by a wide range of both genetic and environmental factors, including patient compliance, metabolic state, and drug and food intake.

Prospective, randomized controlled clinical trials are needed to demonstrate the clinical utility of *CYP450* testing in this patient population. Specifically, additional studies are needed that demonstrate reduced recurrence rates for carriers of *CYP2C19* variants who are prospectively treated according to genotype.

Systematic Reviews

Several systematic reviews and meta-analyses have been published, all suggesting that *CYP2C19* gene polymorphisms do not have a substantial or consistent influence on the clinical efficacy of clopidogrel (see below). Meta-analyses have also compared genotype-guided treatment to standard treatment in patients with acute coronary syndrome or those undergoing PCI or stent implantation, with mixed findings.[21-27] However, in the absence of a significant effect of *CYP2C19* variants on clopidogrel efficacy, it is not clear what mechanisms would lead to outcome differences.

Cargnin (2023) published a systematic review and meta-analysis that evaluated the clinical utility of *CYP2C19* genotyping in stroke and transient ischemic attack patients of non-East Asian ancestry.[28] The review investigated the association of *CYP2C19* loss-of-function status with efficacy and safety of clopidogrel-based antiplatelet therapy. Clopidogrel-treated carriers of *CYP2C19* loss-of-function alleles were found at increased risk of stroke compared to non-carriers (risk ratio [RR]: 1.68, 95%CI: 1.04 to 2.71, p= 0.03). However, no significant association was observed with the risk of composite vascular events (RR: 1.15, 95%CI: 0.58 to 2.28, p=0.69) or bleeding (RR: 0.84, 95%CI: 0.38 to 1.86, p=0.67). Similarly, European ancestry patients carrying *CYP2C19* loss-of-funcion alleles displayed a higher risk of stroke (RR: 2.69 (1.11 to 6.51, p=0.03), but not of composite vascular events or bleeding.

Malik (2022) completed a SR with meta-analysis to evaluate the effectiveness of genotype testing-guided P2Y12 inhibitor prescription therapy to patients after PCI for ACS compared to non-genotype guided conventional treatment. The analysis included seven studies (9617 patients). Genotype-guided strategy arm included prasugrel or ticagrelor prescription to patients with loss of function (LOF) of CYP219 alleles (most commonly alleles being *2 and *3) and clopidogrel prescription to those without the LOF allele. The conventional arm included patients treated with clopidogrel without genotype testing. The genotype arm showed decreased major adverse cardiovascular events, improved cardiovascular (CV) mortality,

reduced incidence of myocardial infarction (MI) and decreased incidence of stent thrombosis. Stroke incidence was similar in the two arms.[27]

Wang (2016) reported results of a meta-analysis of 12 studies involving 8,284 patients to evaluate the association between *CYP3A5* variants and the risk of adverse events in patients undergoing clopidogrel therapy.[29] The *CYP3A5* variant was classified as wild-type, heterozygote, and homozygous variant. There was no statistically significant difference in the odds of major adverse cardiovascular events in the three groups classified by *CYP3A5* variant (wild-type plus heterozygote vs. homozygous variant: OR 1.032, 95% CI 0.583 to 1.824, p=0.915, wild-type vs. heterozygote plus homozygous variant: OR 1.415, 95% CI 0.393 to 5.094, p=0.595). There was no significant relation between *CYP3A5* variants and bleeding (homozygous vs. wild-type plus heterozygote: OR 0.798, 95% CI 0.370 to 1.721, p=0.565) or clopidogrel resistance (wild-type plus heterozygote vs. homozygous variant: OR 1.009, 95% CI 0.685 to 1.488, p=0.963; wild-type vs. heterozygote plus homozygous variant: OR 0.618, 95% CI 0.368 to 1.039, p=0.069).

Osnabrugge (2015) reported a systematic review of 11 meta-analyses which summarized studies evaluating the associations between *CYP2C19* genetic status and outcomes in clopidogrel-treated patients.[30] The 11 meta-analyses included a total of 30 primary studies, but not all studies were included in all meta-analyses. Among the 30 primary studies, there were 23 cohort studies and seven post hoc analyses of RCTs. Eight out of 11 meta-analyses on clinical end points reported a statistically significant association between *CYP2C19* genotype and outcomes, with mean effect sizes ranging from 1.26 to 1.96. Five of these eight concluded that there was an association between *CYP2C19* genotype and the clinical end point, two inferred that there was a possible association, and one concluded that the association was not proven because of publication bias. For the outcome of stent thrombosis, all 11 meta-analyses reported a statistically significant association between *CYP2C19* genotype and stent thrombosis, with mean effect sizes ranging from 1.77 to 3.82.

Mao (2013) conducted a systematic review and meta-analysis of studies assessing the effect of *CYP2C19* polymorphisms on clinical outcomes in patients with coronary artery disease treated with clopidogrel.[31] The authors included 21 studies involving 23,035 patients, including prospective cohort studies and post-hoc analyses of RCTs involving patients with coronary artery disease. Carriers (n=6868) of the *CYP2C19* variant allele had a higher risk of adverse clinical events than the 14,429 noncarriers (OR 1.50, 95% CI 1.21 to 1.87, p<0.000). Patients with a loss-of-function *CYP2C19* allele had a higher risk of myocardial infarction (OR 1.62, 95% CI 1.35 to 1.95, p<0.000) and a higher risk of in-stent thrombosis, among those who underwent stent implantation (OR 2.08, 95% CI 1.67 to 2.60, p<0.000).

Bauer (2011) carried out an extensive literature review and meta-analysis of the genetic studies examining the impact of variants of the *CYP2C19* genotype on the clinical efficacy of clopidogrel.[32] Out of 4,203 identified publications, 15 studies met the prespecified inclusion criteria. When comparing carriers of at least one reduced function allele of *CYP2C19* with noncarriers, the unadjusted odds ratios of major adverse events were higher in three studies, lower in one, and not significantly different in eight. For stent thrombosis the odds ratio associated with reduced function allele carrier status was reduced in four studies but showed no significant difference in five. No studies showed a significant positive or negative impact on outcomes as a result of *CYP2C19*17* testing. The overall quality of evidence was graded as low. The authors concluded that “accumulated information from genetic association studies does not indicate a substantial or consistent influence of *CYP2C19* gene polymorphisms on

the clinical efficacy of clopidogrel. The current evidence does not support the use of individualized antiplatelet regimens guided by *CYP2C19* genotype."

Holmes (2011) systematically reviewed studies linking *CYP2C19* testing to treatment with clopidogrel.[33] They identified 32 studies including 42,106 participants. Twenty-one studies included patients with acute coronary syndromes and eight studies included patients with stable coronary heart disease – the latter usually associated with coronary stent placement. While the authors observed a decrease in the measurable concentration of clopidogrel metabolite in patients with a loss-of-function gene on 75 mg of clopidogrel, they were unable to show that this resulted in a clinically meaningful change in outcomes. Of particular note was the observation that when studies were stratified by numbers of outcome events, there was a clear trend toward the null in larger studies, consistent with small-study bias. The strongest data supporting use of testing was in the prediction of stent thrombosis, with a risk ratio of 1.75 (CI 1.50 to 2.03) for fixed effects and 1.88 (CI 1.46 to 2.41) for random effects modeling. Assuming an event risk of 18 per 1000 in the control group they calculated that this corresponded to an absolute increase of 14 stent thromboses per 1000 patients. Holmes et al. noted a trade-off between decreased risk of bleeding with loss of function that in part appeared to mitigate increased susceptibility to thrombosis. They cautioned that efforts to personalize treatment in the loss-of-function setting should be considered carefully because efforts to improve efficacy might be offset by risks of harms such as bleeding.

In a related editorial, Beitelshees (2012) noted that the results of the Holmes (2011) analysis may have been compromised by the fact that patients who did not undergo percutaneous coronary intervention (PCI) were included.[34] They concluded that the association between *CYP2C19* genotype and adverse outcomes with clopidogrel treatment may not be present in all settings and may be strongest for clopidogrel indications with the greatest effects such as patients undergoing PCI. This observation is supported by observations in the CHARISMA genetics study reported by Bhatt.[35] A total of 4,819 patients were genotyped in this study and no relationship between *CYP2C19* status and ischemic outcomes in stable patients was observed. Bhatt also observed significantly less bleeding in this subgroup.

Xi (2017) published a systematic review and meta-analysis on *CYP2C19* genotype and adverse outcomes with clopidogrel treatment following stent implantations in Asian populations.[36] Twenty studies with a total of 15,056 patients were included. MACE, a composite outcome of myocardial infarction and cardiovascular death, was the primary outcome assessed. Patients that had at least one loss-of-function allele had an increased risk of MACE compared with noncarriers (OR 1.99, 95% CI 1.64 to 2.42, $p<0.001$), and a reduced risk of bleeding (OR 0.66, 95% CI 0.46 to 0.96, $p<0.001$). Subgroup analysis indicated that risk of MACE was significantly elevated for patients with a loss-of-function allele among those who had a high loading dose of clopidogrel (600 mg).

Randomized Controlled Trials

Pereira (2020) published results of the TAILOR-PCI randomized trial comparing genotype-guided antiplatelet therapy to standard clopidogrel therapy in 5,302 patients undergoing PCI for acute coronary syndromes or stable coronary artery disease.[37] This was a multicenter trial carried out in the US, Canada, Mexico, and South Korea. Patients in the genotype-guided group who had a loss-of-function *CYP2C19* allele received ticagrelor, while noncarriers and those in the control group received clopidogrel. The primary outcome of the trial was a composite of cardiovascular death, stroke, myocardial infarction, stent thrombosis, and severe

recurrent ischemia at one year. Major and minor bleeding were also assessed. No significant differences were seen for the primary outcome, which occurred in 113/2,641 (4.4%) of the genotype-guided group and 135/2,635 (5.3%) of the control group (HR 0.84, 95% CI 0.65 to 1.07, p=0.16), or any of the 11 prespecified secondary outcomes.

A randomized trial by Claassens (2019) assigned 2,488 patients undergoing PCI to receive either genotype-guided (n=1,242) or standard selection (n=1,246) of oral platelet inhibitors.[38] For the genotype-guided group, patients carrying *CYP2C19*2* or *CYP2C19*3* loss-of-function alleles were treated with ticagrelor or prasugrel, while non-carriers were treated with clopidogrel. The two primary outcomes of this trial were an adverse event composite of death from any cause, myocardial infarction, stent thrombosis, stroke or major bleeding and a bleeding outcome composed of major or minor bleeding at 12 months according to Platelet Inhibition and Patient Outcomes (PLATO) criteria. A non-inferiority analysis indicated that the genotype-guided treatment selection was not inferior to standard treatment selection for the adverse events and was associated with a lower incidence of bleeding (hazard ratio [HR] 0.78, 95% CI 0.61 to 0.98, p=0.04). A prespecified subanalysis of this study found that the *CYP2C19*17* variant was not associated with the thrombotic or bleeding outcomes.[39]

Roberts (2012) reported on the use of a point-of-care *CYP2C19*C* genetic test for treatment selection (standard treatment [prasugrel] versus clopidogrel).[40] In this controlled trial, patients undergoing PCI for acute coronary syndrome or stable angina were randomized to genotyping for treatment selection or standard treatment. In the tested group, carriers were given 10 mg of prasugrel daily. Noncarriers and all patients in the control group were given 75 mg of clopidogrel per day. The primary endpoint was high on-treatment platelet reactivity. This measure is used as a marker of cardiovascular events. In the group with genotyping none of the 23 carriers had high on-treatment platelet reactivity; in the group receiving standard treatment 30% of 23 carriers had high on-treatment platelet reactivity. These authors concluded that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment reactivity. The authors do note that alternative approaches using either phenotyping or a combination of both phenotyping and genotyping might optimize treatment decision making.

Han (2017) evaluated the impact of *CYP2C19* genotype in a randomized trial designed to compare the effects of triflusal and clopidogrel in patients with a first-time, non-cardiogenic stroke.[41] The study included 784 patients that were randomized 1:1 to either triflusal or clopidogrel, and the primary endpoint was recurrent stroke (ischemic or hemorrhagic). The median follow-up was 2.7 years, and 597 (76%) of patients completed the trial. There were no significant differences found for individuals with a poor-metabolizer *CYP2C19* genotype (**2/*2*, **2/*3*, or **3/*3*, n=484) by treatment group. Additionally, there were no significant differences in outcomes between genotype groups. However, the authors noted that the required sample size for the study (n=1,080) was not reached.

So (2016) tested a pharmacogenomic strategy to guide anti-platelet therapy in patients with ST-elevation myocardial infarction.[42] There were 102 patients enrolled in the study and they received point-of-care genetic testing for *CYP2C19**2, *ABCB1 TT* and *CYP2C19*17*. Those with either the *CYP2C19*2* or the *ABCB1 TT* allele were randomly assigned to either prasugrel 10 mg daily or an augmented clopidogrel strategy (150 mg daily for six days, then 75 mg daily). The primary endpoint of this trial was high on-treatment platelet reactivity (HPR). There were 59 patients that were carriers of at least one of the two variants. Among these, those randomized to prasugrel treatment had reduced rates of HPR compared to the clopidogrel

treatment group (P2Y12 reaction unit thresholds of >234: 0 vs. 24.1%, p=0.0046; and PRU>208:3.3 vs. 34.5%, p=0.0025, respectively). While the results of this study indicate that prasugrel treatment may be superior to clopidogrel treatment in carriers, the effects of the pharmacogenomic strategy itself were not tested in this trial, as there was no group randomized to a non-pharmacogenomic strategy.

Wang (2016) evaluated the association between *CYP2C19* loss-of-function alleles and the efficacy of clopidogrel in patients with minor stroke or transient ischemic attack.[43] In this trial, 2,933 Chinese patients were randomized to treatment with either clopidogrel plus aspirin or aspirin alone. *CYP2C19* genotype and clinical outcomes including new stroke, other vascular events, and bleeding were assessed. There were 1,726 carriers identified with a loss-of-function allele. After 90 days of follow-up, the clopidogrel plus aspirin treatment was more effective in preventing new stroke than aspirin alone only in noncarriers (non-carrier HR 0.51, 95% CI 0.35 to 0.75; carrier HR 0.93, 95% CI 0.69 to 1.26, p=0.02 for interaction). Similar results were seen for other vascular outcomes. Bleeding was more common in the clopidogrel plus aspirin treatment group than the aspirin only group, but there was no difference by carrier status (2.3% for carriers and 2.5% for noncarriers in the clopidogrel-aspirin group vs. 1.4% for carriers and 1.7% for noncarriers in the aspirin only group, p=0.78 for interaction). These results indicate that for carriers of a *CYP2C19* loss-of-function allele, treatment with aspirin alone may result in better outcomes than combined clopidogrel and aspirin treatment.

Zhang (2016) compared the efficacy and safety of ticagrelor and high-dose clopidogrel in 181 patients with acute coronary syndrome that were intermediate or PMs of clopidogrel in an open-label randomized trial.[44] The primary study outcome was a composite outcome of death, stroke, recurrent myocardial infarction, and stent thrombosis. This outcome occurred in 4.4% of the patients in the ticagrelor group compared with 20.0% if the high-dose clopidogrel group (p<0.001). There was no significant difference in bleeding between the treatment groups. The authors concluded that ticagrelor may be a safer and more efficacious treatment than high-dose clopidogrel in patients that are intermediate or PMs.

Similarly, Doll (2016) evaluated the impact of *CYP2C19* variants in acute coronary syndrome patients randomized to treatment with either prasugrel or clopidogrel.[45] This study was a substudy of the double-blind TRILOGY ACS trial, which included 9,326 patients from 52 countries who had unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI). Of these, 5,736 patients participated in the genetics cohort, and a subset of 2,236 of these additionally participated in a platelet function substudy. Patients were classified as either extensive metabolizers (EM) or reduced metabolizers (RM) based on their *CYP2C19* genotype. The primary study endpoint was a composite of cardiovascular death, recurrent myocardial infarction, or stroke, and there was not difference between metabolizer status groups or treatment groups for this outcome. In multivariate analysis, EM patients had a reduced risk of myocardial infarction compared with RM patients (HR: 0.80), but other individual outcomes were similar. Among patients treated with clopidogrel, RM patients had significantly higher platelet reactivity than EM patients. There was no such difference among those treated with prasugrel.

Pare (2010) retrospectively genotyped 5,059 patients from two large randomized trials (the Clopidogrel in Unstable Angina to Prevent Recurrent Events or “CURE” trial and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events or “Active” trial) that showed clopidogrel reducing the rate of cardiovascular events when compared with placebo in patients with acute coronary syndromes and atrial fibrillation.[46] Genotyping was

performed for **2*, **3*, and **17* of the *CYP2C19* allele. These investigators observed that the efficacy and safety of clopidogrel compared with placebo was not affected by *CYP2C19* loss of function alleles. Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed. Although the reason for these divergent findings remains unclear, it was noted that in the populations studied, use of stents was substantially less than in previous reports (19% of patients with acute coronary syndromes and only 14.5% in patients with atrial fibrillation).

Nonrandomized Studies

Nonrandomized studies have reported conflicting findings. Several nonrandomized studies found increased risks of thrombotic events in patients treated with clopidogrel who were *CYP2C19* variant carriers.[47-56] However, others have not found such an association.[57-61] In one large retrospective study of 5,059 patients from two large RCTs that compared clopidogrel with placebo in reducing the rate of cardiovascular events, the authors reported that that the efficacy and safety of clopidogrel as compared with placebo was not affected by *CYP2C19* loss-of-function alleles.[46] Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed. One study of patients with symptomatic intracranial atherosclerotic disease found lower odds of thrombotic events or death in individuals with a loss-of-function allele.[62]

Recent studies have suggested that changes in platelet reactivity in carriers may be dose-dependent,[63, 64] and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level.[65, 66] In homozygous carriers, it has been reported that even with higher clopidogrel doses, platelet reactivity cannot be reduced to the level achieved with clopidogrel treatment in noncarriers. In these patients, other drugs such as prasugrel or ticagrelor may be used as treatment alternatives. However, not all studies have found a difference in platelet response to clopidogrel based on *CYP2C16* genotype.[67]

Cavallari (2018) reported outcomes among 1,815 PCI patients at multiple centers who had antiplatelet therapy guided by *CYP2C19* testing.[68] For individuals with a loss-of-function allele, alternative antiplatelet therapies (prasugrel, ticagrelor) were recommended instead of clopidogrel. Patients were followed for major cardiovascular events (myocardial infarction, stroke, or death) for 12 months following PCI. Among the 572 (31.2%) of patients with a loss-of-function allele, the risk for cardiovascular events was significantly higher in those patients prescribed clopidogrel instead of alternative therapy (adjusted HR 2.26, 95% confidence interval 1.18 to 4.32, p=0.013). There was no difference in cardiovascular events between patients with a loss-of-function allele prescribed alternative therapy and patients without a loss-of-function allele.

Desai (2013) reported results of a study of antiplatelet therapy prescribing behavior for antiplatelet therapy for 499 patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent *CYP2C19* genotyping.[69] Among the 146 subjects (30%) with at least one *CYP2C19* reduced function allele, although providers were more likely to increase antiplatelet therapy intensification than for noncarriers, only 20% had their clopidogrel dose changed or were switched to prasugrel.

U.S. Food and Drug Administration (FDA) Safety Communication

In 2010, the FDA issued a public safety communication and added a boxed warning to the label of Plavix about the availability of genetic testing and alternative drug therapies in patients who are found to be PMs of the drug (patients with *CYP2C19* *2/2, *3/3, or *2/3 genotypes). The FDA endorsement is based on retrospective analyses which suggested that PM status had a higher rate of cardiovascular events or stent thrombosis compared to EM.[66, 70]

Section Summary

Individuals with genetic variants of cytochrome p450 have a decreased ability to metabolize clopidogrel, but the impact on clinically meaningful outcomes is uncertain. Despite this lack of evidence, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of clopidogrel (Plavix®).

SELECTION OR DOSING OF CODEINE

Codeine is metabolized by *CYP2D6* to morphine. Enhanced *CYP2D6* activity (i.e., in *CYP2D6* ultra-rapid metabolizers) predisposes to opioid intoxication.

U.S. Food and Drug Administration (FDA) Safety Communication

In 2013, in response to reports of deaths that have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being UMs of codeine due to a cytochrome *CYP2D6* polymorphism, the FDA added a black box warning to the labeling for codeine, listing its use for postoperative pain management in children following tonsillectomy and/or adenoidectomy as a contraindication. The FDA's guidelines state, "Routine *CYP2D6* genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers."[71]

In 2007, the U.S. Food and Drug Administration (FDA) issued a warning regarding codeine use by nursing mothers. Nursing infants "may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of codeine." However, the FDA is not recommending genotyping for any population prior to prescribing codeine because "there is only limited information about using this test for codeine metabolism."[47]

Section Summary

Enhanced *CYP2D6* activity is associated with risk of accelerated codeine metabolism with high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post-tonsillectomy. The clinical utility of testing for *CYP450* genotyping is uncertain, since management changes for codeine for nursing mothers based on genotyping results has not been evaluated.

DOSE AND SELECTION OF HIGHLY ACTIVE ANTIRETROVIRAL AGENTS

Efavirenz

Current guidelines recommend efavirenz as a preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for HIV-infected patients. Forty to 70% of patients report adverse central nervous system (CNS) effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse

effects.[72] Efavirenz is primarily metabolized by *CYP2B6*, and inactivating polymorphisms are associated with higher efavirenz exposure, although plasma levels appear not to correlate with side effects.

Systematic Reviews

No systematic reviews of genotype-directed efavirenz dosing for the treatment of HIV infection have been identified.

Randomized Controlled Trials

No randomized prospective trials of genotype-directed efavirenz dosing for the treatment of HIV infection have been reported.

Nonrandomized Studies

Limited reports suggest that *CYP2B6* PMs have markedly reduced side effects while maintaining viral immunosuppression at substantially lower doses.[73, 74] Simulations of such dose adjustments support this position.[75] Additional studies also report an association between polymorphism in *CYP2B6* gene and early discontinuation of efavirenz treatment. However, further research is needed in order to examine the clinical utility of the observed association.

Gross (2017) assessed the role of *CYP2B6* genotypes in an observational cohort study of efavirenz-based regimens in Botswana.[76] The primary endpoint of the study was a composite of death, loss to care, or HIV RNA above 25 copies/ml at six months. Among the 801 participants, the slow-metabolism alleles were associated with reduced efavirenz clearance, but not with the study outcomes or CNS toxicity.

Cabrera (2009) reported on an evaluation in 32 patients of the relationship between *CYP2B6* polymorphisms and efavirenz clearance.[77] Although they reported that *CYP2B6* polymorphisms accounted for only 27% of interindividual variability, they noted decreased clearance of 50% in the patient group with the *G/T* genotype and 75% with the *T/T* genotype. Based on this observation, they suggested a gradual reduction in dose of efavirenz be considered in patients with these phenotypes. They proposed use of a model to incorporate factors that affect drug levels. However, based on the complexity of factors involved in dosing, they concluded drug treatment should be carefully evaluated using therapeutic drug monitoring and assessment of clinical efficacy.

Gallien (2017) assessed the role of *CYP2B6* polymorphisms and efavirenz-induced CNS symptoms in a substudy of the ANRS ALIZE trial that included 191 patients.[78] The authors reported an association between the *CYP2B6 516T* allele and higher plasma efavirenz levels, and the occurrence of a first central nervous system event.

Two studies have been published that demonstrated an association between markers and early efavirenz discontinuation: one evaluating 373 patients for polymorphisms in *CYP2B6* and constitutive androstane receptor (CAR)[1], and one evaluating genotyping for 23 markers in 15 genes[70]. Both articles recommended further study to determine the clinical utility of these associations.

Lee (2014) evaluated the effect of *CYP2B6* G516T polymorphisms on the plasma efavirenz concentrations in HIV-infected patients, with or without concomitant rifampicin use.[79] The

study included 171 HIV-infected patients including 18 with tuberculosis, 113 (66.1%) with *CYP2B6 G516G*, 55 (32.2%) with *G/T*, and 3 (1.8%) with *T/T* genotype. Patients with *G/T* or *T/T* genotype had a significantly higher plasma efavirenz concentration than those with *G/G* genotype (2.50 vs. 3.47 mg/L for *G/T* genotype and 8.78 mg/L for *T/T* genotype; p<0.001).

Bienvenu (2014) evaluated the effect of single nucleotide polymorphisms (SNPs) in five drug metabolizing enzymes on plasma efavirenz levels and treatment response in patients treated with efavirenz alone (n=28) and when treated with cotreated with efavirenz and rifampicin-based TB treatment (n=62).[80] Serum efavirenz levels differed based on *CYP1A2* genotype (T/G vs. T/T) when patients were cotreated with efavirenz and rifampicin, but not when patients received efavirenz alone. High serum efavirenz levels were associated with *CYP2B6 516T/T* genotype, both with and without rifampicin treatment. *CYP2B6 516T/T* and *983T/T* genotypes predicted supratherapeutic efavirenz levels (positive predictive value, 100%), particularly in the absence of rifampicin.

A small cohort study by Bolton Moore (2017) compared genotype-directed efavirenz dosing to a pharmacokinetic model of efavirenz exposure based on FDA-approved doses in young children aged 3 to 36 months.[81] This analysis predicted that genotype-directed dosing would avoid subtherapeutic levels in nearly one-third of those with a *516GG/GT* genotype and excessive levels in more than half of those with *516T/T* genotypes.

A study by Mollan (2017) evaluated the relationship between *CYP2B6* and *CYP2A6* genotypes and risk of suicide in four efavirenz clinical trials and found that genotypes associated with higher plasma efavirenz levels were also associated with suicide risk.[82] The association was strongest among white participants.

Other Antiretroviral Therapies

While the preponderance of the evidence related to *CYP450* genetic testing for antiretroviral therapies has focused on efavirenz, there has been some investigation of pharmacogenomics testing for other antiretroviral therapies.

In a case-control analysis of 27 patients with nevirapine-induced Stevens-Johnson syndrome (SJS) induced by the non-nucleoside reverse transcriptase inhibitor nevirapine and 78 controls, Ciccacci (2013) found that polymorphisms in *CYP2B6*, but not in *CYP3A4* and *CYP3A5*, were associated with SJS risk.[83] Additionally, in a prospective cohort study including 66 women receiving nevirapine, Oluka (2015). reported that *CYP2B6* genotype was associated with serum nevirapine concentration and CD4 counts.[84] Finally, Lu (2014) reported that *CYP3A5* polymorphisms are associated with serum concentrations of maraviroc, a CCR5 receptor antagonist used for HIV treatment, in healthy control subjects.[85]

Section Summary

Genetic variants in *CYP2B6* are associated with increased side effects for patients treated with efavirenz, leading to some recommendations to reduce dosing based on genotype results. The impact of this strategy on health outcomes has yet to be evaluated; therefore, the clinical utility of genotyping for efavirenz dose is uncertain. Preliminary evidence suggests that *CYP450* polymorphisms may be associated with serum levels and adverse effects of other antiretroviral therapies, but the clinical utility of these findings is also uncertain.

ELIGLUSTAT (CERDELGA™) FOR GAUCHER DISEASE TYPE I.

Eliglustat (Cerdelga™), a small-molecule oral glucosylceramide analogue that inhibits the enzyme glucosylceramide synthase was developed by Genzyme for the treatment of Gaucher disease type 1 in adults.[86] Inhibition of this enzyme reduces the accumulation of the lipid glucosylceramide in the liver, spleen, bone marrow and other organs. Eliglustat is primarily metabolized by *CYP2D6* and, therefore, *CYP2D6* genotype/phenotype greatly impacts the dosing of eliglustat. A small number of adult patients who metabolize eliglustat more quickly or at an undetermined rate, based on *CYP2D6* genotype, will not be eligible for eliglustat treatment.

There are no published studies that demonstrate how genotyping results for *CYP2D6* affect selection and dosing for eliglustat (Cerdelga™).

U.S Food and Drug Administration (FDA) Safety Communication

In 2014, the U.S. Food and Drug Administration (FDA) labeling for eliglustat (Cerdelga™) included information on personalizing initial selection and dose according to genotyping results for *CYP2D6*. The FDA labeling requires that patients be selected on the basis of *CYP2D6* metabolizer status as determined by genotype, with recommendations based on genotype about dosage and concomitant use of *CYP2D6* and *CYP3A* inhibitors.[87]

Section Summary

Individuals with genetic variants of CYP450 have an increased ability to metabolize eliglustat, a small-molecule oral glucosylceramide analogue that inhibits the enzyme glucosylceramide synthase was for the treatment of Gaucher disease type 1. Although the current evidence is limited to industry-sponsored nonrandomized studies on the efficacy of eliglustat, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of eliglustat. Therefore, *CYP450* genotyping may be considered medically necessary to guide selection and dose management of eliglustat**.**

H. PYLORI INFECTION

Currently, multiple regimens are available for treating *H. pylori* infection. These include proton pump inhibitors (PPI) to suppress acid production, in combination with antibiotic treatment consisting of one or more agents such as amoxicillin, clarithromycin, or metronidazole. Genetic factors may influence the success of *H. pylori* treatment through effects on PPI metabolism. Individuals with polymorphisms in the *CYP2C19* gene, a member of the *CYP450* family, metabolize PPIs more slowly than normal. Observational research suggests that patients who are extensive metabolizers of PPIs have lower eradication rates following standard treatment for *H. pylori*, compared with PMs.

If *CYP2C19* status is known prior to treatment, adjustments could potentially be made in the selection of PPI and/or the dosing schedule to achieve optimal acid suppression in all patients. Improved eradication rates for *H. pylori* could lead to improved health outcomes by reducing the need for re-treatment following treatment failure, reducing recurrences of *H. pylori*-associated disorders, and reducing the morbidity and mortality associated with disease recurrence.

To determine whether treatment decisions based on genetic testing improve health outcomes, direct comparisons with standard treatment selection strategies are needed. Prospective RCTs comparing the two strategies are necessary for reliable comparisons. The optimal trial would isolate the impact of treatment changes made as a result of genetic status, be performed in the

U.S. in a population with rates of *CYP2C19* polymorphisms approximating that of the general U.S. population, use an approach to diagnosing *H. pylori* that reflects usual care in the U.S., and would use a standard treatment regimen recommended for U.S. patients.[88]

Systematic Reviews

Tang (2013) published results from a meta-analysis of RCTs to re-evaluate the impact of *CYP2C19* variants on PPI-based triple therapy for *H. pylori* infection.[89] Authors identified 16 RCT datasets derived from 3,680 patients. There were significant differences in that rate between homozygous (HomEMs) and heterozygous (HetEMs) extensive metabolizers (OR 0.724, 95% CI 0.594 to 0.881), between HomEMs and PMs (OR 0.507, 95% CI 0.379 to 0.679), or between HetEMs and PMs (OR 0.688, 95% CI 0.515 to 0.920), regardless of the PPI being taken. Furthermore, sub-analysis of individual PPIs was carried out to explore the difference across all the PPIs used. A significantly low rate was seen in HomEMs vs. HetEMs taking either omeprazole (OR 0.329, 95% CI 0.195 to 0.553) or lansoprazole (OR 0.692, 95% CI 0.485 to 0.988), and also in HomEMs vs. PMs for omeprazole (OR 0.232, 95% CI 0.105 to 0.515) or lansoprazole (OR 0.441, 95% CI 0.252 to 0.771). However, there was no significant difference between HetEMs and PMs taking either one. No significant differences were observed for rabeprazole or esomeprazole across the *CYP2C19* genotypes of interest.

Authors concluded that carriage of *CYP2C19* loss-of-function variants is associated with increased *H. pylori* eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen. In the meta-analysis, individual PPIs were pooled without considering the dose, duration of therapy and the type of antibiotic agents, resulting in some confounders for *CYP2C19* phenotypes and the eradication rates of PPI-based therapy. Therefore, results may not be generalizable to clinical practice.

Similar results were seen in a meta-analysis by Morino (2021), which included 25 RCTs of PPI-amoxicillin-clarithromycin regimen among different *CYP2C19* genotypes.[90] In an intention-to-treat analysis, eradication rates were highest among poor metabolizers (86.8% [644/742], 95% CI 83.9 to 88.9%), followed by intermediate (81.2% [1,498/1,844], 95% CI 79.3 to 83.0%) and extensive metabolizers (77.7% [1,137/1,464], 95% CI 75.3 to 79.6%), but these were not significantly different (p=0.696). This analysis also pooled various drug regimens, limiting generalizability.

Randomized Controlled Trials

Choi (2022) published the results of a double-blind, controlled, multicenter study to evaluate whether tegoprazan (50 mg)-based triple therapy (TPZ) was noninferior to lansoprazole (30 mg)- based triple therapy (LPZ) for treating H. pylori. The primary endpoint was the H. pylori eradication rate. Subgroup analyses were performed according to the cytochrome P450 (CYP) 2C19 genotype, the minimum inhibitory concentration (MIC) of amoxicillin and clarithromycin, and underlying gastric diseases. Subgroup analyses according to MICs or CYP2C19 did not show differences in eradication rate.[91]

A randomized, controlled trial comparing a pharmacogenomics-based treatment regimen with a standard regimen was evaluated.[92] This study randomized 300 Japanese patients to a pharmacogenomics-based treatment regimen versus a standard treatment regimen. The TEC Assessment offered the following observations and conclusions concerning this study:

> “Eradication rates after first-line treatment were higher in this study for the pharmacogenomics group compared with the standard treatment group. However, because of numerous variations in treatment protocol within the pharmacogenomics group, it was not possible to determine whether the improvement resulted from the tailored PPI dosages according to *CYP2C19* genetic status, or due to other variations in the treatment protocol unrelated to *CYP2C19* status.
>
> There were numerous variations in the treatment regimen within the experimental group that made it difficult to determine which specific aspects of the treatment regimen may have led to benefit. In particular, it appeared that clarithromycin resistance was an important factor in treatment success, and that there may have been an interaction between clarithromycin resistance and *CYP2C19* status. From the data reported in the study, it was not possible to separate the potential impact of clarithromycin resistance on eradication rates from the impact of pharmacogenetically tailored PPI dosage schedules.
>
> In addition to the limitations on internal validity, the clinical relevance of the study was also limited for several reasons. The treatment approach used was relatively intensive, including genetic testing for *CYP2C19*, esophagogastroduodenoscopy with biopsy for all patients, and testing of *H. pylori* isolates for clarithromycin resistance. This treatment approach was much more intensive than that generally used in the United States, where the diagnosis of *H. pylori* is usually made by noninvasive methods, and initial empiric treatment is instituted without isolating *H. pylori* or testing for resistance. Furthermore, the patient population was from Japan, limiting the generalizability of the results, especially given the ethnic differences in *CYP2C19* genetic status.”

A similar trial by Zhou (2016) compared tailored therapy, based on *CYP2C19* genotype and clarithromycin sensitivity, to triple therapy plus bismuth and concomitant therapy.[93] In this study, 1,050 *H. pylori* patients at three tertiary hospitals in China were randomized to ten days of one of the three treatment regimens. While the authors reported a significantly higher eradication rate in the tailored treatment group in the setting of high antibiotic resistance rates, this study has many of the same limitations noted for the Japanese study described above.

A much smaller trial by Arévalo Galvis (2019) found no significant difference between triple therapy with standard omeprazole compared with personalized therapy based on *CYP2C19* genotype.[94] This trial included 133 patients in Columbia.

Additional RCTs evaluating *H. pylori* eradication rates for different treatment regimens reported that the *CYP2C19* genotype appears to play a role in eradication rates,[95-97] though not all trials have found this to be the case.[98] However, these trials were not designed to compare a pharmacogenomics-based treatment regimen with a standard regimen.

Nonrandomized Studies

Several nonrandomized studies have evaluated the impact of *CYP2C19* variants on PPI metabolism, *H. pylori* eradication, and ulcer healing.[99-102] These studies have had mixed results. Additional small, nonrandomized and retrospective studies of *CYP2C19* gene polymorphisms and *H. pylori* treatment have been published; however, the clinical utility of genotyping was not addressed.[95, 103-114]

Section Summary

The clinical utility of testing for *CYP450* genotyping is uncertain, since management changes to select and dose treatment for H. *pylori* eradication based on genotyping results has not been evaluated.

IMMUNOSUPPRESSANT DOSING FOR ORGAN TRANSPLANTATION

Immunosuppressive drugs administered to organ transplant patients have a narrow therapeutic index with the consequences of rejection or toxicity on either side. In addition, there is variability in patient response, requiring close clinical follow-up and routine therapeutic drug monitoring to maintain safety and efficacy. *CYP3A5* genetic polymorphisms have been evaluated in relation to metabolism of immunosuppressant drugs.

Tacrolimus blood levels are related to *CYP3A5* genetic variants, with an approximately 2.3-fold difference in daily dose required to maintain target concentration between *CYP3A5*3* and *CYP3A5*1* homozygous variants.[115] *CYP3A5*1* carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to noncarriers. Although the overall rate of acute rejection episodes was not higher in *CYP3A5*1* carriers, their rejection episodes did occur earlier.[116]

Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children.[117, 118] These models predict clearance based on *CYP3A5*3/*3* as well as clinical factors. Results show that oral clearance of tacrolimus is impacted by body weight, hematocrit and time since transplant, in addition to *CYP3A5*3/*3* polymorphisms.

Pharmacogenetic applications for other immunosuppressants (sirolimus and cyclosporine) have also been investigated; however, evidence for clinical utility of genotyping for dosing of these drugs is even less clear than for tacrolimus.

Systematic Reviews

Yang (2021) published a systematic review and meta-analysis of RCTs comparing genotype-guided and conventional tacrolimus dosing in kidney transplant patients.[119] Five RCTs with a total of 684 patients were included, and all trials were judged to be of high quality using GRADE methodology. The proportion of patients with a tacrolimus exposure within the therapeutic range at steady state, which was the primary outcome, was higher among the genotype-guided group (relative risk [RR] 1.40, 95% CI 1.14 to 1.72, p=0.001). However, there were no significant differences between groups in the health outcomes assessed, including incidences of acute graft rejection, delayed graft function, adverse events, or graft survival censored for death, suggesting that there “was no utility in pharmacogenetics for tacrolimus based on the [*CYP3A5*].”

A meta-analysis by Hendijani (2018) focused on the effect of *CYP3A5*1* expression on tacrolimus dose in pediatric transplant patients.[120] Data from 11 studies (n=596) were included. The results of the analysis indicated that *CYP3A5*1* expressers required a tacrolimus dose that was 0.06 mg/kg/day higher to achieve the same blood level as non-expressers.

Rojas (2015) published results from a systematic review and meta-analysis evaluating the effect of the *CYP3A5* polymorphism on kidney transplant recipients treated with tacrolimus. The authors found that *CYP3A5*1* carriers had significantly lower plasma tacrolimus concentration per daily dose per body weight than carriers of the *CYP3A5*3/*3* genotype.[121] It is important to note that this review only included observational studies thereby precluding firm

conclusions. A similar meta-analysis by Khan (2020) of kidney transplant recipients reported that *CYP3A5* genotype was significantly associated with the trough concentration-dose ratio, but not with allograft rejection in European patients.[122]

In a meta-analysis, Rojas (2013) investigated the effect of the *CYP3A5 6986A>G* polymorphism in liver donors and transplant recipients on tacrolimus pharmacokinetics.[123] The meta-analysis demonstrated the trough blood concentration normalized for the daily dose (C) per kilogram body weight (D) (C/D, ng/ml/mg/kg/day) ratio to be significantly higher in recipients with non-expressed donor variants at all time points. In recipients, the variant did not influence the C/D ratio. The authors concluded the presence of the *CYP3A5 6986A>G* polymorphism in the donor affects tacrolimus pharmacokinetics in the recipient for the first month after transplantation. Authors note the evidence provided shows no effect of the recipient genotype; however, the quality of the evidence was low, thereby precluding the drawing of firm conclusions.

Buendia (2014) used a random effects model to conduct a meta-analysis comparing tacrolimus daily dose, trough concentrations, and dose-adjusted trough concentrations across liver transplant donor and recipient genotype pairs.[124] Eight studies (n=694) met inclusion criteria. Significantly lower tacrolimus trough concentrations were found when either the donor or recipient expressed a **1* allele up to 12 months post-transplant, requiring higher daily dose to maintain target drug concentrations.

Randomized Controlled Trials

Based on observations that patients with genetic variants of *CYP3A5* require higher tacrolimus doses to achieve a therapeutic trough concentration (C0), Thervet (2010) conducted an RCT to compare the proportion of tacrolimus-treated renal transplant patients within a targeted C0 range for two tacrolimus dosing strategies, *CYP3A5* genotype-informed dosing or standard dosing.[125] The study included 280 patients, 140 who received standard dosing and 140 who received *CYP3A5* genotype-specific dosing. The genotype-directed therapy group was more likely to achieve the study's primary outcome, proportion of patients with tacrolimus C0 in the target range after six oral doses, than the control group (43.2%, 95% CI 36% to 51.2%; vs. 29.1%, 95% CI 22.8% to 35.5%, p=0.030). The genotype-directed therapy group had fewer dose adaptations (281 vs. 420, p=0.004). Graft function and survival were similar between groups.

An RCT by Min (2018) evaluating genotype-guided tacrolimus dosing after pediatric solid organ transplantation showed similar results to the Thervet (2010) trial regarding reduced time to targeted therapeutic tacrolimus concentrations with the guided approach, but was similarly not powered to assess differences in health outcomes.[126]

Nonrandomized Studies

Passey (2011) used tacrolimus blood trough and dose information from 681 kidney transplant recipients to develop a predictive tool for tacrolimus apparent clearance, from which individual tacrolimus dosing could be extrapolated.[127] The study's final model included *CYP3A5* genotype, along with other clinical factors, but was not validated in an independent population. A similar, but smaller study (n=59) was published by Woillard (2017), which used *CYP3A4* and *CYP3A5* alleles for model development.[128]

Boughton (2013) evaluated the model developed by Passey (2011)[127] in a single-center cohort of renal transplant recipients.[129] The study found a weak correlation (*R*=0.431) between clearance based on dose-normalized tacrolimus trough concentrations and the algorithm-predicted clearance.

Tapirdamaz (2014) studied the influence of SNPs in the genes of donor and recipient calcineurin inhibitor (CNI) enzyme *CYP3A5* and the CNI-transporting ABCB1 on the development of chronic kidney disease (CKD) following liver transplantation (LT).[130] Tacrolimus predose concentrations and *CYP3A5 6986A>G* and *ABCB1 3435C>T* SNPs were determined in 125 LT recipients and their donors. Median follow-up was 5.7 years. CKD developed in 47 patients (36%). No correlation was found between CKD and tacrolimus levels or the investigated SNPs.

In 410 living-donor LT patients, Uesugi (2014) found no significant effect of *CYP3A5* genotype on the rate of acute cellular rejection between postoperative days 14 and 23.[131] However, higher rates of acute cellular rejection were found in patients who received a graft liver with *CYP3A5*1* allele than those with graft liver with the *CYP3A5*3/*3* genotype.

Kato (2016) reported long-term outcomes for 67 donor/recipient couples and their relation to tacrolimus pharmacokinetics and *CYP3A5* genotype.[132] Donor/recipient couples from 2002 to 2009 with tacrolimus administration were included in the study. Recipients who had a **1* allele and/or who had a donor with a **1* allele required significantly higher doses of the drug than those couples without the allele. Additionally, five-year survival rates for recipients with two **1* alleles were significantly worse than for those with a **1*3* or a **3*3* genotype (28.6% vs. 78.8% and 84.3%, respectively).

Section Summary

CYP3A5 genetic variants may be used to predict tacrolimus clearance. One RCT demonstrated that the use of a *CYP3A5* genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges. No differences in morbidity or mortality or graft survival were reported, which the authors attribute to a patient population at low risk of acute rejection or other clinical events. Additional studies of the clinical utility of *CYP3A5* genetic testing-based algorithms in tacrolimus management are needed. There is limited evidence on the impact of genotype on dosing on immunosuppressant medications.

TAMOXIFEN: MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER[133]

The CYP450 metabolic enzyme CYP2D6 has a major role in tamoxifen (TAM) metabolism. Variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on TAM treatment efficacy.

Potential indications for *CYP2D6* pharmacogenomic testing include patients who are to be treated with TAM (alone or prior to treatment with an aromatase inhibitor) for:

- Prevention of breast cancer in high risk women or women with ductal carcinoma in situ (DCIS)
- Adjuvant treatment to prevent breast cancer recurrence

- Treatment of metastatic disease

Post-menopausal patients determined to be *CYP2D6* PMs could avoid TAM therapy and be treated with aromatase inhibitors alone. Pre-menopausal patients might consider ovarian ablation.

Systematic Reviews

In 2010, the Agency for Healthcare Research and Quality (AHRQ) carried out a systematic review of the published evidence of the *CYP2D6* variants and response to tamoxifen therapy in breast cancer.[134] There were 16 publications of *CYP2D6* testing met the eligibility criteria and were included in the review (15 studies in the adjuvant setting and one study in the metastatic setting). However, the meta-analysis was not performed due to extensive heterogeneity in the definition of slow, intermediate, and extreme metabolizers across eligible studies. Instead, the results from individual studies on the strength of the association between *CYP2D6* testing results and clinical outcomes were presented. The assessment concluded the following:

- There were no consistent associations between *CYP2D6* polymorphism status and outcomes in tamoxifen-treated women with breast cancer across 16 studies included in the review.
- The reviewed studies were generally small, followed poor analytic practices, and differed both in the direction and in the formal statistical significance of their results.
- It is questionable whether pharmacogenetic testing of germline variations in *CYP2D6* can predict differential response to adjuvant tamoxifen in women with non-metastatic breast cancer.
- Evidence is severely limited for tamoxifen-treated women with metastatic disease.

A 2008 BlueCross BlueShield Association Technology Evaluation Center Assessment, found that evidence from clinical validity studies of *CYP2D6* for use in tamoxifen management was uncertain.[135] Results from two higher quality trials of adjuvant TAM in relatively homogeneous patient populations suggest that women treated with TAM who are functional PMs or IMs, whether by genotype or by co-medication with *CYP2D6* inhibitors, have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to extensive metabolizers. The significance levels are marginal but might have been stronger and more convincing if PMs alone could have been compared to extensive metabolizers, but numbers of PMs were insufficient. Few variant alleles have been typed in these studies; more extensive genotyping and better categorization might also strengthen results.

The International Tamoxifen Pharmacogenomics Consortium was established to address the controversy regarding *CYP2D6* status and clinical outcomes in tamoxifen therapy. Authors from this consortium performed a meta-analysis on data from 4,973 tamoxifen-treated patients (12 globally distributed sites).[136] Using strict eligibility requirements (postmenopausal women with estrogen receptor-positive breast cancer, receiving 20 mg/day tamoxifen for five years, criterion 1); *CYP2D6* poor metabolizer status was associated with poorer invasive disease-free survival (IDFS HR 1.25, 95% CI 1.06 to 1.47, p=0.009). However, *CYP2D6* status was not statistically significant when tamoxifen duration, menopausal status, and annual follow-up were not specified (criterion 2, n=2,443, p=0.25) or when no exclusions were applied (criterion 3, n=4,935, p=0.38). Authors concluded, although *CYP2D6* is a strong predictor of IDFS using strict inclusion criteria, because the results are not robust to inclusion criteria (these were not

defined a priori), prospective studies are necessary to fully establish the value of *CYP2D6* genotyping in tamoxifen therapy.

Drögemöller (2019) conducted a systematic review of the association between *CYP2D6* genetic variation and survival outcomes after tamoxifen treatment.[137] Included studies showed conflicting conclusions. In multivariate analyses, there was no significant relationship between survival outcomes and the confounders of sample size (p=0.83), ethnicity (p=0.33), or source of DNA (p=0.14). Comprehensive genotyping panels were more likely to report a significant association with *CYP2D6*-survival outcome: 11 of 13 studies that used comprehensive genotyping found a significant association between *CYP2D6* and survival outcomes. Limitations of the studies identified by the review authors included differences in survival outcome definitions, differences in metabolizer group classifications, low consent rates, and not controlling for CYP2D6-inhibitor use. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data (e.g., concomitant medications), and detailed clinical outcomes data.

Lu (2017) published a meta-analysis of studies evaluating the role of *CYP2D6 *10* genotype on clinical outcomes for Asian women treated with tamoxifen for breast cancer.[138] The *CYP2D6 *10 T/T* genotype has been linked to low enzyme activity. Fifteen studies with a total of 1,794 patients were included. Pooled analysis of the effect of the *CYP2D6 *10* genotype identified significant associations with disease-free survival in several comparison models (*TT* vs. *CC*: HR 1.79, 95% CI 1.14 to 2.80, p=0.011; *CT* vs. *CC*: HR 2.02, 95% CI 1.04 to 3.19, p=0.037; *TT* vs. *CT*: HR 2.03, 95% CI 1.41 to 2.93, p<0.001; *TT* vs. *CT/CC*: HR 2.19, 95% CI 1.07 to 4.50, p=0.033).

Randomized Controlled Trials

One trial of genotype-directed dosing that assessed outcomes of breast cancer recurrence was identified. The RCT, published by Tamura (2020) was a phase II, proof-of-concept study performed at multiple centers in Japan.[139] A total of 184 patients were included in this study, of which 136 had at least one *CYP2D6* variant-type allele. Only one patient classified as a poor metabolizer with two null alleles was included in this trial. The results of this trial did not find a significant difference in outcomes between increased tamoxifen dosing and standard dosing in patients with *CYP2D6* genotypic variants Nonrandomized Studies.

Nonrandomized studies have reported conflicting findings regarding the role of *CYP2D6* variant status in the selection and dosing of tamoxifen, with some in support[140-153] and others not.[154-163]

Among the most influential studies of the association between *CYP2D6* genotype and tamoxifen effectiveness are three nonconcurrent, prospective studies nested within large RCTs that compared tamoxifen with anastrozole, letrozole, or combination tamoxifen and anastrozole in postmenopausal women with hormone receptor-positive early-stage breast cancer. In the Arimidex, Tamoxifen, Alone or in Combination trial,[155] and Breast International Group 1-98 trial,[154] a subset of patients who received tamoxifen and were genotyped for *CYP2D6* variants (n=588 and n=1,243, respectively) did not show any statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and breast cancer recurrence. In the Austrian Breast and Colorectal Cancer Study Group trial, a case-control study was done using a subset of patients where cases were defined as those with disease recurrence, contralateral breast cancer, second non-breast cancer, or died and

controls were identified from the same treatment arm of similar age, surgery/radiation, and stage.[164] Results showed that patients with two poor-metabolizer alleles had a higher likelihood of recurrence than women with two extensive-metabolizer alleles. Concerns about the substantial departure from Hardy-Weinberg equilibrium for the *CYP2D6* allele, *4 and analyses not meeting the Simon-Paik-Hayes criteria for nonconcurrent prospective studies have been raised to explain the lack of effect in the Arimidex, Tamoxifen, Alone or in Combination trial and Breast International Group 1-98 trials.[165]

Section Summary

The evidence for *CYP2D6* genotype-guided tamoxifen treatment includes one RCT, several meta-analyses and systematic reviews, multiple nonrandomized studies. Published data on the association between *CYP2D6* genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data, and detailed clinical outcomes data. Three influential nonconcurrent prospective studies nested within large RCTs that included postmenopausal women with hormone receptor-positive early-stage breast cancer also reported contradictory results, with two larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression free survival between standard dose and increased dose; however, this trial was limited by its proof-of-concept design. No trials of genotype-directed drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether *CYP2D6* genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or OS, or reduce adverse events.

TETRABENAZINE FOR HUNTINGTON DISEASE

Tetrabenazine (Xenazine) is a monoamine depleter and reduces the amount of certain chemicals in the brain (e.g., dopamine, norepinephrine, and serotonin) to reduce chorea, or involuntary muscle movements, in Huntington disease. Its primary metabolites are metabolized mainly by *CYP2D6*, and people with *CYP2D6* poor metabolizer genotypes should be treated with lower doses.

Systematic Reviews

No systematic reviews of *CYP2D6* genotyping for tetrabenazine management were identified.

Randomized Controlled Trials

There were no RCTs reported for this indication.

Nonrandomized studies

Mehanna (2013) published results from a study that performed sequential *CYP2D6* genotyping on 127 patients treated with tetrabenazine.[166] The majority of patients (n=100) were categorized as extensive metabolizers, 14 as IMs, 11 as PMs, and two as ultrarapid metabolizers (UMs). UMs needed a longer titration (8 vs. 3.3, 4.4, and 3 weeks, respectively, p<.01) to achieve optimal benefit and required a higher average daily dose than the other patients, but this difference did not reach statistical significance. The treatment response was

less robust in the intermediate metabolizer group when compared with the extensive metabolizer patients (p=.013), but there were no statistically significant differences between the various groups with regard to adverse effects. Therefore, the current recommendation to systematically genotype all patients prescribed more than 50 mg/day of tetrabenazine should be reconsidered.

U.S Food and Drug Administration (FDA) Safety Communication

In 2015, the FDA published a warning labeling for tetrabenazine includes recommendations for genotyping for *CYP2D6* for patients who are being considered for doses above 50 mg per day. The labeling states: "Patients should be genotyped for CY2D6 prior to treatment with daily doses of tetrabenazine over 50 mg."[167]

Section Summary

There is limited published evidence regarding the changes in outcomes associated with genotype-directed therapy for tetrabenazine in Huntington disease; however, given the FDA labeling and high variation in drug exposure based on metabolizer status, *CYP2D6* to determine metabolizer status before the use of tetrabenazine when a dosage greater than 50 mg per day may be considered medically necessary.

SIPONIMOD FOR MULTIPLE SCLEROSIS

The FDA has approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a *CYP2C9*1/*3* or **2/*3* genotype is 1 mg. Siponimod is contraindicated in patients with a *CYP2C9*3/*3* genotype.[168]

WARFARIN DOSING AND MANAGEMENT[169]

Warfarin (Coumadin®) is administered for preventing and treating thromboembolic events in high-risk individuals. Dosing of warfarin is a challenging process, due to narrow therapeutic windows, variable response to dosing, and serious bleeding events.

Stable or maintenance warfarin dose varies significantly among individuals. Factors influencing stable dose include body mass index (BMI), age, interacting drugs, and indication for therapy. In addition, genetic variants of *CYP450 2C9* (*CYP2C9*) and vitamin K epoxide reductase subunit C1 (*VKORC1*) genes together account for a substantial proportion of variability:

- Genetic variants of *CYP2C9* result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and a higher risk of serious bleeding.
- *VKORC1* genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses.

The purpose of *CYP2C9* and *VKORC1* genetic testing is to predict an individual's likely maintenance warfarin dose by incorporating demographic, clinical, and genotype data. Warfarin is then initiated at that predicted dose to limit over-anticoagulation and increased risk of serious bleeding events.

Regulatory Status

In 2010, the FDA updated labeling for Coumadin® to include information on personalizing initial dose according to genotyping results for *CYP2C9* and *VKORC1*. However, the information on genetic variation is not included in the black box warning and the label indicates that genetic testing is not required.

Systematic Reviews

Wang (2022) completed a SR to analyze the impact of CYP2C19 polymorphisms on warfarin maintenance dose. Nine studies were included in the analysis (1393 patients). Three CYP2C19 SNPs were identified: rs4244285, rs4986893 and rs3814637. Warfarin maintenance dose was significantly reduced by 10% in individuals with the rs4986893 A allele compared with the GG carriers and was 34%, 16% and 18% lower in patients with rs3814637 TT and CT genotypes and T allele, respectively, than that in CC carriers. No significant dose difference was observed among the rs4244285 genotypes. The authors conclude that CYP2C19 rs4986893 and rs3814637 are associated with significantly reduced warfarin dose requirements. These results were largely driven by the Zhu (2020) RCT.[170]

The Washington Health Care Authority completed a technology assessment of pharmacogenetic testing for anticoagulants in 2018, which included 13 RCTs.[171] In the meta-analysis of mortality, thromboembolic events, and major bleeding, no differences between groups were seen in mortality or thromboembolism but there was a reduction in major bleeding seen in the pharmacogenetic testing group. There were no statistically significant differences in the percentage of time in therapeutic range or over-anticoagulation. The authors noted that the evidence for the thromboembolic events was rated as moderate quality, while the evidence for the other outcomes was low quality.

A meta-analysis by Yang (2019) included 15 RCTs (total n=4,852) evaluating genotype-guided warfarin dosing.[172] The primary outcome of the analysis was the percentage time in therapeutic range (PTTR). Within a one-month follow-up period, there was no significant difference in PTTR between genotype-guided and control (fixed initial dosage) groups, based on data from eight trials. Three trials reported on PTTR at three months, which was significantly higher for the genotype-guided patients compared to controls (weighted mean difference 5.62%, 95% CI 2.33% to 8.90%, p=0.001). Genotype-guided patients also had a shorter time to first therapeutic international normalized ratio (INR), shorter time to stable therapeutic dose, and decreased risk of warfarin-related major bleeding events. No differences were seen for thromboembolism risk, bleeding events, and all-cause mortality. The authors completed a risk of bias assessment of included studies. All trials claimed to be randomized, however, the random sequence generation was only explicitly described in nine studies. Only seven studies discussed allocation concealment, and blinding was not implemented in most of the included RCTs.

A network meta-analysis by Sridharan and Sivaramakrishnan (2020) compared three different genotyping strategies for warfarin dosing: *CYP2C9* alone, *CYP2C9* with *VKORC1*, and *CYP2C9* with both *VKORC1* and *CYP4F2*.[173] The analysis included data from 28 RCTs, and the primary outcomes were the time to first therapeutic INR, time to stable INR or warfarin dose, PTTR, and the proportion of patients with supra-therapeutic INR. The results of the meta-analysis indicated that the *CYP2C9*-alone strategy and the *CYP2C9* with *VKORC1* strategy were associated with a shorter time to first therapeutic INR and stable INR/warfarin dose, while only the *CYP2C9* with *VKORC1* strategy was associated with a greater PTTR.

Tse (2018) published a meta-analysis of 18 trials of genotype-guided versus standard warfarin dosing.[174] The analysis included 2,626 patients in the genotype-guided group and 2,604 patients in the control group, and the mean follow-up duration was 64 days. Genotype-guided dosing was associated with a shorter time to therapeutic international normalized ratio (INR) (mean difference 2.6 days, p<0.0001, I^2 0%) and stable INR (mean difference 5.9 days, p<0.01, I^2 94%), but no difference was seen in thromboembolism or mortality. Similar results were seen in a meta-analysis by Kheiri (2018) that included 20 RCTs.[175]

Five systematic reviews with meta-analyses of RCTs were published in 2014 and 2015.[176-181] The included RCTs compared genotype-guided warfarin dosing with other dose selection strategies. The RCTs overlapped across analyses, though not all RCTs were included in all analyses. Meta-analyses used random effects models or fixed effects models when statistical heterogeneity (I^2) was 0%. Most studies were included in all systematic reviews.

Two systematic reviews[176, 177] included the same nine RCTs[71, 182-189] comparing genotype-guided versus clinically-guided warfarin dosing (n=2,812); the RCTs were rated as high quality. Range of follow-up duration was 4 to 24 weeks (median 12 weeks). Publication bias was not detected. With one exception, pooled results from both systematic reviews were consistent. There was no statistical difference between dosing strategies in the percentage of time that the INR was in therapeutic range (I^2=89%), the proportion of INRs that exceeded 4 (I^2=0%), or thromboembolic events (I^2=0%). However, Stergiopoulos (2014) found no difference in major bleeding events (pooled RR 0.60, 95% CI 0.29 to 1.22, I^2=0%), while Franchini (2014) found reduced major bleeding events with genotype-guided warfarin dosing (pooled RR=0.48, 95% CI 0.23 to 0.97, I^2=0%). This inconsistency may be attributed to the exclusion of the EU-PACT trial[183] (n=455) from the analysis of major bleeding in Franchini (2014) systematic review; EU-PACT reported no major bleeding events in either warfarin dosing group.

Goulding (2014) reported improved clinical outcomes with genotype-guided versus other (i.e., fixed or clinically-guided) warfarin dosing.[178] Literature was reviewed through December 2013; nine RCTs were included, seven of which overlapped with the systematic reviews previously described, and six of which were rated high or very high quality. Range of follow-up duration was 2 to 12 weeks. Pooled mean difference in the percentage of time within the therapeutic range (TTR) was 6.67 percentage points (95% CI 1.34 to 12.00, I^2=80%). However, this meta-analysis included one trial[190] that showed benefit of genotype-guided dosing compared with fixed initial warfarin dosing (2.5 mg/day), and excluded two trials[182, 186] that showed no benefit of genotype-guided dosing compared with clinically-guided dosing. Meta-analysis also showed decreased risk of bleeding or thromboembolic events with genotype-guided dosing (pooled risk ratio 0.57, 95% CI 0.33 to 0.99, I^2=60%).

In an analysis of eight RCTs Xu (2014) reported a significantly increased TTR for genotype-guided dosing compared to fixed initial dose, but no significant difference between genotype-guided and clinically-guided dosing. The authors also reported no significant between-group differences in adverse events. The authors noted high between-group participant heterogeneity that hindered pooled estimates.

Liao (2015) reported increased TTR with genotype-guided dosing compared with fixed initial warfarin dosing (three RCTs, I^2=48%) but not compared with clinically-guided dosing (two RCTs, I^2=0%).[179] These authors also found no overall difference between pooled groups in adverse events (major bleeding [defined as a decrease in hemoglobin ≥2 g/dL], clinically relevant non-major bleeding, thromboembolism, myocardial infarction, death from any cause,

or other condition requiring emergency medical management; four RCTs, I^2=0%) or mortality (three RCTs, I^2=10%).

A systematic review by Zhang (2017) evaluated *CYP2C9* polymorphisms and warfarin maintenance dosage in pediatric patients.[191] The review included eight studies with a total of 507 patients. Of these, five studies investigated the role of the *CYP2C9 *1/*2* genotype, and meta-analysis indicated that this genotype was associated with warfarin maintenance dose that was 15% lower than that for patients with *CYP2C9 *1/*1.* In five studies that evaluated the *CYP2C9 *1/*3,* this genotype was associated with 41% lower maintenance dose compared with **1/*1*. However, this study did not evaluate the use of genotyping in pediatric warfarin dose selection.

Prior systematic reviews and meta-analyses focused on analysis of associations between *CYP2C9* and *VKORC1* gene variants and warfarin dosing.

The 2009 Agency for Healthcare Research and Quality (AHRQ) Technology assessment of selected pharmacogenetic tests for non-cancer and cancer conditions included a systematic review of the published evidence of *CYP2C9* and *VKORC1* gene polymorphisms and response to warfarin therapy (29 studies of *CYP2C9* and 19 studies of *VKORC1* polymorphisms).[192] The review concluded the following:

- Carriers of the *CYP2C9* gene variant alleles **2* or **3* require lower mean maintenance warfarin doses than do noncarriers.
- Few studies investigated the relationship between genetic variations in *CYP2C9* or *VKORC1* and warfarin dose requirements in the induction phase. *CYP2C9* variants were associated with an increased rate of bleeding complications during the induction phase of warfarin therapy, but the studies did not report whether affected patients had normal or supratherapeutic INR ranges.
- The clinical utility of genetic testing for *CYP2C9* in everyday clinical practice is not straightforward.
- It is unclear whether dose-prediction algorithms using genetic information improve clinical outcomes over those of standard practice. Only three RCT addressed this question, but all had flaws in design and inclusion criteria, and had inadequate power to reach statistical conclusions.
- Carriers of the three common *VKORC1* variants (alleles *T*, *G*, and *C*) required lower mean maintenance doses of warfarin than did noncarriers. Data were not adequate to address any other questions.

New genetic associations such as *CYP4F2* are under investigation and evaluating interactions among *CYP2C9, VKORC1*, and this new variant along with gene-environmental interactions may result in better risk predictive instruments for clinical use.

A systematic review commissioned by the American College of Medical Genetics (ACMG), evaluated *CYP2C9* and *VKORC1* genetic testing prior to warfarin dosing and concluded that no large study had yet shown this to be acceptable or effective.[193]

Jorgensen (2012) investigated the influence of *CYP2C9* and *VKORC1* on patient response to warfarin in a systematic review and meta-analysis of 117 studies.[194] Authors concluded that genetic associations with warfarin response vary between ethnicities. In addition, authors suggest that a high level of methodological rigor must be maintained and that studies should

report sufficient data to enable inclusion in meta-analyses and achieve unbiased estimates in different populations.

A systematic review and meta-analysis by Liang (2012) suggested a more substantial contribution of *CYP4F2* genetic variants.[195] Compared with wild type patients, carriers of *CYP4F2* variants required warfarin doses 11% and 21% higher for heterozygous and homozygous patients, respectively.

Randomized Controlled Trials

A total of 28 RCTs comparing genotype-guided with clinical dosing of warfarin were identified. Twenty-seven of these RCTs were included in at least one systematic review. We identified one additional RCTs not included in any of the systematic reviews. Zhu (2020) found that INR time in therapeutic range was improved with genotype-guided dosing based on *CYP2C9* and *VKORC1* compared with clinically-guided dosing in elderly Chinese patients with nonvalvular atrial fibrillation.[196] Additionally, bleeding events did not differ between groups, but ischemic stroke occurred less frequently with genotype-guided dosing.

Nonrandomized Studies

A number of nonrandomized and retrospective studies of genotype-based vs. standard warfarin dosing have been published,[197] including preliminary findings in children.[198-212] However, evidence from these studies does not permit conclusions due to methodological limitations such as non-random allocation of dosing management and lack of appropriate comparison groups.[198-209]

Section Summary

Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence does not support the conclusion that clinically relevant outcomes, such as rates of bleeding or thromboembolism, are improved. Proposed dosing algorithms require evaluation in large, prospective, randomized trials comparing genotype-guided dosing with current standard-of-care approaches to determine net health benefit.

PRACTICE GUIDELINE SUMMARY

ANTI-TUBERCULOSIS MEDICATIONS

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and dosing of anti-tuberculosis medications**.**

BETA BLOCKER SELECTION AND DOSING

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and dosing of beta-blocker medications.

CLOPIDOGREL: DETERMINING RISK OF ATHEROTHROMBOTIC EVENTS AFTER AN ACUTE CORONARY SYNDROME OR A PERCUTANEOUS CORONARY INTERVENTION

American College of Cardiology (ACC) foundation and the American Heart Association (AHA)

A consensus statement by the American College of Cardiology (ACC) foundation and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010.[213] The recommendations for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.
- Clinicians must be aware that genetic variability in CYP enzymes alters clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined.
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. Both the selection of the specific test and the issue of reimbursement are important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

SELECTION OR DOSING OF CODEINE

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and dosing of codeine for nursing mothers.

DOSE AND SELECTION OF HIGHLY ACTIVE ANTIRETROVIRAL AGENTS

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the dosing of efavirenz.

ELIGLUSTAT (CERDELGA™) FOR GAUCHER DISEASE TYPE I.

Currently no published clinical practice guidelines recommend *CYP2D6* genotyping for the dosing of eliglustat.

H. PYLORI INFECTION

No evidence-based clinical practice guidelines were identified that recommend *CYP450* (i.e., *CYP2C19*) genotyping to select and dose treatment for *H. pylori* eradication.

IMMUNOSUPPRESSANT DOSING FOR ORGAN TRANSPLANTATION

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the dosing of immunosuppressant medications**.**

TAMOXIFEN: MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER

Currently no published clinical practice guidelines recommend *CYP450* genotyping for the selection and dosing of tamoxifen.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (v.1.2024) state that, "CYP2D6 genotype testing is not recommended in women who are considering tamoxifen."[214]

American Society of Clinical Oncology

The 2016 guideline on the use of biomarkers to guide adjuvant systemic therapy decisions for women with early-stage invasive breast cancer states that, "The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.[215]."

TETRABENAZINE FOR HUNTINGTON DISEASE

Currently no published clinical practice guidelines recommend *CYP2D6* genotyping for chorea in HD.

WARFARIN DOSING AND MANAGEMENT

American College of Chest Physicians

The 2012 American College of Chest Physicians evidence-based clinical practice guidelines on "Antithrombotic Therapy and Prevention of Thrombosis," states, "For patients initiating VKA [vitamin K antagonist] therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)."[216]

American College of Medical Genetics

Per the 2008 statement from the American College of Medical genetics, "there is insufficient evidence at this time to recommend for or against routine *CYP2C9* and *VKORC1* testing in warfarin-naive patients."[217]

SUMMARY

ANTI-TUBERCULOSIS MEDICATIONS:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking anti-tuberculosis medications. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping for the management of anti-tuberculosis medications is considered investigational.

BETA BLOCKER SELECTION AND DOSING:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking beta blockers. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* (including *CYP2D6*) genotyping for selection or dosing of beta blockers is considered investigational.

CLOPIDOGREL - DETERMINING RISK OF ATHEROTHROMBOTIC EVENTS AFTER AN ACUTE CORONARY SYNDROME OR A PERCUTANEOUS CORONARY INTERVENTION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking anti-tuberculosis medications. Despite this, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of clopidogrel (Plavix®). Therefore, *CYP450* genotyping may be considered medically necessary to guide selection and dose management of clopidogrel.

CODEINE PRESCRIPTION FOR NURSING MOTHERS:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking codeine, including nursing mothers. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* (including *CYP2D6*) for codeine selection and dosing is considered investigational.

EFAVIRENZ DOSING FOR THE TREATMENT OF HIV INFECTION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients taking efavirenz to treat HIV infection. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including CYP2B6) to select or dose efavirenz is considered investigational.

ELIGLUSTAT (CERDELGA™) FOR GAUCHER DISEASE TYPE I:

There is very little research on *CYP450* genetic testing for people with Gaucher disease considering eliglustat. However, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of eliglustat. Therefore, *CYP450* genotyping may be considered medically necessary to guide selection and dose management of eliglustat.

H. PYLORI INFECTION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for people with *H. pylori* infections taking proton pump inhibitors (PPIs). There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including *CYP2C19*) to select or dose PPIs is considered investigational.

IMMUNOSUPPRESSANT DOSING FOR ORGAN TRANSPLANTATION:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for organ transplantation patients taking immunosuppressant medications. There are no clinical guidelines based on research that recommend genetic testing for this purpose. Therefore, *CYP450* genotyping (including *CYP3A5*) to select or dose immunosuppressant drugs is considered investigational.

TAMOXIFEN - MANAGING TREATMENT FOR WOMEN AT HIGH RISK FOR OR WITH BREAST CANCER:

There is not enough research to show that genetic testing of *CYP450* genes can improve health outcomes for patients with breast cancer or at high risk for breast cancer that are considering tamoxifen treatment. Additionally, there are clinical guidelines based on research that specifically recommend against genetic testing for this purpose. Therefore, *CYP450* genotyping (e.g., *CYP2D6*) for selection and dosing of tamoxifen is considered investigational.

TETRABENAZINE FOR HUNTINGTON DISEASE

There is very little research showing how genetic testing can help with tetrabenazine dosing decisions. However, because of the FDA labeling for the medication and evidence that genetics can greatly affect the metabolism of the medication, *CYP2D6* testing to determine metabolizer status may be considered medically necessary before the use of tetrabenazine, when a dosage greater than 50mg per day may be considered.

SIPONIMOD FOR MULTIPLE SCEROSIS

There is limited research showing how genetic testing can help with siponimod dosing decisions. However, because of the FDA labeling for the medication and evidence that genetics can greatly affect the metabolism of the medication, *CYP2C9* testing to determine metabolizer status may be considered medically necessary before the use of siponimod for patients with relapsing forms of multiple sclerosis.

WARFARIN DOSING AND MANAGEMENT:

There is research that shows that *CYP2C9* and *VKORC1* genes are related to warfarin dosing, but there is not enough research to show that genetic testing for these genes improves health outcomes for people taking this medication. Therefore, genotyping for variants to predict initial warfarin dose is considered investigational.

OTHER INDICATIONS

CYP2C19 testing may be useful for selecting anti-platelet treatments, and CYP2D6 testing can aid in medication selection for patients with Gaucher or Huntington disease. While testing for various CYP450 genes has been proposed to help with selection of other medications, there is not enough research to show that this testing is helpful for guiding medication selection and improving health outcomes for patients. In addition, there are no clinical guidelines based on research that recommend such testing. Therefore, CYP450 genetic testing that does not meet the policy criteria is considered investigational.

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CODES

Codes	Number	Description
CPT	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, *CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1* and rs12777823)
	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, *CYP2C9, CYP4F2, VKORC1*, rs12777823)
	0031U	*CYP1A2* (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)
	0070U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)

Codes	Number	Description
		CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to
	0072U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
	0073U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
	0075U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	0076U	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	~~0380U~~	~~Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype~~ (Deleted 01/01/2025)
	0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
	0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted genedrug interactions
	0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
	0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes
	0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and *CYP2D6* copy number variant analysis, reported as metabolizer status
	0533U	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5,

Codes	Number	Description
		CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function
	81225	*CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
	81226	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
	81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)
	81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
	81355	*VKORC1* (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
HCPCS	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Date of Origin: *March 2011*

Regence

Medical Policy Manual Genetic Testing, Policy No. 11

Genetic Testing for Familial Hypercholesterolemia

Effective: March 1, 2025

Next Review: November 2025
Last Review: January 2025

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

Homozygous familial hypercholesterolemia (FH) is a rare disorder that causes extremely high levels of low-density lipoprotein (LDL), leading to very early cardiovascular disease. Heterozygous FH is more common and can also cause elevated LDL levels and premature cardiovascular disease, though with reduced severity and more variable presentation than homozygous FH.

MEDICAL POLICY CRITERIA

I. Genetic testing of *LDLR, APOB, PCSK9,* and/or *LDLRAP1* genes to confirm a diagnosis of familial hypercholesterolemia (FH) may be considered **medically necessary** when there is documentation of an uncertain diagnosis of FH (see Policy Guidelines) and a definitive diagnosis is required for selection of specialty medications (e.g., PCSK9 inhibitors).

II. Genetic testing for known familial FH-causing gene variants may be considered **medically necessary** for children (younger than age 18) when there is an affected first or second-degree relative, to determine future risk of disease.

III. Genetic testing for FH is **investigational** for all other indications, including but not limited to, a diagnosis when Criterion I. or II. is not met, and genetic testing for other genes.

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

POLICY GUIDELINES

UNCERTAIN DIAGNOSIS OF FH

There are no standardized definitions of uncertain diagnosis of FH, however there are tools that can be useful for this determination, including but not limited to the Simon Broom Registry Criteria and the Dutch Lipid Clinic Network Criteria (score of 3-8).

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. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
    - History and physical exam
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic and Molecular Testing, Genetic Testing, Policy No. 20
2. High-cost medications for cholesterol, Medication Policy Manual, Policy No. dru779

BACKGROUND

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. FH can be categorized as homozygous or heterozygous FH. Homozygous FH is an extremely rare disorder that arises from biallelic homozygous or compound heterozygous variants and has a prevalence of between 1:160,000 and 1:4,000,000. Individuals with homozygous (which includes compound heterozygous) FH have extreme elevations of LDL, and typically develop coronary artery disease (CAD) in the second or third decade of life[1].

Heterozygous FH is relatively common, with an estimated prevalence of 1 in 311 in the general population. Some populations such as Ashkenazi Jews and South Africans have higher prevalence of up to 1 in 100. The prevalence of FH in people with atherosclerotic cardiovascular disease (ASCVD) is 1 in 17. For affected individuals, the burden of illness is high. If untreated, the average age for presentation with CAD is in the fourth decade for males and the fifth decade for females, and there is a 30% to 50% risk of a fatal or nonfatal cardiac event for men and women in the fifth and sixth decades, respectively[2-4].

The diagnosis of FH relies on elevated LDL levels in conjunction with a personal and/or family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for patients with FH, and considerable overlap in levels between patients with FH and patients with non-FH. Physical exam findings can include tendinous xanthomas, xanthelasma, and corneal arcus. Physical signs of FH are uncommon in children. Xanthelasma and corneal arcus are common in the elderly population and therefore not specific. Tendinous xanthomas are relatively specific for FH but are not sensitive findings. They occur mostly in patients with higher LDL levels and treatment with statins likely delays or prevents the development of xanthomas.

Because of the variable cholesterol levels, and the low sensitivity of physical exam findings, there are a considerable number of patients in whom the diagnosis is uncertain. For these individuals, there are a number of formal diagnostic tools for determining the likelihood of FH, including the Dutch Lipid Clinic Criteria, the Simon Broome Registry Criteria, and the Make Early Diagnosis Prevent Early Deaths Program Diagnostic Criteria.[5] Not all diagnostic tools for FH are appropriate for use in pediatric settings due to their reliance on physical signs of FH.

Treatment for FH in adults is similar to that for non-familial hypercholesterolemia and is based on LDL levels. Treatment for FH differs in that the approach is more aggressive (i.e., treatment may be initiated sooner, and a higher intensity medication regimen may be used). In children with FH, lipid screening and statin therapy are initiated at younger ages than in average risk children.

As with other forms of hypercholesterolemia, statins are the mainstay of treatment for FH. However, because of the degree of elevated LDL in many patients with FH, statins will often not be sufficient to achieve target lipid levels. Additional medications can be used in these patients. Ezetimibe inhibits absorption of cholesterol from the gastrointestinal tract and is effective for reducing LDL levels by up to 25% in patients already on statins. The IMPROVE-IT trial randomized patients with acute coronary syndrome to a combination of ezetimibe plus statins versus statins alone and reported that cardiovascular events were reduced for patients treated with combination therapy.[6]

The PCSK9 inhibitors are the most recently approved drugs for hyperlipidemia. These medications have potent LDL-lowering properties and have been tested in patients with FH. When added to statins, these drugs can result in additional LDL reduction of 30% to 70% and have been reported to reduce the incidence of nonfatal myocardial infarction.[4] Other antilipid medications (e.g., bile acid sequestrants, niacin) are effective at reducing LDL levels but have not demonstrated efficacy in reducing cardiovascular events when added to statins. For patients who continue to have elevated LDL levels despite maximum medical treatment, lipid apheresis is an option.

FH is most often inherited as an autosomal dominant condition. The primary physiologic defect in FH is impaired ability to clear LDL from the circulation, resulting in elevated serum levels. Four genes have been identified as harboring variants associated with FH. The LDL receptor gene (*LDLR*) is the most common gene in which a variant is identified, accounting for between 85-90% of genetically confirmed FH[2] Because the LDL receptor binds LDL and allows removal of LDL from the circulation, a defect in this receptor leads to reduced clearance of LDL. Over 1,500 different pathogenic variants have been identified in this gene.[5]

Other genes associated with FH include the *APOB* and *PCSK9* genes. Changes in the *APOB* gene account for approximately 5%-15% of FH cases. Apolipoprotein B is a cofactor in the

binding of LDL to the LDL receptor, and variants in *APOB* lead to reduced clearance of LDL. Variants in the *PCSK9* gene that increase the levels of PCSK9, impairing the function of LDL receptors, account for approximately 1% of FH. *APOB* and *PCSK9* variants result in increased PCSK9 levels, which impair the function of the LDL receptors leading to reduced clearance of LDL.[2] Recessive FH is caused by homozygous *LDLRAP1* pathogenic (or likely pathogenic) variants.

Penetrance for heterozygous FH varies by gene and in some cases by specific variant but is at least 70%. Variable clinical expressivity may also be mediated by both environmental factors such as diet and exercise, and unknown genetic factors that modify gene expression.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[7] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on clinical validity and utility.

CLINICAL VALIDITY

The clinical sensitivity is defined as the proportion of patients with FH who have a pathogenic variant for FH, and the clinical specificity is defined as the proportion of patients without FH who do not have a pathogenic variant for FH.

Six of the larger, more recent published studies of clinical validity were identified and are shown in Table 1.[8-13] These cohorts included sample sizes ranging from 254 to 6,015 patients with definite or suspected FH. These studies were conducted in different countries in Western Europe; no similar studies of US individuals were identified. All studies reported clinical sensitivity and two studies reported on clinical specificity. In some cases, the analysis was stratified by the clinical likelihood of FH prior to genetic testing using the Dutch Lipid Clinic Network (DLCN) criteria.

The largest cohort, studied by Abul-Husn (2016), focused on genetic testing through exome sequencing of 46,321 adults from a single health system.[13] The test had low sensitivity (2%)

and high specificity (99%), complicated by reliance on an incomplete electronic medical record for retrospective clinical diagnosis by the Dutch Lipid Clinic Network diagnostic criteria. This study further went on to note that within the 215 patients found to have genetic variants in the *LDR*, *PCSK9*, and *APOB* genes, only 25% met criteria for a clinical diagnosis of FH. Patients with relevant variants had higher LDL-H levels (p<0.001) with an increased risk of both general CAD (OR 2.6, p<0.001) and premature CAD (OR 3.7, p<0.001). Weaknesses of this study include reliance on a partially incomplete electronic medical record, as well as an ascertainment bias due to sampling within a single health care delivery system.

The clinical sensitivity of these studies ranged from 2% to 66.5%, with four studies clustering in the 34.5% to 41.2% range. The study that reported a substantially higher sensitivity of 66.5% included only patients with definite FH, unlike the other studies that included both definite and suspected FH cases. Two studies used the DLCN criteria to categorize individuals as definite, probable or possible FH.[9, 11] The proportion of individuals testing positive for FH varied by category. In the definite FH category, the sensitivity was 56.3% and 70.3%, respectively. This is in the same range as the study by Diakou (2011), which reported a sensitivity of 66.5% in patients with definite FH. In patients with probable or possible FH, the sensitivity was substantially lower (range, 10.8% to 29.5%).

Differences in the methodology of these studies may impact the reported sensitivities. The populations are from different countries and are comprised mostly of patients from tertiary referral centers. Different populations, especially those seen in primary care, may have different rates of variants. The type and number of variants tested for, and the methods of testing, also varied in these studies. For example, for *LDLR* gene variants, some studies used a defined set of known pathogenic variants while other studies searched for any variants and reported both known and unknown variants. There were also differences in the method for making a clinical diagnosis, and different diagnostic criteria may have resulted in different populations. Future studies may report on additional genes associated with FH (i.e., *STAP1*), and on copy number variation. Sensitivity and specificity have not yet been reported in large cohort studies for these tests.[14]

Table 1. Clinical Validity of Genetic Testing for FH

Study (Year)	Location	N	Genes Tested (Variants)	Clinical Sensitivity				Clinical Specificity
				Definite FH	Probable FH	Possible FH	Overall	
Diakou (2011)	Greece	254	*LDLR* (n=10) *APOB* (n=1) *PCSK9* (n=1) *ARH* (n=1)	66.5% (169/254)[a]	–	–	66.5% (169/254)[a]	100% (40/40)
Hooper (2012)	Australia	343	*LDLR* (n=18) *APOB* (n=2) *PCSK9* (n=1)	70.3% (90/128)	29.5% (26/88)	10.8% (12/111)	37.3% (128/343)	–
Palacios (2012)	Spain	5430	*LDLR* (any) *APOB* (n=1) *PCSK9* (n=4)	–	–	–	41.4%[b] (2246/5430)	–
Taylor (2010)	United Kingdom	635	*LDLR* (n=18) *APOB* (n=1) *PCSK9* (n=1)	56.3% (107/190)	–	28.4% (112/394)	34.5% (219/635)	–
Tichy (2012)	Czech Republic	2239	*LDLR* (any) *APOB* (n=1)	–	–	–	35.7%[c] (800/2239)	–
Abul-Husn (2016)	U.S.	50,726	*LDLR* (n=29) *APOB* (n=2) *PCSK9* (n=4)	30.2% (16/53)[a]	7.0% (35/497)	1.2% (68/5465)	2.0% (119/6015)[a]	99.8% (40,174/40,270)

Study (Year)	Location	N	Genes Tested (Variants)	Clinical Sensitivity				Clinical Specificity
				Definite FH	Probable FH	Possible FH	Overall	
Hedegaard (2023)[15]	Denmark	1243	*LDLR* *APOB* *PCSK9*	41.3 (19/46)	31.8 (34/107)	19.0 (97/511)	27.9% (350/1243)	

FH: familial hypercholesterolemia.
a Individuals with a clinical diagnosis of FH based on Williams's clinical criteria.
b Individuals with possible, probable, definite FH but not separated by category.
c Individuals with a high clinical suspicion for FH based on personal history, family history, and low-density lipoprotein levels.

Section Summary: Clinical Validity

Evidence on clinical validity includes cohorts of patients with definite or suspected FH tested for genetic variants, and cohorts of unaffected patients tested for genetic variants. Five moderate-to-large cohorts were reviewed, from the U.S. and Europe. A wide range of clinical sensitivity was reported (range 2% to 66.5%). The sensitivity is higher in patients with definite FH (range 50% to 70%). In patients with probable or possible FH, the sensitivity is low (range 1.2% to 30%). Two studies reported clinical specificity (range 2% to 66.5%).

CLINICAL UTILITY

There is no direct evidence on the clinical utility of genetic testing for FH. However, FH is a disorder with a high burden of illness and potentially preventable morbidity and mortality. Accelerated atherosclerotic disease in the absence of treatment leads to premature CAD and increased morbidity and mortality for affected patients. There are cases in which the diagnosis cannot be made by standard clinical workup without genetic testing. There is an overlap in cholesterol levels between individuals with FH and those with other types of hypercholesterolemia, and family history of premature CAD may or may not be apparent for all individuals, leading to a substantial number of cases in which the diagnosis is uncertain based on family history and cholesterol levels.

For patients with an uncertain diagnosis of FH, genetic testing can confirm the diagnosis in a substantial proportion of patients. Identification of a known pathogenic variant has a high specificity for FH and therefore will confirm the disorder with a high degree of certainty. On the other hand, the sensitivity for identifying a pathogenic variant is suboptimal and therefore a negative genetic test will not rule out FH in the absence of a known pathogenic/likely pathogenic variant in a blood relative. For patients who are in an uncertain category by clinical criteria, a positive genetic test will confirm the diagnosis of FH. These patients will then be eligible for specialty medications (e.g., PCSK9 inhibitors) and these medications will be initiated in patients who have uncontrolled lipid levels despite treatment with statins and/or other agents. In patients who have uncontrolled lipid levels despite treatment with standard medications, these drugs have been demonstrated to improve outcomes.[16, 17]

There is evidence that children with FH benefit from genetic testing in order to confirm their diagnosis. A Cochrane meta-analysis found that statin therapy use in children with FH was safe and effectively lowered cholesterol levels. The meta-analysis included studies involving children treated with statins as young as age 6, which is younger than current population-based cholesterol screening guidelines of age 9. The Cochrane review emphasized the importance of molecular diagnosis of FH in order to identify children who are more likely to need specialty medications.[18]

A long-term follow-up study reported that former participants in a placebo-controlled RCT involving statin therapy in children for genetically confirmed FH had reduced risk for cardiovascular disease 20 years later. The follow-up study compared patients who received statins between age 8 and 18 to their parents who were not treated with statin therapy before adulthood.[19]

Section Summary: Clinical Utility

There is a lack of direct evidence for clinical utility, therefore indirect chains of evidence are used to determine whether testing has clinical utility. For diagnostic genetic testing, when a definitive diagnosis of FH is required to establish eligibility for specialty medications, the links in the chain of indirect evidence are intact and clinical utility is demonstrated. In other situations, there are gaps in the chain of indirect evidence that preclude conclusions on clinical utility. For this indication, genetic testing can confirm the presence of FH in some individuals who have an uncertain clinical diagnosis, but treatment decisions are made primarily on LDL levels and the establishment of definite FH will not change treatment recommendations. It is possible that some types of management changes are undertaken after a diagnosis of FH, such as intensification of medication treatment or referral to a lipid specialist, but these management changes have an uncertain impact on outcomes.

TESTING INDIVIDUALS WITH A CLOSE RELATIVE WITH A DIAGNOSIS OF FH FOR FUTURE RISK OF DISEASE

Genetic testing for children at risk for FH has clinical utility. Targeted testing for a known pathogenic variant has positive and negative predictive values, both approaching 100%. Genetic testing in children is superior to standard risk stratification in determining future disease risk. Genetic testing is used to determine the age to start cholesterol testing in order to enable prompt statin therapy, and to rule out FH in children who have a blood relative with a known FH-causing gene variant. Evidence is sufficient that the technology leads to improvement in net health outcome.

There is no direct evidence on the clinical utility of genetic testing for FH in adults based on known familial variants. Cascade testing for FH in adults is unlikely to lead to changes in clinical management or improved outcomes for adults with FH since cholesterol levels are routinely assessed during adulthood. FH treatment is based on LDL levels and response to therapy. However, some studies have investigated whether FH diagnosis through genetic testing leads to better identification of FH in the family.

Miller (2022) conducted a pragmatic trial in the United States of cascade testing for FH that used direct contact between the investigators and family members.[20] Family members of 52 FH probands with a pathogenic variant in *LDLR*, *APOB*, or *PCSK9* were offered genetic testing. Family members of 73 probands without a pathogenic variant were asked to undergo lipid testing. A total of 111 family members of individuals with a pathogenic variant underwent genetic testing, and 48 new cases were identified (43.2% yield; 0.92 new cases per index case; p=.032 and p<.001, respectively compared to the other group). Among the 63 family members of individuals without a pathogenic variant who underwent lipid testing, 17 new cases were identified (27% yield; 0.23 new cases per index case). The cascade testing uptake rate was 43.9% versus 21.4%, respectively (p<.001). The authors concluded that direct contact and coordinated genetic testing may increase cascade testing uptake and yield. The study did not address whether cascade testing affected medical management or clinical outcomes.

The "Is Family screening Improved by Genetic Testing in FH" ("I FIGhT FH") RCT (2021) conducted in the United States compared cascade screening uptake in adult relatives following proband genetic testing or usual care (lipid testing) for diagnosis of FH.[21] Of 240 enrolled probands, only 43 relatives enrolled in the trial (0.2 relatives per proband). The trial did not find a difference in cascade screening uptake among relatives whether the proband was diagnosed with FH using genetic testing or usual care (0.2 vs. 0.1 relatives per proband; p=.14) nor was there a difference between group in relatives diagnosed with FH as a results of cascade screening (0.1 vs. 0.1 new cases per index case; p=.27). Results of this study may be limited due to the low participation rate by relatives eligible for cascade screening.

There is some evidence regarding the outcomes of familial testing from studies of cascade screening in countries where this method has been used.

A systematic review (2019) of cascade screening included six studies of genetic cascade testing and four studies of biochemical testing.[22] Due to the constraints associated with cascade screening noted below, none of the included studies were conducted in the United States. The review found similar diagnostic yield with genetic (44.3%) and biochemical (45.2%) testing, but the new cases identified per index case by genetic testing was nearly six times larger than cases identified by biochemical testing (2.42 versus 0.42 cases). Results favoring new case identification with genetic testing were consistent when excluding one outlier study (1.37 versus 0.42 cases).

Cascade screening for FH was evaluated by Leren (2004) in a national screening program from the Netherlands in a large study not included in the systematic review.[23] This program was initiated at a time when cholesterol screening was recommended for the general population. The addition of cascade screening for FH led to more than 9000 additional individuals diagnosed with FH. The rate of statin use increased in this population from an estimate of 39% prior to initiation of the program to 85% after full implementation. s While cascade screening is likely to improve outcomes, it requires an infrastructure that allows access to the entire population, and that is not likely to be feasible when only a limited population is available for screening. As a result of these barriers, cascade screening has not been used in the U.S., and the applicability of these studies to a U.S. population is unclear.

SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of familial hypercholesterolemia (FH) and who receive genetic testing to confirm the diagnosis of FH, the evidence includes case series and cross-sectional studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empiric evidence on analytic validity was identified; however, there are claims in the literature that the analytic validity approaches 100%. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH variants. In these cohorts of patients, the clinical sensitivity ranges from 30% to 70% for those with definite FH. For suspected FH, the sensitivity is lower, ranging from 1% to 30%. Clinical specificity ranges from 99% to 100%. False positives are expected to be low for known pathogenic variants, but the false-positive rate is unknown for novel variants or for variants of unknown significance.

Direct evidence of clinical utility is lacking. However, for patients who are in an uncertain diagnostic category, a positive genetic test can confirm the diagnosis of FH and establish eligibility for specialty medications. Specialty medications (e.g., PCSK9 inhibitors) have known

efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications.

There is evidence that children with blood relatives who have known FH-causing gene variants benefit from targeted testing to determine future disease risk. Long-term follow-up data demonstrate reduced disease risk after childhood statin therapy for FH. Because FH causes, on average, earlier onset of symptoms, and there is a long pre-symptomatic phase; identification through genetic testing in order to enable preventative strategies and prompt treatment is warranted. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A 2023 guideline from the international atherosclerosis society includes recommendations about genetic testing as part of a best practice approach to managing FH.[24] All patients with a phenotypic diagnosis or strong suspicion of FH should be offered genetic testing. Testing should include the following genes: *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*. Cascade testing (consisting of both phenotype and genotype testing) of all close relatives of an index case is recommended, with a focus on the specific variant(s) identified in the index case. Children should receive genetic testing at the earliest opportunity if an FH-causing variant has been identified in a parent or other first-degree relative. Reverse cascade testing (from child to parent) should be offered after a child is found to be a proband. Any potential index case should be confirmed with genetic testing. In all cases, genetic testing should include genetic counseling.

NATIONAL LIPID ASSOCIATION EXPERT PANEL

Recommendations on the diagnosis and screening for FH were developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia and published in 2011[25] and built upon by a scientific statement published in 2020.[26] This statement includes the following recommendations:

- Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone. (Strength of recommendation: IIa, Level of evidence: B-NR [Nonrandomized])
- Cascade screening for FH either by lipid profile or genetic testing is recommended in all first-degree relatives (children and siblings) of an individual who has tested genetically positive for FH. (Strength of recommendation: I; Level of evidence: C-EO [Consensus of expert opinion])

AMERICAN COLLEGE OF CARDIOLOGY

The Journal of the American College of Cardiology (JACC) Scientific Expert Panel published consensus guidelines regarding clinical genetic testing for FH in 2018.[27] These included the following recommendations:

- Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:

    - Children with persistent LDL-C levels ≥160 mg/dl or adults with persistent LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia and with at least 1 first-degree relative similarly affected or with premature CAD or where family history is not available (e.g., adoption)
    - Children with persistent LDL-C levels ≥190 mg/dl or adults with persistent LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia, even in the absence of a positive family history
- Genetic testing for FH may be considered in the following clinical scenarios:
    - Children with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) with and LDL-C level ≥190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD
    - Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD
    - Adults with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD.

In 2017, the American College of Cardiology (ACC) published a focused update to the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.[28] This guide included definitions of heterozygous and homozygous FH, based on clinical criteria alone or with genetic testing performed. However, no specific recommendations regarding such testing.

AMERICAN HEART ASSOCIATION

According to a scientific statement from the American Heart Association (2021), “Children with a strong clinical suspicion for FH should be offered genetic testing for diagnosis. Furthermore, if a pathogenic/likely pathogenic variant is found in an individual with FH, risk-predictive genetic testing should be performed in the family, including children.”[29]

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Recommendations from an expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011.[30] The report contained the following recommendations:

- “The evidence review supports the concept that early identification and control of dyslipidemia throughout youth and into adulthood will substantially reduce clinical CVD risk beginning in young adult life. Preliminary evidence in children with heterozygous FH with markedly elevated LDL-C indicates that earlier treatment is associated with reduced subclinical evidence of atherosclerosis. (Grade B)
- TC and LDL-C levels fall as much as10-20% or more during puberty. (Grade B) Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (range age 9-11 years) is a stable time for lipid assessment in children. (Grade D) For most children, this age range will precede onset of puberty.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (2023) published an evidence update and recommendation statement on screening for lipid disorders in asymptomatic children and adolescents.[31] The report states the evidence is insufficient to recommend for or against lipid screening in children and adolescents age 20 years and younger. The evidence review for FH is focused on heterozygous FH, with a statement that homozygous FH is beyond the scope of the report. Regarding treatment of lipid disorders, the report states the benefit is strongest for statins in children and adolescents with FH.

The U.S. Preventive Services Task Force (2022) published recommendations on statin use for primary prevention of cardiovascular disease in adults.[32] This publication did not make specific recommendations for genetic testing for FH.

SUMMARY

There is enough research to show that genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) can help identify patients that may benefit from certain cholesterol-lowering medications. Treatment with these medications can lower the risk of cardiovascular disease and improve health outcomes in patients with FH. Clinical guidelines based on research state that genetic testing may be useful when patients have an uncertain diagnosis of FH. Therefore, genetic testing of the genes *LDLR, APOB, PCSK9,* and *LDLRAP1* to confirm a diagnosis of FH may be considered medically necessary when policy criteria are met.

There is enough research to show that testing in children for known familial FH-causing gene variants in order to determine future disease risk can improve health outcomes. Standard approaches without genetic testing are insufficient to identify and prevent complications from FH in children. Therefore, this testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing in other situations can improve health outcomes for patients. This includes testing patients that already have a diagnosis of FH, , and testing genes other than genes *LDLR, APOB, PCSK9,* and *LDLRAP1.* Therefore, testing that does not meet the policy criteria is considered investigational.

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CODES

Codes	Number	Description
	81405	Molecular pathology procedure, Level 6

Codes	Number	Description
	81407	Molecular pathology procedure, Level 8
HCPCS	None	

Date of Origin: *December 2016*

Regence

Medical Policy Manual Genetic Testing, Policy No. 13

KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer

Effective: March 1, 2025

Next Review: December 2025
Last Review: January 2025

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

Variants in the *KRAS*, *NRAS*, and *BRAF* genes can substantially reduce the efficacy of certain antibody-based therapies for metastatic colon cancer. Testing for such variants can help to guide treatment decisions.

MEDICAL POLICY CRITERIA

I. *KRAS*, *NRAS*, and *BRAF* variant analysis may be considered **medically necessary** for treatment selection in patients with metastatic, unresectable, or advanced colorectal cancer.

II. *KRAS*, *NRAS*, and *BRAF* variant analysis is considered **investigational** for colorectal cancer that is not metastatic, unresectable, or advanced.

III. MicroRNA expression testing to predict anti-EGFR therapy response, including but not limited to the miR-31now™ test, 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 GENETIC TESTING DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
    - History and physical exam
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes, Genetic Testing, Policy No. 06
2. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. BRAF Genetic Testing To Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
5. Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
6. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
7. Serologic Genetic and Molecular Screening for Colorectal Cancer, Genetic Testing, Policy No. 86

BACKGROUND

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The *KRAS* gene can harbor oncogenic variants that may result in tumor resistance to therapies that target the epidermal growth factor receptor (EGFR). *KRAS* variants are found in approximately 30–50% of colorectal cancer tumors and are common in other tumor types.

The *NRAS* gene can harbor variants in codons 12, 13 and 61 that constitutively activate the EGFR-mediated signaling pathway similar to variants in *KRAS*. Thus, the *NRAS* oncogene may also have an impact on outcomes of anti-EGFR treatments for advanced colorectal cancer. Although *NRAS* variants account for some 15% of all *RAS* variants, they are rare compared to *KRAS* variants and are found in perhaps 2-7% % of all CRC. As a consequence of the low prevalence of *NRAS* variants, it is difficult to assess their effect on cancer behavior or therapy.

BRAF encodes a protein kinase and is involved in intracellular signaling and cell growth and is

a principal downstream effector of *KRAS*. *BRAF* variants occur in less than 10-15% of colorectal cancers.

It has been shown that patients with a *KRAS* mutant tumor do not respond to cetuximab or panitumumab. However, there are still patients with *KRAS* wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, *BRAF* variants are now increasingly being investigated in metastatic colorectal cancer. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

REGULATORY STATUS

Most *KRAS*, *NRAS*, and *BRAF* variant and microRNA tests using PCR methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Two companion diagnostic tests for KRAS variant analysis have been premarket approval from the FDA:

- "The cobas® KRAS Mutation Test, for use with the cobas® 4800 System, [which] is a real-time PCR [polymerase chain reaction] test for the detection of seven somatic mutations in codons 12 and 13 of the KRAS gene in DNA derived from formalin-fixed paraffin-embedded human colorectal cancer (CRC) tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux® (cetuximab) or with Vectibix® (panitumumab) may be indicated based on a no mutation detected result."[1]

- "The therascreen® KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin-fixed paraffin-embedded (FFPE), colorectal cancer (CRC) tissue. The therascreen® KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a KRAS no mutation detected test result."[1]

In 2015, the FDA prescribing information for panitumumab was updated to indicate that panitumumab was not indicated for treatment in colorectal cancer patients with variants in exon 2, 3, or 4 of either *KRAS* or *NRAS* in combination with oxaliplatin-based chemotherapy.

In June 2022, FDA granted accelerated approval to dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the treatment of adult and pediatric patients six years of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. However, dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found

in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The focus of the scientific evidence is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

For *KRAS, NRAS,* and *BRAF* testing in individuals with metastatic, unresectable, or advanced colorectal cancer, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher, and evidence reviews below for these genes will not be updated.

KRAS

Agency for Healthcare Research and Quality (AHRQ) Technology Assessment[3]

In 2010, AHRQ conducted a systematic review of the published evidence on *KRAS* variant testing and its ability to predict patient response to treatment with the anti-EGFR antibodies cetuximab and panitumumab. Forty-seven publications of *KRAS* variant testing met the eligibility criteria and were included in the review (45 in metastatic setting and two in neo-adjuvant setting). The review of evidence identified both small, retrospective studies and randomized controlled trials (RCTs). The assessment concluded that there is substantial and consistent evidence that *KRAS* testing can predict response to anti-EGFR therapy in colorectal cancer patients, and that,

> "For all outcomes assessed, patients with *KRAS* mutations were less likely to experience benefit with anti-EGFR antibody treatment, compared to patients whose tumors were wild-type for *KRAS* mutations. The direction of the association is consistent for overall mortality, disease progression and treatment failure by radiologic imaging."

BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment

The 2008 BlueCross BlueShield Association TEC Assessment concluded that the data are sufficient to demonstrate both the analytical and clinical validity of *KRAS* variant testing.[4] The evidence from five randomized trials and five single-arm studies is sufficient to indicate that metastatic colorectal cancer patients with mutated *KRAS* tumors do not respond to anti-EGFR monoclonal antibody therapy (either as monotherapy or in combination with other treatment regimens), do not derive survival benefit, and may experience decreased progression-free survival. Identifying patients whose tumors express mutated *KRAS* avoids exposing them to ineffective drugs, avoids exposure to unnecessary drug toxicities, and expedites the use of the best available alternative therapy.

Several studies published after the TEC and AHRQ assessments, including a meta-analysis and systematic review, continue to support the above findings.[5-12]

NRAS

A 2014 meta-analysis evaluated the predictive value of *NRAS* variants on clinical outcomes of anti-EGFR therapy in CRC[13] and included data from three nonrandomized studies.[14-16] The investigators suggest that the pooled analyses showed a trend towards poor objective response based on 17 events, but with significant effects on progression free survival (PFS) (hazard ratio [HR] 2.30, 95% CI 1.30 to 4.07) and overall survival (OS) (HR 1.85, 95% CI 1.23 to 2.78) among patients with wild-type *KRAS*. These results are limited by the small pool of variants, with studies reporting a prevalence of 2.2-5%.

Sorich (2015) published a systematic review and meta-analysis of nine RCTs that included 5948 metastatic colorectal cancer patients evaluated for *KRAS* exon 2 variants and new *RAS* variants, which were defined as variants in exons 3 and 4 of *KRAS* and exons 2, 3, and 4 of *NRAS*.[17] The prevalence of *NRAS* exon 2, 3, and 4 variants ranged from 0.5% to 4.8% and was similar to the prevalence of *KRAS* exon 3 and 4 variants, which ranged from 4.3% to 6.7% of tumors. Pooled data indicated that tumors without *KRAS* exon 2 variants or new *RAS* variants were found to have significantly superior PFS ($p<0.001$) and OS ($p=0.008$) with anti-EGFR monoclonal antibody (mAb) treatment compared to tumors with these variants. In addition, there were no differences noted in the PFS or OS of tumors with *KRAS* exon 2 variants when compared to new *RAS* variants. These results were consistent between different anti-EGFR mAb agents, lines of therapy, and chemotherapy. No PFS or OS benefit was observed with the use of anti-EGFR mAb agents in tumors with *KRAS* exon 2 variants or new *RAS* variants ($p>0.05$). Based on these results, authors concluded that approximately 53% of metastatic colorectal tumors (~42% with *KRAS* exon 2 and ~11% with new *RAS* variants) are unlikely to have a positive response to anti-EGFR mAb therapy. Results from this pooled data analysis suggest *NRAS* variant results may be used to guide treatment decisions in patients with metastatic colorectal tumors, as patients with *NRAS* variants are unlikely to benefit from anti-EGFR mAb therapy.

A systematic review and meta-analysis by Lin (2016) evaluated the efficacy of cetuximab-based chemotherapy according to *RAS* and *BRAF* variant subgroups in nine studies.[12] Cetuximab was associated with longer overall survival in tumors that had no variants in exon 2 of *KRAS* ($p=0.004$), tumors with wild-type (exons 2, 3, and 4) *KRAS*/*NRAS* ($p=0.0002$). There were no significant differences in OS or PFS between tumors with *KRAS* exon 2 variants and other exon 2, 3, or 4 *KRAS* or *NRAS* variants.

Additional studies published since the systematic reviews have shown similar differences in response to EGFR inhibitors according to *RAS* variant status.[18]

BRAF

Systematic Reviews

Pietrantonio (2015) published a systematic review and meta-analysis of randomized trials that compared cetuximab or panitumumab plus chemotherapy compared to standard therapy or best supportive care in patients with advanced colorectal cancer that have a *BRAF* variant.[19] Pooled results were reported for the efficacy of anti-EGFR-based therapy according to variant status as a first-line, second-line or refractory setting. Nine phase III trials and one phase II trial with a total of 463 patients with metastatic colon cancer were analyzed. Treatment with cetuximab or panitumumab did not significantly improve PFS (HR 0.88, 95% CI 0.67 to 1.14), OS (HR 0.91, 95% CI 0.62 to 1.34), or overall response rates (RR 1.31, 95% CI 0.83 to 2.08) compared to the control groups.

Rowland (2015) also published a systematic review and meta-analysis RCTs which evaluated the impact of *BRAF* variant status upon anti-EGFR mAb treatment outcomes in patients with metastatic colorectal cancer.[20] Seven RCTs met inclusion criteria for OS and eight studies met inclusion criteria for PFS. Pooled data indicated that cetuximab and panitumumab did not improve PFS (HR 0.86, 95% CI 0.61 to 1.21) or OS (HR 0.97, 95% CI 0.67 to 1.41) in patients with *BRAF* variants.

Other Studies

An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for tumor *KRAS* status and considered the clinical significance of the tumor variant status of *BRAF* in the expanded population of patients with *KRAS* wild-type tumors.[8] The impact of *BRAF* tumor variant status in relation to the efficacy of the chemotherapy regimen consisting of cetuximab plus folinic acid (leucovorin), 5-FU, and irinotecan (FOLFIRI) was examined in the population of patients with *KRAS* wild-type disease (n=625). There was no evidence of an independent treatment interaction by tumor *BRAF* variant status. The authors concluded that *BRAF* variant status was not predictive of treatment effects of cetuximab plus FOLFIRI but that *BRAF* tumor variant was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild-type. Other studies have been published that report mixed results.[8, 21-29]

The data regarding the utility of variant testing as a predictive marker which informs the use of anti-EGFR mAb is less substantial for *BRAF* testing than for *KRAS* or *NRAS* testing. However, the evidence suggests that *BRAF* variant testing may be useful in directing treatment decisions, as anti-EGFR therapies do not improve PFS or OS in metastatic colorectal cancer patients with *BRAF* variants.

MICRORNA

Several studies have evaluated the association between the expression of the miR-31-3p microRNA and colorectal cancer progression in patients treated with anti-EGFR therapies.[30-34] For example, an industry-sponsored study published by Laurent-Puig (2018) reported that individuals with low miR-31-3p expression derived more benefit from cetuximab than bevacizumab (PFS HR 0.74, 95% CI 0.55 to 1.00, p=0.05; OS HR 0.61, 95% CI 0.41 to 0.88, p<0.01).[30] However, no studies have assessed the use of microRNA expression test results to guide treatment decisions or impact health outcomes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN)[35] guidelines (v.6.2024) on the treatment of colon cancer make the following recommendation regarding *KRAS*, *NRAS*, and *BRAF* variant testing:

> "All patients with metastatic colorectal cancer should have tumor genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Patients with any known *KRAS* mutation (exons 2, 3, and 4) or *NRAS* mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a *KRAS* G12C mutation. *BRAF* V600E mutation makes

response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor."

The guidelines did not discuss microRNA testing.

SUMMARY

There is enough evidence to show that cetuximab and panitumumab are not effective treatments for colorectal cancers with *KRAS*, *NRAS* or *BRAF* variants. Clinical guidelines based on research recommend testing patients with metastatic colorectal cancer for variants in the *KRAS*, *NRAS*, and *BRAF* genes to help with treatment decisions. Therefore, *KRAS*, *NRAS* and *BRAF* variant analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

Anti-EGFR monoclonal antibodies are approved to treat advanced forms of colorectal cancer. These therapies are not approved for patients with non-metastatic, resectable colorectal cancer. Therefore, *KRAS*, *NRAS*, and *BRAF* variant analysis is considered investigational for colorectal cancer that is not metastatic, unresectable, or advanced.

There is not enough research to show that testing for microRNA expression can improve treatment decisions or health outcomes for patients with colorectal cancer. In addition, there are no clinical guidelines based on research that recommend microRNA testing for these patients. Therefore, microRNA expression testing to predict anti-EGFR therapy response, including but not limited to the miR-31now™ test, is considered investigational.

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CODES

Codes	Number	Description
CPT	0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
	0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
	0471U	Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalinfixed paraffin-embedded (FFPE), predictive, identification of detected mutations
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
HCPCS	None	

Date of Origin: *January 2011*

Regence

Medical Policy Manual Genetic Testing, Policy No. 18

Preimplantation Genetic Testing of Embryos

Effective: October 1, 2024

Next Review: March 2025
Last Review: September 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

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into two categories: 1) Preimplantation genetic testing for monogenic conditions (PGT-M) or for structural rearrangements (PGT-SR), are used to detect a specific inherited disorder, and aim to prevent the birth of affected children in people at high risk of transmitting a disorder. 2) Preimplantation genetic testing for aneuploidy (PGT-A) uses similar techniques to screen for potential genetic abnormalities in conjunction with in vitro fertilization for people without a specific known inherited disorder.

MEDICAL POLICY CRITERIA

Notes:

- Preimplantation genetic testing is an associated service, an adjunct to in vitro fertilization. Member contracts for covered services vary. Member contract language takes precedent over medical policy.
- This policy does not address whole exome sequencing (WES), whole genome sequencing (WGS), or carrier screening (see Cross References section).

I. Preimplantation genetic testing for monogenic conditions (PGT-M) or structural rearrangements (PGT-SR) may be considered **medically necessary** as an adjunct to

in vitro fertilization (IVF) in people who meet at least one of the following criteria, subject to careful consideration of the technical and ethical issues involved:

A. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
   1. Both partners are known carriers of a single-gene autosomal recessive disorder
   2. One partner is a known carrier of a single-gene autosomal recessive disorder, and the partners have one offspring that has been diagnosed with that recessive disorder
   3. One partner is a known carrier of a single-gene autosomal dominant disorder
   4. One partner is a known carrier of a single X-linked disorder

B. For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality, such as for a parent with balanced or unbalanced chromosomal translocation.

II. Preimplantation genetic testing for monogenic conditions (PGT-M) or structural rearrangements (PGT-SR) as an adjunct to IVF is considered **investigational** in people who are undergoing IVF in all situations other than those specified above.

III. Preimplantation genetic testing for aneuploidy (PGT-A), as an adjunct to IVF is considered **investigational** in people who are undergoing IVF in all situations.

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

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Chromosomal Microarray Analysis (CMA) or Copy number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies,

Genetic Testing, Pol. No. 58
3. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
4. Genetic Testing for Macular Degeneration, Genetic Testing, Policy No. 75
5. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
6. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
7. Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss, Genetic Testing, Policy No. 79
8. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81
9. Maternal Serum Analysis for Risk of Preterm Birth, Laboratory, Policy No. 75

BACKGROUND

Preimplantation genetic testing (PGT) describes a variety of adjuncts to an assisted reproductive procedure, in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a pathogenic gene abnormality prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with pathogenic gene variants before the initiation of pregnancy provides an attractive alternative to amniocentesis or chorionic villous sampling (CVS) with selective pregnancy termination of affected fetuses. Preimplantation genetic testing can be viewed as either diagnostic, including (PGT-M, formerly known as preimplantation genetic diagnosis; PGD) and preimplantation genetic testing for structural chromosomal rearrangements (PGT-SR); or screening for aneuploidy (PGT-A, formerly known as preimplantation genetic screening; PGS). PGT-M and PGM-SR are used to detect genetic evidence of a specific inherited disorder in the oocyte or embryo derived from biologic mother or reproductive partner that has a high risk of transmission. PGT-A is not used to detect a specific abnormality but instead uses similar techniques to identify genetic abnormalities to identify embryos at risk. This terminology, however, is not used consistently (e.g., some authors use the term preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder).

Biopsy for PGT-M can take place at three stages; the oocyte, the cleavage stage embryo or the blastocyst. In the earliest stage, the first and second polar bodies are extruded from the oocyte as it completes meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the biologic mother is a known carrier of a pathogenic gene variant, and genetic analysis of the polar body is normal, then it is assumed that the variant was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of six to eight cells (i.e., blastomeres). Sampling involves aspiration of one and sometimes two blastomeres from the embryo. Analysis of two cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form five to six days after insemination. Three to 10 trophectoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, if they do, there is a short time before embryo transfer needs to

take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic variants. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay-Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, sex determination, or to identify chromosomal translocations. Fluorescent in situ hybridization cannot be used to diagnose single gene variant disorders. However, molecular techniques can be applied with FISH, and thus single-gene variants (eg, microdeletions, duplications) can be recognized with this technique.

A more recent approach for preimplantation genetic testing is with comprehensive chromosome screening using techniques such as array comparative genome hybridization and next generation sequencing.

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single gene abnormality (PGT-M and PGT-SR)

Inherited single-gene pathogenic variants fall into three general categories: autosomal recessive, autosomal dominant, and X-linked. When either or both biologic parents are a known carrier of a pathogenic gene variant, PGT-M testing can be used to deselect embryos harboring the variant. Gender selection of a female embryo is another strategy when the biologic mother is a known carrier of an X-linked disorder for which there is not yet a specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGT-M is used to deselect male embryos, half of which would be affected. PGT-M could also be used to deselect affected male embryos. While there is a growing list of single gene variants for which molecular diagnosis is possible, the most common indications include cystic fibrosis, beta thalassemia, muscular dystrophy, Huntington's disease, hemophilia, and fragile X disease. It should be noted that when PGT-M is used to deselect affected embryos, the treated reproductive partners are not technically infertile but are undergoing an assisted reproductive procedure for the sole purpose of PGT-M. In this setting, PGT-M may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

Inherited chromosomal structural rearrangements may be either balanced, with no loss or gain of genetic material, or unbalanced, with some deletion or duplication. The risk of passing such a rearrangement on to offspring varies but can be as high as 50%. PGT-SR is testing to detect these rearrangements.

2. Identification of aneuploid embryos

Implantation failure of fertilized embryos is a common cause for failure of assisted reproductive procedures. Aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGT-A of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women. In

addition to advanced maternal age, PGT-A has been proposed for people with repeated implantation failure.

3. Embryos at a higher risk of translocations

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in people with infertility or recurrent spontaneous abortions. PGT-SR for structural rearrangements (translocations or inversions) can be used to deselect those embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

TECHNICAL FEASIBILITY

Preimplantation genetic diagnosis (PGT-M) has been shown to be a feasible technique to detect pathogenic genetic variants and to deselect affected embryos. Recent reviews continue to state that PGT-M using either polymerase chain reaction (PCR) or FISH can be used to identify numerous single gene disorders and unbalanced chromosomal translocation.[2, 3] According to a PGT-M registry initiated by the European Society of Hormone Reproduction and Embryology (ESHRE), the most common indications for PGT-M were thalassemia, sickle cell syndromes, cystic fibrosis (CF), spinal muscular disease, and Huntington’s disease.[4]

In 2007 the ESHRE PGT-M registry reported PGT-M testing on 3,753 oocyte retrievals, resulting in 729 with chromosomal abnormalities, 110 with X-linked diseases, 1,203 with monogenic diseases, and 92 for social sexing.[4] These registry data suggest that PGT-M, using either PCR or FISH, can be used to deselect affected embryos.

Several studies have suggested that the role of preimplantation genetic testing (PGT) has expanded to a broader variety of conditions that have not been considered as an indication for genetic testing via amniocentesis or chorionic villus sampling. The report of PGT used to deselect embryos at risk for early-onset Alzheimer’s disease prompted considerable controversy, both in lay and scientific publications.[5-7] Other reports focus on other applications

of PGT for *predispositions* to late-onset disorders.[8] This contrasts with the initial use of PGT-M in deselecting embryos with genetic variants highly predictive of lethal diseases. PGT-M has also been used for gender selection and "family balancing."[9-11] A representative sample of case series and reports on the technical feasibility of PGT to deselect embryos for different indications follows.

Several smaller case series reported on individual diseases. For example, Goossens (2000) reported on 48 cycles of PGT-M in 24 couples at risk for cystic fibrosis (CF). Thirteen patients became pregnant, and 12 healthy babies were born.[12] In an additional 2013 study on cystic fibrosis, there were 44 PGT-M cycles performed for 25 CF-affected homozygous or double-heterozygous CF patients (18 male and seven female partners), which involved testing simultaneously for three variants, resulting in the birth of 13 healthy CF-free children and no misdiagnosis. PGT-M was also performed for six couples at a combined risk of producing offspring with CF and another genetic disorder. Concomitant testing for CF and other variants resulted in birth of six healthy children, free of both CF and another genetic disorder in all but one cycle.[13] Other anecdotal studies have reported successful PGT-M in patients with osteogenesis imperfecta,[14] Lesch-Nyhan syndrome,[15] bulbar muscular atrophy,[16] and phenylketonuria.[17]

EFFICACY AND SAFETY

An area of clinical concern is the impact of PGT on overall IVF success rates. The available evidence is largely focused on people undergoing IVF due to infertility, and not specifically for PGT-M**.** The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on infertility management.[18] The AHRQ reviewed studies compared all types of PGT cycles with non-PGT cycles and found that for women younger than 35 years live birth per embryo transfer was lower for PGT cycles compared to non-PGT cycles.

An important general clinical issue is whether PGT-M is associated with adverse obstetric outcomes, specifically fetal malformations related to the biopsy procedure. Strom (2000) addressed this issue in an analysis of 102 pregnant women who had undergone PGT with genetic material from the polar body.[19] All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. PGT-M did not appear to be associated with an increased risk of obstetric complications compared to data reported for obstetric outcomes for in vitro fertilization. However, it should be noted that biopsy of the polar body is extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. The patients in this study had undergone PGT for both unspecified chromosomal disorders and various disorders associated with a single gene variant (e.g., CF, sickle cell disease, and others).

Preimplantation Genetic Testing for Monogenic Conditions

Systematic Reviews

Li (2022) published a systematic review and meta-analysis that included eleven studies to compare pregnancy outcomes in couples with recurrent pregnancy loss (RPL) and abnormal karyotypes to couples with RPL and normal karyotypes.[20] First pregnancy live birth rate (LBR) after RPL was lower in couples with abnormal karyotypes than in couples with normal karyotype (9 studies, OR, 0.55; 95% CI 0.46-0.65; I^2=27%; p<0.00001). Accumulated LBR was not significantly different between couples with abnormal vs. normal karyotype after RPL (4 studies; OR, 0.96; 95% CI, 0.90-1.03; I^2=0; p=0.26) However, miscarriages were more

common in couples with an abnormal karyotype (4 studies; OR, 2.21; 95% CI, 1.69-2.89; I^2=0; p<0.00001). A second analysis reported pregnancy outcomes of couples with RPL and abnormal karyotype that had expectant management compared to those that had PGD. While limited by the availability of only two non-randomized studies, the meta-analysis found the difference in accumulated LBR was not significant (2 studies; OR 0.55; 95% CI, 0.11-2.62; I^2=71%; 0=0.45) but PGD was associated with a lower miscarriage rate (2 studies; OR 0.15; 95% CI, 0.04-0.51; I^2=45%; p=0.002). The findings suggest that while miscarriages and unsuccessful first pregnancy are more common in people with chromosomal abnormalities, their overall LBR was the same as for people with normal karyotypes. However, the evidence also suggests repeated attempts are required after unsuccessful first pregnancy to achieve similar outcomes.

A systematic review by Iews (2018) evaluated reproductive outcomes with PGD among patients who had recurrent pregnancy losses due to structural chromosomal rearrangements.[21] There were 20 studies included in the review. There was significant heterogeneity between these studies, precluding meta-analysis. Among the 847 couples who conceived naturally, the live birth rate ranged from 25% to 71%, while among the 526 couples who underwent IVF with PDG the live birth rate ranged from 27% to 87%. The authors noted that the review was limited by the lack of large comparative or randomized studies.

Hasson (2017) published a systematic review of studies comparing obstetric and neonatal outcomes after intracytoplasmic sperm injection (ICSI) without PGD compared with ICSI with PGD.[22] Studies focused on cases in which there were known parental genetic aberrations. Reviewers identified six studies, including data published by the investigators in the same article. Pooled analysis found no significant differences between the two groups for four of the five reported outcomes, mean gestational age at birth, the rate of preterm delivery, and the rate of malformations. There was a significantly lower rate of low birth weight neonates (<2500 g) in the PGD group compared with the non-PGD group (relative risk [RR] 0.84, 95% confidence interval [CI] 0.72 to 1.00, p=0.04).

Randomized Controlled Trials

No randomized controlled trials (RCTs) of PGT-M were identified.

Nonrandomized Studies

A study by Heijligers (2018) evaluated perinatal outcomes following PGD between 1995 and 2014 in the Netherlands.[23] The study included 439 pregnancies in 381 women leading to 366 live born children. Of these, two were lost to follow-up. Nine of the remaining 364 children (2.5%) had major congenital malformations, which was consistent with other PGD cohorts, and five had a minor malformation. One misdiagnosis resulted in the spontaneous abortion of a fetus with an unbalanced 47,XX,+der(5)t(X;5)(q13;p14)mat karyotype. Seventy-one (20%) of the children were premature, including eight, all from twin pregnancies, that were very premature (<32 weeks). The authors concluded that there was no evidence that PGD was associated with an increased risk of adverse perinatal outcomes or congenital malformations.

Won (2018) reported clinical outcomes for patients who underwent PGD or PGS at a single center in Korea from January 2014 through December 2015.[24] This included samples from 116 PGD cycles for 76 couples. Of these PGD cases, there were 24 Robertsonian translocations, 60 reciprocal translocations, 23 with mosaicism, three inversions, four additions, and two deletions. Implantation and clinical pregnancy rates with PGD were higher

when testing was performed at the blastocyst stage (n=26) as compared with the cleavage stage (n=90) (27.5% vs. 17.8% and 38.5% vs. 18.9, respectively).

Maithripala (2017) performed a retrospective chart review of 36 couples with recurrent pregnancy loss due to structural chromosomal rearrangements.[25] Couples were more likely to choose natural conception than IVF with PGD, and no significant differences in live birth rate were seen between treatment groups.

A study by Kato (2016) included 52 couples with a reciprocal translocation (n=46) or Robertsonian translocation (n=6) in at least one partner.[26] All couples had a history of at least two miscarriages. The average live birth rate was 76.9% over 4.6 oocyte retrieval cycles. In the subgroups of young (<38 years) female carriers, young male carriers, older (≥38 years) female carriers, and older male carriers, live birth rates were 77.8%, 72.7%, 66.7%, and 50.0%, respectively.

Chow (2015) reported on 124 cycles of PGD in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant).[27] The most common genetic conditions were α-thalassemia (64 cycles) and β-thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 PGD cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8 to 10 weeks of gestation) in 28.2% of initiated cycles and an implantation rate of 35%. The live birth rate was not reported.

A study by Scriven (2013) evaluated PGD for couples carrying reciprocal translocations.[28] This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two out of the 59 couples (54%) had a history of recurrent miscarriages. The 59 couples underwent a total of 132 cycles. Twenty-eight couples (47%) had at least one pregnancy, 21 couples (36%) had at least one live birth and 10 couples (36%) had at least one pregnancy loss. The estimated live birth rate per couple was 30 of 59 (51%) after three to six cycles. The live birth rate estimate assumed that couples who were unsuccessful and did not return for additional treatment would have had the same success rate as couples who did return.

Keymolen (2012) reported clinical outcomes of 312 cycles performed for 142 couples with reciprocal translocations.[29] Data were collected at one center over 11 years. Seventy-five of 142 couples (53%) had PGD due to infertility, 40 couples (28%) due to a history of miscarriage, and the remainder due to a variety of other reasons. Embryo transfer was feasible in 150 of 312 cycles and 40 women had a successful singleton or twin pregnancy. The live birth rate per cycle was thus 12.8% (40 of 312), and the live birth rate per cycle with embryo transfer was 26.7% (40 of 150).

No studies were identified that specifically addressed PGT-M for evaluation of embryos in people with a history of aneuploidy in a previous pregnancy.

Section Summary

Studies have shown that PGT-M for evaluation of an embryo at identified risk of a genetic disorder or structural chromosomal abnormality is feasible and does not appear to increase the risk of obstetric complications.

Preimplantation Genetic Screening for Aneuploidy

Technology Assessments

A 2008 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) found two randomized controlled trials that assessed the use of PGT-A for embryo selection in women 35 years or older.[30] The first study reported lower pregnancy and live birth rates in the PGS group compared with the control group which did not undergo PGS, though this difference was not statistically significant (p=0.09).[31] About 25% of the embryos biopsied were genetically abnormal; therefore, fewer embryos were transferred in the PGT-A group. In the second study, which also studied women 35 years or older, Mastenbroek (2007) reported significantly lower pregnancy and live birth rates in the PGS group.[32] In this study, all women had two embryos transferred; thus, the between-group difference could not be attributed to differences in the number of transferred embryos. A 2019 comparative review by the Agency for Healthcare Research and Quality (AHRQ) states that available evidence on PGS screening for unexplained fertility is too dated to be applicable to current clinical practice.[18]

Systematic Reviews

Vitagliano (2023) published a systematic review and meta-analysis of seven studies involving 11,335 transfers of euploid embryos that compared maternal age <35 years to maternal age ≥35 years.[33] Maternal age <35 years was associated with a higher ongoing pregnancy rate or live birth rate (OR 1.29; 95% CI, 1.07-1.54; I^2 = 40%), and higher implantation rate (OR 1.22; 95% CI, 1.12-1.32; I^2=0%). The authors concluded that maternal age >35 years is associated with lower success rates for assisted reproductive technology independent of embryo ploidy.

Liang (2023) conducted a systematic review and meta-analysis focused on PGT-A outcomes after recurrent pregnancy failure (RPF).[34] RPF includes recurrent spontaneous abortion (RSA) and recurrent implantation failure (RIF). Thirteen studies were included in the analysis.

The analysis divided the overall outcomes into five groups:

- Six studies of implantation rate showed a significantly higher implantation rate after PGT-A compared to in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) (p<0.00001).
- The analysis of clinical pregnancy rate (CPR) involved 12 studies and found PGT-A was associated with higher CPR than IVF/ICSI (p<0.0001).
- Clinical miscarriage rate (CMR) was analyzed in 11 studies that found CMR was significantly lower in the PGT-A group compared to IVF/ICSI (p=0.0047).
- Four studies were included in the analysis of ongoing pregnancy rate (OPR) which found that OPR was higher in the PGT-A group than in the IVF/ICSI group (p<0.0001).
- Nine studies were included in the analysis of live birth rate (LBR) which found LBR was significantly higher in the PGT-A group compared to the IVF/ICSI group (p<0.0001).

Subgroup analysis found that when outcomes were stratified by maternal age, for both women younger than 35 years and women aged 35 and older, CPR and LBR were significantly higher in the PGT-A groups but there was no difference in clinical miscarriage rates (CMR) in either maternal age group when comparing PGT-A to IVF/ICSI.

The authors conclude that for patients with RPF, PGT-A may improve outcomes, but note that PGT-A by itself is inadequate to address RPF. The authors also note the analysis was limited

by the small number of studies, and particularly the small number of studies included in sub-group analyses.

Kasaven (2023) published a systematic review and meta-analysis comparing PGT-A to conventional morphologic assessment.[35] The primary outcomes were live birth rate (LBR) and ongoing pregnancy rate (OPR) per embryo transfer. The analysis included 16 studies of which six were randomized controlled trials (RCTs) and 10 were cohort studies. LBR was higher in both the RCTs (p=0.03) and the cohort studies (p<0.001). The OPR per embryo transfer was also higher in the PGT-A group in the RCTs (p=0.04) and in the cohort studies (p<0.001). The authors conclude that PGT-A results in higher rates of LBR and OPR than conventional morphologic assessment but acknowledge that studies comparing PGT-A to other strategies, e.g., FISH and the use of cleavage-stage biopsies, have not found that PGT-A is superior. The authors also note that PGT-A in most of the included studies was not performed for a specific indication and some studies excluded women with risk factors for unsuccessful pregnancy outcomes (e.g., diminished ovarian reserve, history of implantation failure).

Cheng (2022) published a systematic review and meta-analysis to assess whether preimplantation genetic screening for aneuploidy (PGT-A) leads to higher live-birth rates than IVF without PGT-A.[36] Nine RCTs with 3,334 participants were included. The overall live-birth rate was not significantly different (RR 1.13, 95% CI 0.96-1.34, I^2=50%). However, when stratified by maternal age, PGT-A was associated with a higher rate of live births to woman of advanced maternal age (RR 1.34, 95% CI 1.02-1.77, I^2=50), but not women of nonadvanced maternal age (RR 0.94, 95% CI 0,89-0.99, I^2=0%). Miscarriage rates were compared in eight studies. The PGT-A group experienced significantly fewer miscarriages than the control group (RR 0.53%, 95% CI 0.35-0.81, I^2=50). Other secondary outcomes; clinical pregnancy, ongoing pregnancy, multiple pregnancy, and birth weight were not significantly different. Funnel plot showed low risk of publication bias, but four of the nine studies had unclear risk of bias. The authors note the main limitation of the study is high heterogeneity (;<0.001, I^2=79%). The quality of the evidence for live births was deemed moderate.

Chromosomal mosaicism occurs when two or more distinct cell populations are present in the same embryo. Mosaicism is common, occurring in up to 80% of embryos using next generation sequencing (NGS) for PGT.[37] There have been conflicting reports of the impact of mosaicism on pregnancy outcomes, and some people have no embryos without mosaicism available for transfer. Further, healthy babies have been born after mosaic embryo transfer. [37, 38] Wang (2023) published a systematic review and meta-analysis of transfer outcomes of aneuploid mosaicism after PGT-A between 2016 and 2021 in China. [37] The authors reported institutional data from 448 women and meta-analysis was performed with data from five other studies. The focus was on the effects of aneuploid mosaicism, especially single chromosome abnormality subtypes, on reproductive outcomes. Outcomes of interest were implantation, ongoing pregnancy, and miscarriage. Implantation and clinical pregnancy rates were lower in single aneuploid embryos compared to euploid embryos for all single aneuploidy subtypes (implantation: whole chromosome loss (WCL), p<0.00001; whole chromosome gain (WCG), p=0.002; chromosome segment gain (CSG), p=0.001; chromosome segment loss (CSL), p=0.002; clinical pregnancy: WCL, p<0.00001**;** WCG, p=0.0007; CSG, p=0.0001; CSL p<0.0001). Miscarriage rates were higher with WCL (p=0.0007) and SCL (p=0.03) compared to euploid embryos, but differences in WSG (p=0.27) and CSG (p=0.22) were not significant. Maternal age >35 years was associated with lower rates of implantation and clinical pregnancy for every subtype of single aneuploid abnormality compared to euploid. However, for miscarriage, WCL was the only aneuploid subtype associated with maternal age >35 years

(p=0.0001). Maternal age ≤35 years was varied in its associations of implantation, clinical pregnancy, and miscarriage rates by single aneuploid subtype. Comparisons of mosaic ratio to euploid embryos found that higher level mosaic ratio (>30% to 60%) was associated with reduced implantation and clinical pregnancy in all aneuploid subtypes (implantation: WCG (p=0.005), WCL (p<0.00001), CSG (p=0.03) and CSL (p=0.002; clinical pregnancy: WCG (p=0.001), WCL (p<0.00001), CSG (p=0.009), and CSL (p<0.0001). WCL was associated with increased miscarriage rates at both lower-level (≤30%) and higher-level mosaic ratios (higher level, p=0.04; lower level, p=0.007). Bias was not addressed in the meta-analysis. The authors did not address limitations of the study.

Using three of the same studies as Wang (2023), Ma (2022) performed a systematic review and meta-analysis focused on pregnancy outcomes after mosaic embryo transfers.[38]. Twelve studies were included in the systematic review and six of those were included in the meta-analysis. The six studies involved 1106 transfer cycles. Three studies used NGS platforms for PGT, two used array comparative genome hybridization (cCGH), and one reported on a combination of NGS and cCGH data. Comparison of mosaicism level <50% to ≥50% found improved rates of implementation and fewer miscarriages at mosaicism levels <50% [Implementation: OR 1.42, 95% CI (1.06, 1.89); Miscarriage: OR 0.45, 95% CI (027, 0.75)]. There was no significant difference between embryos with one mosaic chromosome compared to two, but embryos with three or more mosaic chromosomes had worse outcomes than embryos with single chromosome mosaicism [Implementation rate: OR 1.76, 95% CI (1.23, 2.52) Miscarriage rate: OR 0.78, 95% CI (0.40, 1.54)]. The authors suggest a 50% mosaicism threshold for embryo transfer. Strengths of the study include low heterogeneity (I^2>50%). The authors note limitations of the study include the lack of prospective studies, and variety of genetic screening platforms involved. Importantly, they point out that there is little information on the children that result from mosaic chromosome transfer. Neither Wang (2023) nor Ma (2022) compare universal screening for PGT-A to no screening, or to screening based on risk factors, such as advanced maternal age.

A number of RCTs evaluating PGS (PGT-A) have been published, and these findings have been summarized in a several systematic reviews and meta-analyses.[39-44] One of the most recent and comprehensive meta-analysis was a Cochrane review published by Cornelisse (2020), which included 13 RCTs involving 2,794 women.[39] The quality of the included trials ranged from low to moderate, and the main limitations were reported to be imprecision, inconsistency, and risk of publication bias. One study by Verpoest (2018, described below) compared PGT-A with the use of aCGH to no PGT-A,[45] while another, by Munné (2019, described below) compared PGT-A with the use of NGS–based genome-wide analyses to no PGT-A.[46] The other studies compared PGT-A with FISH to no PGT-A. The review concluded that there was “insufficient good-quality evidence of a difference in cumulative live birth rate, live birth rate after the first embryo transfer, or miscarriage rate between IVF with and IVF without PGT-A as currently performed.” The authors noted that the use of FISH for the PGT-A genetic analysis is outdated and probably harmful.

A systematic review and meta-analysis by Shi (2021) evaluated PGS specifically in the setting of advanced maternal age, with a comparison between FISH and newer technologies. The meta-analysis included nine RCTs, six of which had high or unclear risk of bias in at least one domain. These studies had differing definitions of advanced maternal age, which generally ranged from 35 to 44 years of age. The pooled analysis of all nine trials showed no difference in live birth rate (risk ratio [RR] 1.01, 95% CI 0.75 to 1.35), though an analysis restricted to the three studies that used comprehensive chromosome screening technology, including real-time

qPCR, aCGH, and NGS, found a higher birth rate in those randomized to PGS (RR 1.30, 95% CI 1.03 to 1.65).

In meta-analysis limited to PGT-A with comprehensive chromosomal screening conducted on day 3 or day 5, Simopoulou (2021) identified 11 RCTs.[47] In the overall population PGT-A did not improve live birth rates (RR 1.11; 95% CI, 0.87 to 1.42; 6 trials; n=1513; I^2=75%). However, in a subgroup of patients over 35 years of age, live birth rates improved with PGT-A (RR 1.29; 95% CI, 1.05 to 1.60; 4 trials; n=629). Clinical pregnancy rates were also not significantly improved in the overall population (RR 1.14; 95% CI, 0.95 to 1.37; 9 trials; n=1824); however, miscarriage rates were improved with PGT-A (RR 0.36; 95% CI, 0.17 to 0.73; 7 trials; n=912). The authors concluded that PGT-A with comprehensive chromosomal screening did not generally improve outcomes, but when performed on blastocyst stage embryos in women over 35 years of age live birth rates were improved.

Randomized Controlled Trials

A randomized trial by Yan (2021) evaluated the impact of PGT-A on live birth rate in subfertile women between 20 and 37 years of age.[48] The trial included 1,212 patients who were considered to have a “good prognosis for a live birth,” were planning to undergo their first IVF cycle, and had at least three good-quality blastocysts. The patients were randomized 1:1 to receive PGS or standard IVF, and the primary outcome was live births within one year of randomization from up to three embryo transfers. The proportion of patients with the primary outcome was 77.2% (468) in the PGS group and 81.8% (496) in the control group, which met the prespecified noninferiority margin of a 7% difference.

Munné (2019) published the results of a multi-center RCT called the Single Embryo Transfer of Euploid Embryo (STAR) study.[46] The study reported similar (50.0% versus 45.7%) ongoing pregnancy rates (≥ 20 weeks gestation) for NGS-based PGS versus morphology in good-prognosis patients aged 25 to 40 years. In the subgroup of 267 women aged 35 to 40 years, NGS-based PGS improved ongoing pregnancy rates (50.8% versus 37.2%, p=0.0349).

A multi-center trial by Verpoest (2018) evaluated prenatal screening for aneuploidy for women between 36 and 40 years of age.[45] A total of 396 women undergoing ICSI treatment were randomized to either receive PGS or conventional ICSI without screening. There were no significant differences between groups for clinical pregnancy or live birth rates. However, the PGS group had reduced rates of transfer (RR 0.81, 95% CI 0.74 to 0.89, p<0.001) and miscarriage (RR 0.48, 95% CI 0.26 to 0.90, p=0.02).

Rubio (2017) published a randomized trial comparing outcomes in women of advanced maternal age who underwent PGS for aneuploidy prior to blastocyst transfer compared with blastocyst transfer without PGS.[49] The trial included women between 38 and 41 years of age with normal karyotypes who were on their first or second cycle of ICSI. A total of 138 patients were randomized to the PGS group and 140 to the non-PGS control group. Of these, 100 patients in the PGS group and 105 in the non-PGS group completed the intervention. In an intention-to-treat analysis, there was a significantly higher live birth rate in the PGS group (31.9%) than in the control group (18.6%, odds ratio [OR] 2.4, 95% CI 1.3 to 4.2, p=0.003). In the per-protocol analysis, there was a significantly higher rate of live birth in the PGS group than in the control group, both in the per transfer and per patient analyses. Per transfer, there were live births in 65% of the PGS group and 27% of the control group (OR 4.86, 95% CI 2.49 to 9.53, p<0.001). Per patient, there were live births in 44% of the PGS group and 25% of the control group (OR 2.39, 95% CI 1.32 to 4.32, p=0.005). In addition, the implantation was

significantly higher in the PGS group (53%) than in the control group (43%, p<0.001) and the miscarriage rate was significantly lower in the PGS group (3%) than in the control group (39%, p=0.007).

Yang (2015) performed a two-phase pilot study that randomly compared next-generation sequencing (NGS) and aCGH for preimplantation genetic screening.[50] Phase I retrospectively evaluated the accuracy of NGS for aneuploidy screening in comparison to aCGH from previous IVF-PGS cycles (n=38). Phase II compared clinical pregnancy and implantation outcomes between NGS and aCGH for 172 IVF-PGS patients randomized into two groups: 1) NGS (Group A): patients (n=86) had embryos screened with NGS and 2) aCGH (Group B): patients (n=86) had embryos screened with aCGH. The investigators reported that in phase I, NGS detected all types of aneuploidies of human blastocysts accurately and provided a 100 % 24-chromosome diagnosis consistency with the highly validated aCGH method. In phase II, NGS screening resulted in similarly high ongoing pregnancy rates for PGS patients compared to aCGH screening (74.7% vs. 69.2%, respectively, p=0.56). The observed implantation rates were also comparable between the NGS and aCGH groups (70.5% vs. 66.2%, respectively, p=0.564). The investigators acknowledged that the improved pregnancy rates achieved in this study may not be applied to all IVF-PGS patients, especially those at advanced maternal age or with diminished ovarian reserve.

An RCT by Scott (2013) compared sustained implantation and delivery rates in pregnant females between the ages of 21 and 42 years who had blastocysts tested by real-time polymerase chain reaction-based comprehensive chromosome screening (CCS) versus no screening (routine care group).[51] In the CCS intervention group (n=72 patients) 134 blastocysts were transferred, while in the routine care group (n=83), 163 blastocysts were transferred. Sustained implantation rates (probability that an embryo will implant and progress to delivery) were statistically significantly higher in the CCS group compared with those from the routine care group (89/134, 66.4% vs. 78/163, 47.9%, p=0.002). However, the embryologists were not blinded to the CCS results, potentially inflating the implantation rates in the CCS group. Delivery rates per cycle were also statistically significantly higher in the CCS group (61/72, [84.7%] vs. 56/83 [67.5%], p=0.001).

Forman (2013) performed a randomized trial to compare ongoing pregnant and multiple gestation rates in in pregnant women under the age of 43 who had blastocysts tested by qPCR-based comprehensive chromosome screening (CCS) versus no screening.[52] The intervention group (n=89) had all viable blastocysts biopsied for CCS and single euploid blastocyst transfer, while the control group (n=86) had their two best-quality, untested blastocysts transferred. Implantation rates were 60.7% in the intervention group and 65.1% in the control group. The rate appeared lower in the intervention group, but this was considered “noninferior.” The authors used a 20% noninferiority margin which may not be the most appropriate approach to evaluating the impact of PGS-v2 on health outcomes. The investigators noted that this study only focused on patients with good prognoses, meaning good responders with normal markers of ovarian reserve and large oocyte yields and an abundance of embryos to evaluate. Further prospective studies will be required to validate the best way to apply CCS in women who are low responders or who have other abnormal markers of ovarian reserve.

Schendelaar (2013) reported on outcomes when children were four years old. Data were available on 49 children (31 singletons, nine sets of twins) born after IVF with PGS and 64 children (42 singletons, 11 sets of twins) born after IVF without PGS.[53] The primary outcome

of this analysis was the child's neurological condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15 and is a sub-scale of the neurological optimality score. In the sample as a whole, and among singletons, the fluency score did not differ among children in the PGS and non-PGS groups. However, among twins, the fluency score was significantly lower among those in the PGS group (mean score 10.6, 95% CI 9.8 to 11.3) than those in the non-PGS group (mean score: 12.3, 95% CI 11.5 to 13.1). Cognitive development as measured by IQ score and behavioral development as measured by the total problem score were similar between non-PGS and PGS groups.

Rubio (2013) published findings of two RCTs evaluating PGS.[54] Studies designs were similar but one included women of advanced maternal age (41 to 44 years old) and the other included couples under 40 years old with repetitive implantation failure (RIF), defined as failing three or more previous attempts at implantation. All couples were infertile and did not have a history of pregnancy or miscarriage with chromosomal abnormality. In all cases, blastocysts were transferred at day five. In the groups receiving PGS, single-cell biopsies were done at the cleavage stage. A total of 91 patients enrolled in the RIF study (48 in the PGS group and 43 in the non-PGS group) and 183 patients in the advanced maternal age study (93 patients in the PGS group and 90 patients in the non-PGS group). Among RIF patients, the live birth rate did not differ significantly between groups. Twenty-three of 48 patients (48%) in the PGS group and 12 of 43 patients (28%) in the non-PGS groups had live births. (The exact p-value was not provided). However, the live birth rate was significantly higher with PGS in the advanced maternal age study. Thirty of 93 patients (32%) in the PGS group and 14 of 90 patients (16%) in the non-PGS group had live births: The difference between groups was statistically significant (p=0.001).

Yang (2012) performed a pilot study to assess embryos selected on the basis of morphology and comprehensive chromosomal screening via aCGH compared to embryos selected by morphology only.[55] Fifty five patients (n=425 blastocysts) were biopsied and analyzed via aCGH, and 48 patients (n=389 blastocysts) were examined by microscopy only. Clinical pregnancy rate and ongoing pregnancy rate were significantly higher in the aCGH group compared to the morphology-only group (70.9% vs. 45.8%, p=0.017) and (69.1% vs. 41.7%, p=0.009), respectively. Aneuploidy was detected in 191/425 (44.9%) of blastocysts in the aCGH group, highlighting the imprecision of the morphology-only group.

Nonrandomized Studies

There have been many nonrandomized studies of PGS, however, the conclusions that can be drawn from these are limited by study design and they are not discussed in detail.[24, 32, 56-61]

Section Summary

Most RCTs and meta-analyses of RCTs of initial techniques used for PGT-A found similar or lower ongoing pregnancy and/or live birth rates after IVF with PGT-A compared with IVF without PGT-A. These initial PGT-A tests were not found to improve the net health outcome. Three RCTs evaluating newer PGT-A methods have been published, as well as systematic reviews of these trials. Recent studies of newer methods have found some benefit in subgroups of patients (e.g., advanced maternal age); however, the evidence is limited because the studies tended to include good prognosis patients and study methods had potential biases. Well-conducted RCTs evaluating PGT-A in the target population (e.g., women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued Committee Opinion #799 on Preimplantation Genetic Testing.[62] Recommendations are as follows:

- "Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic (known as PGT-M) is targeted to single gene disorders. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered."
- "To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements (known as PGT-SR) is used. Confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered."
- "The main purpose of preimplantation genetic testing-aneuploidy (known as PGT-A) is to screen embryos for whole chromosome abnormalities. Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients."

In 2015 (reaffirmed in 2017), ACOG issued an opinion statement that recommends “[p]atients with established causative mutations for a genetic condition” who are undergoing in vitro fertilization and desire prenatal genetic testing should be offered the testing, either preimplantation or once pregnancy is established.[63]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2023, the American Society for Reproductive Medicine published a joint practice committee opinion with the Genetic Counseling Professional Group on the clinical management of mosaic results from preimplantation genetic testing for aneuploidy of blastocysts, which states:[64]

> The value of preimplantation genetic testing for aneuploidy (PGT-A) as a universal screening test for all patients undergoing in vitro fertilization (IVF) has not been established. Indeed, two randomized controlled trials have shown no benefit of PGT-A in improving live birth rates, particularly in women <38 years of age. Nonetheless, the use of PGT-A has continued to increase in the US. In particular, the significance of suspected chromosomal mosaicism in embryos has been a widely discussed and controversial topic since the first known live births from these embryos were documented in 2015. Although previous interpretations of mosaic results and patient counseling relied heavily on prenatal and pediatric literature about mosaicism, a growing body of evidence suggests that these data may not apply to preimplantation embryos.

The committee opinion also states:

> True embryonic mosaicism has long been recognized as a potential limiting factor in the interpretation of PGT-A and as a contributing factor in misdiagnosis related to biopsy

sample size. Suspected mosaicism has typically gone undetected or unreported with prior methods of PGT-A, such as fluorescent in situ hybridization, which tested single cells, and array comparative genomic hybridization, as well as the single nucleotide polymorphism microarray (currently in use). With more recent and sensitive assays, such as NGS, it has become increasingly common to identify and report results consistent with an intermediate copy number. Further, the opinion states, "The frequency and clinical relevance of mosaicism have been the subject of much debate."

Also in 2023, the American Society of Reproductive Medicine published a committee opinion; The Indications and Management of Preimplantation Genetic Testing for Monogenic Conditions:[65]

- Preimplantation genetic testing for monogenic conditions should be offered if a significant reproductive risk is identified. Acceptance of PGT-M by patients should be optional.
- Preimplantation genetic testing should not be offered for autosomal recessive carrier status without manifestations of symptoms, combination of variants not associated with disease, pseudodeficiency alleles, or somatic-only variants.
- Patients should have genetic counseling about the condition and all reproductive options before PGT-M is performed.
- Patients may also benefit from genetic counseling about PGT-M results, particularly when making embryo transfer decisions.
- Given technical limitations that may result in embryo misdiagnosis, prenatal testing should be offered for pregnancies conceived using PGT-M to confirm the embryo testing results and screen for other fetal anomalies unrelated to the indication for PGT-M.
- Although PGT laboratory genetic counselors support providers and patients in the PGT-M process, IVF clinics should consider employing genetic counselors to result in smoother case management, more efficient workflows, and improved patient experiences.

A 2018 practice committee opinion on preimplantation screening for aneuploidy issued by the American Society for Reproductive Medicine concluded the following:[66]

> The value of PGT-A as a universal screening test for all IVF patients has yet to be determined. While research suggests improved outcomes from PGT-A screening, the available evidence has important limitations. Participants in RCTs likely do not accurately represent the patient population that would be affected by broadly applied PGT-A screening. Large, prospective, well-controlled trials are needed to determine the effectiveness and safety of universal PGT-A screening.

SUMMARY

There is enough research to show that preimplantation genetic testing for monogenic disorders (PGT-M) and structural chromosomal rearrangements (PGT-SR) leads to improved health outcomes (e.g., birth of unaffected fetuses) when used for evaluation of an

embryo that is known to be at elevated risk of a genetic disorder or structural chromosomal abnormality. Therefore, PGT-M and PGT-SR may be considered medically necessary when the evaluation is focused on an elevated risk for a known disease or disorder and the policy criteria are met.

There is not enough research to show that preimplantation genetic testing for monogenic disorders (PGT-M) or structural rearrangements (PGT-SR) leads to improved health outcomes for the evaluation of an embryo without an elevated risk or in all other situations not outlined in the medically necessary policy criteria. More research is needed to know if or how well PGT-M and PGT-SR will impact outcomes in these situations. Therefore, PGT-M and PGT-SR are considered investigational when the policy criteria are not met.

There is not enough research to show that preimplantation genetic testing for aneuploidy (PGT-A) improves health outcomes, including pregnancy and live birth rates. Recent studies of newer methods have found some benefit in subgroups of patients (e.g., advanced maternal age); however, the evidence is limited, and larger trials are needed to understand how to use the information on ploidy PGT-A provides to improve patient outcomes. Therefore, preimplantation genetic testing for aneuploidy as a part of the in vitro fertilization process is considered investigational in all situations.

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CODES

Codes	Number	Description
		Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo
	~~0396U~~	~~Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions~~ (Deleted 10/01/2024)
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis

Codes	Number	Description
	81479	Unlisted molecular pathology procedure
	88271 – 88275	Molecular cytogenetics (i.e., FISH), code range
	89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis), less than or equal to 5 embryo(s)
	89291	;greater than 5 embryo(s)
HCPCS	None	

Date of Origin: *August 2010*

Regence

Medical Policy Manual Genetic Testing, Policy No. 19

IDH1 and IDH2 Genetic Testing for Conditions Other Than Myeloid Neoplasms or Leukemia

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

Isocitrate dehydrogenase genes, *IDH1* and *IDH2*, are involved in cellular metabolism and epigenetic regulation. These genes are defining features in classifying primary brain tumors and are proposed as diagnostic and prognostic indicators for a number of other cancers.

MEDICAL POLICY CRITERIA

Notes:

- This policy does *not* address *IDH1* and *IDH2* testing for myeloid neoplasms or leukemia which is addressed in a separate policy.
- Please refer to the Cross References section below for genetic testing not addressed in this policy.

I. Genetic testing for *IDH1* and *IDH2* variants may be considered **medically necessary** for patients with gliomas of any grade (Note: gliomas include, but are not limited to astrocytoma, ependymoma, and oligodendroglioma).

II. Genetic testing for *IDH1* variants may be considered **medically necessary** for patients with cholangiocarcinoma who are considering treatment with ivosidenib (Tibsovo®).

III. Genetic testing for *IDH1* and *IDH2* variants is considered **investigational** for all other circumstances, including but not limited to chondrosarcoma and colorectal cancer.

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

POLICY GUIDELINES

GLIOMAS

Gliomas are the most common types of brain tumors, and are named for their origin (i.e., the tumor begins in cells called glial cells, which surround nerve cells). The three major types of glioma include:

- Astrocytoma,
- Ependymomas, and
- Oligodendrogliomas.

Initial workup will include radiologic evaluation, wherein a tumor may be initially stratified as a high- or low-grade glioma. Further workup, including genetic molecular studies will further classify the tumor.

GENETIC TESTING

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

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:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any
   - Sample collection date

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing Policy No. 59
3. Medication Policy Manual, Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

ISOCITRATE DEHYDROGENASE

Isocitrate dehydrogenase (IDH) genes encode IDH proteins which are homodimeric enzymes involved in numerous cellular processes, including adaptation to hypoxia, histone demethylation and DNA modification. In humans, IDH exists in three isoforms. IDH3 is a catalyst in the citric acid cycle, converting NAD^+ to NADH in mitochondria. IDH1 and IDH2 catalyze the same reaction outside the citric acid cycle and are associated with the formation of (D)-2-hydroxyglutarate. High concentrations of (D)-2-hydroxyglutarate inhibits the function of other enzymes, causing differentiated gene expression which ultimately may lead to activated oncogenes and inactivated tumor-suppressor genes. This cascade effect may ultimately develop into cancer.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

The 2016 World Health Organization Classification of Tumors of the Central Nervous System presented a major restructuring of CNS tumor categorization.[1] Specifically, diffuse gliomas, medulloblastomas and other embryonal tumors were better defined by a combination of histologic and molecular features. As of this update, diagnostic criteria heavily rely on IDH gene status. The combined genotypic and phenotypic approach improves the diagnostic process compared to previous versions by inclusion of the objective utilization of genotyping. Potential for discordance is increased with this approach, e.g., tumors that histologically appear astrocytic are proven to have an IDH mutation, however, according to the criteria, genotype trumps phenotype in these situations. Tumors of the CNS are hence designated by their histological name followed by a comma, and the genetic features as adjectives, as in: *Diffuse astrocytoma, IDH-wildtype*.

REGULATORY STATUS

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for genetic testing related to *IDH1* and *IDH2*. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of Clinical Laboratory Improvement Act (CLIA) and laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA does not require regulatory review of LDTs.

For *IDH1* and *IDH2* testing related to treatment with Tibsovo® (ivosidenib) and Idhifa® (enasidenib) for hematologic disorders, please refer to Genetic Testing for Myeloid Neoplasms and Leukemia in the Cross References section, above.

EVIDENCE SUMMARY

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in DNA and serves as an international standard.[2] It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used

terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

SCOPE OF THIS REVIEW

The clinical utility of testing for variants in the *IDH1* and *IDH2* genes to inform the combined process of phenotypic and genotypic classification for the diagnosis of glioma brain tumors has been unequivocally demonstrated. These molecular markers also inform prognosis and treatment selection for the management of gliomas. Therefore, the scientific evidence for the clinical utility of *IDH1* and *IDH2* related to gliomas will not be included, as testing may be considered medically necessary.

Validation of the clinical use of any genetic test focuses on three main principles: 1) The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent; 2) The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and 3) The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

SYSTEMATIC REVIEWS

No systematic reviews regarding IDH genes within the scope of this review were identified.

RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials regarding IDH genes within the scope of this review were identified.

NONRANDOMIZED STUDIES

Associations between *IDH1* and *IDH2* variants are being investigated for potential diagnostic and prognostic significance in several other cancers, including but not limited to: chondrosarcoma[3-8], and colorectal cancer[9]. Although *IDH1* and *IDH2* variants may be present in approximately half of chondrosarcoma cases, the evidence for clinical utility regarding these markers for the many conditions is uncertain. Reported associations are typically in small case series or cohorts, demonstrating potential targets for additional investigation in larger, well-designed studies.

PRACTICE GUIDELINE SUMMARY

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for central nervous system cancers (v.1.2023) are consistent with World Health Organization diagnostic criteria, and

recommend ivosidenib for certain gliomas with an *IDH1* variant.[10]

NCCN guidelines for bone cancers (v.1.2024) list ivosidenib as a treatment option for *IDH1*-mutated chondrosarcoma,[11] however this medication is only FDA approved for acute myeloid leukemia and cholangiocarcinoma. Other guidelines based on research regarding *IDH1* and *IDH2* genetic testing were not identified.

SUMMARY

There is enough research to show that genetic testing for *IDH1* and *IDH2* contributes to diagnoses and risk stratification in people with gliomas, which contributes to improved overall health outcomes. Therefore, genetic testing for *IDH1* and *IDH2* variants may be considered medically necessary for gliomas of any grade (including but not limited to astrocytoma and glioblastoma).

There is enough research to show that genetic testing for *IDH1* can be used to identify patients with cholangiocarcinoma that may be eligible for treatment with ivosidenib, has been FDA-approved for the treatment of this disease. Therefore, genetic testing for *IDH1* variants may be considered medically necessary for patients with cholangiocarcinoma considering this treatment.

There is not enough research to show that genetic testing for *IDH1* and *IDH2* variants improves overall health outcomes in any other condition. Therefore, genetic testing for *IDH1* and *IDH2* variants is considered investigational for all other circumstances, including but not limited evaluation for chondrosarcoma and colorectal cancers.

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11. National Comprehensive Cancer Network (NCCN) Guidelines. Bone Cancer. [cited 1/30/2024]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/bone_blocks.pdf.

CODES

Codes	Number	Description
CPT	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
HCPCS	None	

Date of Origin: *May 2010*

Regence

Medical Policy Manual Genetic Testing, Policy No. 20

Genetic and Molecular Diagnostic Testing

Effective: May 1, 2024

Next Review: February 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

Genetic testing, which detects changes in DNA, RNA, and chromosomes, may be performed to diagnose or determine susceptibility to inherited conditions, screen for potential genetic risk factors for common conditions, and aid in the selection of medications or other treatments.

MEDICAL POLICY CRITERIA

Note: This policy only applies when there is not a more specific medical policy available (see the Genetic Testing Section of the Medical Policy Manual). This policy is not intended to address asymptomatic carrier screening, which is addressed in the Carrier Screening for Genetic Diseases policy (Genetic Testing, Policy No. 81).

The following general criteria are applied to genetic and molecular diagnostic testing.

I. Genetic testing to establish a diagnosis or susceptibility for an inherited disease may be considered **medically necessary** when *all* of the following criteria are met:

   A. The genetic test is not a panel test listed in Genetic Testing Policy No. 64, *Evaluating the Utility of Genetic Panels*, as these tests are always investigational. Genetic panel tests that are not listed in GT64 or addressed by another specific policy will be reviewed by the criteria below.

B. There must be a reasonable expectation based on family history (pedigree analysis), risk factors, and symptomatology that a genetically inherited condition exists.

C. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain.

D. The clinical utility of all requested genes and gene variants must be established (including all genes and gene variants in a panel test, as applicable). The clinical records must document:

1. How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnoses, and
2. These treatment decisions would not otherwise be made in the absence of the genetic test results.

II. Genetic testing to establish a diagnosis or susceptibility for an inherited disease is considered **not medically necessary** if Criterion I. above is not met.

III. Genetic testing of children to predict adult-onset diseases is considered **not medically necessary** unless test results will guide current decisions concerning prevention and this benefit would be lost by waiting until the child has reached adulthood.

IV. Genetic testing for indications *other than* determining risk or establishing a diagnosis for a genetically inherited disease (e.g., genotyping for drug selection and dosing) may be considered **medically necessary** when *all* of the following criteria are met:

A. The genetic test is not a panel test listed in Genetic Testing Policy No. 64, *Evaluating the Utility of Genetic Panels*, as these tests are always investigational. Genetic panel tests that are not listed in GT64 or addressed by another specific policy will be reviewed by the criteria below.

B. Diagnostic results from physical examination and conventional testing are inconclusive; and

C. The clinical records document how results of genetic testing are necessary to guide treatment decisions; and

D. There is reliable evidence in the peer-reviewed scientific literature that health outcomes are improved as a result of treatment decisions based on molecular genetic test results.

V. Genetic testing for indications other than determining risk or establishing a diagnosis for a genetically inherited disease is considered **not medically necessary** if any of criteria IV. A.-D. above are not met.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), <u>all of the following information must be submitted for review</u>:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)

3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
    - History and physical exam
    - Date of sample collection (e.g., blood draw)
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.
2. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

GENETIC TESTING

Genetic testing may be performed for several different purposes, including:

- Diagnosing or predicting susceptibility for inherited conditions[1]
- Screening for common disorders
- Selecting appropriate treatments (also known as pharmacogenetic testing)

GENETIC PANEL TESTING

New genetic technology, such as next generation sequencing and chromosomal microarray, has led to the ability to examine many genes simultaneously.[2] This in turn has resulted in a proliferation of genetic panels. Panels using next generation technology are intuitively attractive to use in clinical care because they can screen for numerous variants within a single gene or multiple genes quickly and may lead to greater efficiency in the work-up of genetic disorders. One potential challenge of genetic panel testing is the identification of genetic variants of unknown significance and variants for which the clinical management is uncertain and may lead to unnecessary follow-up testing and procedures.

GENETIC COUNSELING

Due to the complexity of interpreting genetic test results, patients should receive pre- and post-test genetic counseling from a qualified professional when testing is performed to diagnose or predict susceptibility for inherited diseases. The benefits and risks of genetic testing should be fully disclosed to individuals prior to testing, and counseling concerning the test results should be provided.

REGULATORY STATUS

The majority of genetic tests and genetic panel tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval.[3] The degree of oversight by the FDA depends on the intended use of the test and risk of inaccurate results. Clinical laboratories may develop and validate tests in-house (“lab-developed tests”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical

Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Note: Separate Medical Policies may apply to some specific genetic tests and panels. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.

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3. National Institutes of Health. Regulation of Genetic Tests. [cited 03/08/2024]. 'Available from:' http://www.genome.gov/10002335.

CODES

NOTE: If the specific analyte (gene or gene variant) is listed with a CPT code, the specific CPT code should be reported. If the specific analyte is not listed with a specific CPT code, unlisted code 81479 should be reported.

Codes	Number	Description
	0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue

Codes	Number	Description
	81105 – 81112	HPA genotyping code range
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81200 – 81257	Molecular pathology code range
	81260 – 81268	Molecular pathology code range
	81270 – 81276	Molecular pathology code range
	81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
	81290 – 81300	Molecular pathology code range
	81302 – 81304	Molecular pathology code range
	81310 – 81332	Molecular pathology code range
	81336 – 81355	Molecular pathology code range
	81370 - 81408	Molecular pathology code range
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
	81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromicXLID); genomic sequence analysis panel, must include sequencing of at least60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1,IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3,and SLC16A2
	81471	;duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81479	Unlisted molecular pathology procedure
HCPCS	G0452	Molecular pathology procedure; physician interpretation and report
	S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)

Codes	Number	Description
	S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
	S3841	Genetic testing for retinoblastoma
	S3842	Genetic testing for Von Hippel-Lindau disease
	S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
	S3845	Genetic testing for alpha thalassemia
	S3846	Genetic testing for hemoglobin E beta-thalassemia
	S3849	Genetic testing for Niemann-Pick disease
	S3850	Genetic testing for sickle cell anemia
	S3853	Genetic testing for muscular dystrophy
	S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome
	S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
	S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

Date of Origin: *September 1999*

Regence

Medical Policy Manual Genetic Testing, Policy No. 21

Genetic Testing for Biallelic RPE65 Variant-Associated Retinal Dystrophy

Effective: June 1, 2024

Next Review: February 2025
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

RPE65 genetic testing can be used to predict treatment response to targeted therapy in patients with biallelic RPE65 variant-associated retinal dystrophy.

MEDICAL POLICY CRITERIA

I. Genetic testing for the *RPE65* variant may be considered **medically necessary** to confirm a diagnosis of biallelic *RPE65* variant-associated retinal dystrophy when Luxturna (voretigene neparvovec-rzyl) is being considered as a treatment option.

II. Genetic testing for the *RPE65* variant is considered **investigational** for all other indications.

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

POLICY GUIDELINES

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

Diagnosis of Biallelic *RPE65*-Mediated Inherited Retinal Dystrophies

Genetic testing is required to detect the presence of pathogenic(s) variants in the *RPE65* gene. By definition, pathogenic variant(s) must be present in both copies of the *RPE65* gene to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy.

A single *RPE65* pathogenic variant found in the homozygous state (e.g., the presence of the same pathogenic variant in both copies alleles of the *RPE65* gene) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy.

However, if two different *RPE65* pathogenic variants are detected (e.g., compound heterozygous state), confirmatory testing such as linkage analysis by family studies may be required to determine the *trans* vs *cis* configuration (e.g., whether the two different pathogenic variants are found in different copies or in the same copy of the *RPE65* gene). The presence of two different *RPE65* pathogenic variants in separate copies of the *RPE65* gene (*trans* configuration) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy. The presence of two different *RPE65* pathogenic variants in only one copy of the *RPE65* gene (*cis* configuration) is not considered a biallelic *RPE65*-mediated dystrophinopathy.

Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (e.g., *trans* vs *cis* configuration) when two *RPE65* pathogenic variants are detected. In this scenario, additional documentation of the *trans* configuration is required to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy.

REGULATORY STATUS

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna™; Spark Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) for use in patients with vision loss due to confirmed biallelic *RPE65* variant-associated retinal dystrophy. Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - o History and physical exam including any relevant diagnoses related to the genetic testing
    - o Conventional testing and outcomes
    - o Conservative treatments, if any

CROSS REFERENCES

None

BACKGROUND

INHERITED RETINAL DYSTROPHIES

Inherited retinal dystrophies (IRDs) are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina[1]. The most common subgroup is retinitis pigmentosa, which is characterized by a loss of retinal photoreceptors, both cones and rods. The hallmark of the condition is night blindness (nyctalopia) and loss of peripheral vision. These losses lead to difficulties in performing visually dependent activities of daily living such as orientation and navigation in dimly lit areas. Visual acuity may be maintained longer than peripheral vision, though eventually most individuals progress to vision loss.

RPE65 Gene

Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in *RPE65*. *RPE65* (retinal pigment epithelium–specific protein 65-kD) gene encodes the RPE54 protein is an all-*trans* retinal isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-*cis*-retinol in the visual cycle[2]. The *RPE65* gene is located on the short (p) arm of chromosome 1 at position 31.3 (1p31.3). Individuals with biallelic variations in *RPE65* lack the RPE65 enzyme; this lack leads to build-up of toxic precursors and damage to RPE cells, loss of photoreceptors, and eventually complete blindness[3].

Epidemiology

RPE65-associated IRD is rare. The prevalence of LCA has been estimated to be between 1 in 33,000 and 1 in 81,000 individuals in the United States[4, 5]. LCA subtype 2 (*RPE65*-associated LCA) accounts for between 5% and 16% of cases of LCA4[6-8]. The prevalence of RP in the United States is approximately 1 in 3500 to 1 in 4000 with approximately 1% of patients with RP having *RPE65* variants[9, 10]. Assuming a U.S. population of approximately 326.4 million at the end of 2017, the prevalence of *RPE65*-associated retinal dystrophies in the United States would therefore be roughly 1000 to 3000 individuals[11].

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

LITERATURE REVIEWS AND SUMMARY OF THE EVIDENCE TO SUPPORT OUR POSITION

Systematic Reviews

There are no systematic reviews for this indication.

Randomized Controlled Trials

One gene therapy (voretigene neparvovec) for patients with biallelic *RPE65* variant-associated retinal dystrophy has RCT evidence. The pivotal RCT (NCT00999609) for voretigene neparvovec was an open-label trial of patients ages three or older with biallelic *RPE65* variants, VA worse than 20/60, and/or a VF less than 20o in any meridian, with sufficient viable retinal cells[13, 14]. Those patients meeting these criteria were randomized 2:1 to intervention (n=21) or control (n=10). The trial was conducted at a children's hospital and university medical center. Patients were enrolled between 2012 and 2013. The intervention treatment group received sequential injections of 1.5E11 vg AAV2-hRPE65v2 (voretigene neparvovec) to each eye no more than 18 days apart (target, 12 days; standard deviation [SD], 6 days). The injections were delivered in a total subretinal volume of 0.3 mL under general anesthesia. The control treatment group received voretigene neparvovec one year after the baseline evaluation. Patients received prednisone 1 mg/kg/d (max, 40 mg/d) for seven days starting three days before injection in the first eye and tapered until three days before injection of the second eye at which point the steroid regimen was repeated. During the first year, follow-up visits occurred at 30, 90, 180 days, and one year. Extended follow-up is planned for 15 years. The efficacy outcomes were compared at 1 year. The primary outcome was the difference in mean bilateral MLMT score change. MLMT graders were masked to treatment group. The trial was powered to have greater than 90% power to detect a difference of one light level in the MLMT score at a two-sided type I error rate of 5%. Secondary outcomes were hierarchically ranked: (1) difference in change in full-field light sensitivity threshold (FST) testing averaged over both eyes for white light; (2) difference in change in monocular (first eye) MLMT score change; (3) difference in change in VA averaged over both eyes. Patient-reported vision-related activities of daily living (ADLs) using a Visual Function Questionnaire (VFQ) and VF testing (Humphrey and Goldmann) were also reported. The VFQ has not been validated.

At baseline, the mean age was about 15 years old (range, 4-44 years) and approximately 42% of the participants were male. The MLMT passing level differed between the groups at baseline; about 60% passed at less than 125 lux in the intervention group vs 40% in the control group. The mean baseline VA was not reported but appears to have been between approximately 20/200 and 20/250 based on a figure in the manufacturer briefing document. One patient in each treatment group withdrew before the year one visit; neither received voretigene neparvovec. The remaining 20 patients in the intervention treatment and nine patients in the control treatment groups completed the year one study visit. The intention-to-treat (ITT) population included all randomized patients. The efficacy outcome results at year one for the ITT population are shown in Table 3. In summary, the differences in change in MLMT and FST scores were statistically significant. No patients in the intervention group had worsening MLMT scores at one year compared with three patients in the control group. Almost two-thirds of the intervention arm showed maximal improvement in MLMT scores (passing at one lux) while no participants in the control arm were able to do so. Significant improvements were also observed in Goldmann III4e and Humphrey static perimetry macular threshold VF exams. The difference in change in VA was not statistically significant although the changes correspond to an improvement of about eight letters in the intervention group and a loss of one letter in the control group. The original VA analysis used the Holladay method to assign values to off-chart results. Using, instead the Lange method for off-chart results, the treatment effect estimate was similar but variability estimates were reduced (difference in change, 7.4 letters; 95% confidence interval [CI], 0.1 to 14.6 letters). No control patients experienced a gain of 15

or more letters (≤0.3 logMAR) at year one while 6 of 20 patients in the intervention group gained 15 or more letters in the first eye and four patients also experienced this improvement in the second eye. Contrast sensitivity data were collected but were not reported.

The manufacturer briefing document reports results out to two years of follow-up21. In the intervention group, both functional vision and visual function improvements were observed for at least two years. At year one, all 9 control patients received bilateral injections of voretigene neparvovec. After receiving treatment, the control group experienced improvement in MLMT (change score, 2.1, SD=1.6) and FST (change, -2.86, SD=1.49). VA in the control group improved an average of 4.5 letters between years 1 and 2. Overall, 72% (21/29) of all treated patients achieved the maximum possible MLMT improvement at one year following injection.

Two patients (one in each group) experienced serious adverse events, both were unrelated to study participation. The most common ocular adverse events in the 20 patients treated with voretigene neparvovec were mild to moderate: elevated intraocular pressure, four (20%) patients; cataract, three (15%) patients; retinal tear, two (10%) patients; and eye inflammation, two (10%) patients. Several ocular adverse events occurred only in one patient each: conjunctival cyst, conjunctivitis, eye irritation, eye pain, eye pruritus, eye swelling, foreign body sensation, iritis, macular hold, maculopathy, pseudopapilledema, and retinal hemorrhage. One patient experienced a loss of VA (2.05 logMAR) in the first eye injected with voretigene neparvovec; the eye was profoundly impaired at 1.95 logMAR (approximately 20/1783 on a Snellen chart) at baseline.

Maguire (2019) recently published the results of the open-label follow-on phase 1 study at year four and the phase 3 study at year two.[15] Mean (SD) MLMT lux score change was 2.4 (1.3) at four years compared with 2.6 (1.6) at one year after administration in phase 1 follow-on subjects (n=8). Mean (SD) MLMT lux score change was 1.9 (1.0) at two years and 1.9 (1.0) at one year post-administration in the original intervention group (n=20). The mean (SD) MLMT lux score change was 2.1 (1.6) at one year post-administration in control subjects (n=9). Therefore, durability for up to four years has been reported, with observation ongoing.

Evidence Summary

In the pivotal RCT, patients in the voretigene neparvovec group demonstrated greater improvements on the MLMT, which measures the ability to navigate in dim lighting conditions, compared with patients in the control group. The difference in mean improvement was both statistically significant and larger than the a priori defined clinically meaningful difference. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group, with the exception of VA. Improvements seemed durable over a period of two years. The adverse events were mostly mild to moderate; however, one patient lost 2.05 logMAR in the first eye treated with voretigene neparvovec by the one year visit. There are limitations in the evidence. There is limited follow-up available, therefore, long-term efficacy and safety are unknown. The primary outcome measure has not been used previously in RCTs and has limited data to support its use. Only the MLMT assessors were blinded to treatment assignment, which could have introduced bias assessment of other outcomes. The modified VFQ is not validated, so effects on quality of life remain uncertain.

PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines that recommend RPE65 variant

testing to confirm a diagnosis of biallelic RPE65 variant-associated retinal dystrophy.

SUMMARY

There is enough research to show that testing for RPE65 variants can help to identify patients with biallelic RPE65 variant-associated retinal dystrophy who are likely to benefit from certain gene therapies. Therefore, RPE65 genetic variant testing may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, and therefore, RPE65 variant testing is considered investigational for all other indications.

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CODES

Codes	Number	Description
CPT	81406	Molecular pathology procedure level 7
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *February 2018*

Regence

Medical Policy Manual Genetic Testing, Policy No. 29

Gene Expression Profiling for Melanoma

Effective: August 1, 2024

Next Review: April 2025
Last Review: June 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

Gene expression assays have been created to aid risk stratification in patients with melanoma or pigmented lesions suspected of being melanoma.

MEDICAL POLICY CRITERIA

I. The DecisionDx-UM™ gene expression assay may be considered **medically necessary** in patients with primary, localized uveal melanoma.

II. The DecisionDx-UM™ gene expression assay is considered **investigational** for patients that do not meet criterion I.

III. All other gene expression assays for melanoma are considered **investigational**, including but not limited to DecisionDX-Melanoma™, Pigmented Lesion Assay, PLAplus™, AMBLor®, and myPath Melanoma™.

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.

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or mutations being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test
    - History and physical exam
    - Date of blood draw for test
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Cutaneous Malignant Melanoma, Genetic Testing, Policy No. 08
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, Genetic Testing, Policy No. 42
4. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77
5. Skin Lesion Imaging and Spectroscopy, Medicine, Policy No. 174

BACKGROUND

CUTANEOUS MELANOMA

Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment for stage 1 and 2 melanoma is excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. Regional lymph node involvement, the likelihood of which increases with increasing tumor thickness, significantly negatively impacts the rate of survival.

UVEAL MELANOMA

Uveal melanoma, also referred to as ocular or choroidal melanoma, is the most common, but rare, primary ocular malignancy in adults and shows a strong tendency for metastases to the liver. Approximately four million cases of uveal melanoma occur each year.[1] Even with successful treatment of the primary tumor, up to 50% of individuals subsequently develop systemic metastases, with liver involvement in up to 90% of these individuals. Despite aggressive systemic treatments, metastatic liver disease remains the most common cause of tumor-related mortality in choroidal malignant melanoma, with a median survival time of two to seven months and a one-year survival rate of less than 10%. The primary clinical issue in the management of uveal melanoma is accurately predicting risk of metastasis.

Identifying patients at high risk for metastatic disease might assist in selecting patients for adjuvant treatment and more intensive surveillance for metastatic disease, if such changes lead to improved outcomes. The optimal method and interval for surveillance are not well-

defined, and it has not been established in prospective trials whether surveillance identifies metastatic disease earlier. Potential methods for metastases include magnetic resonance imaging, ultrasound, liver function testing, and positron emission tomography scans.

COMMERCIALLY AVAILABLE TESTING

The DermTech Pigmented Lesion Assay (PLA) test measures expression of six genes (*PRAME*, *LINC00518*, *CMIP*, *B2M*, *ACTB*, *PPIA*). The test is performed on skin samples of lesions at least 5 mm in diameter obtained via noninvasive, proprietary adhesive patch biopsies of a stratum corneum specimen. The test does not work on the palms of hands, soles of feet, nails, or mucous membranes and should not be used on bleeding or ulcerated lesions. The PLA test report includes two results. The first is the PLA MAGE (Melanoma Associated Gene Expression), which indicates low risk (neither *PRAME* nor *LINC00518* expression was detected), moderate risk (expression of either *PRAME* or *LINC00518* was detected), or high risk (expression of both *PRAME* and *LINC00518* was detected). The second result is as an algorithmic PLA score that ranges from 0 to 100, with higher scores indicating higher suspicion of malignant disease. It is not clear whether the PLA test is meant to be used as a replacement, triage, or add-on test with respect to dermoscopy. The PLAplus™ test additionally includes testing for *TERT* variants.

The Myriad myPath test measures expression of 23 genes. Fourteen genes are involved in melanoma pathogenesis and are grouped into three components related to cell differentiation, cell signaling, and the immune response, and nine housekeeper genes are also included. The test is performed on five standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy specimen, and the test report includes an algorithmic myPath score ranging from -16.7 to 11.1, with higher, positive scores indicating higher suspicion of malignant disease. The myPath report classifies these scores: -16.7 to -2.1 are “benign”; -2.0 to -0.1 are “indeterminate”; and 0.0 to +11.1 are “malignant”.

The DecisionDx-Melanoma™ is a gene expression profile test that is a signature of 31 genes, 28 discriminating genes, and three control genes. The test is used to measure risk of metastasis in patients with stage 1 and 2 cutaneous melanoma and classifies tumors into two groups of risk of metastasis, high or low (Class 1 and 2, respectively). The test purports to give an independent prediction of risk of tumor metastatic risk, independent of currently used metrics of risk assessment (e.g., Breslow’s thickness, ulceration status, and mitotic rate; American Joint Committee on Cancer stage, sentinel lymph node biopsy [SLNB] status), so that patients with high-risk stage 1 or 2 disease can possibly undergo more aggressive surveillance treatment than they would have otherwise received.

The Clinicopathological and Gene Expression Profile (CP-GEP, Skyline Dx), also known as the Merlin Assay, uses a combination of gene expression profiling, age, and Breslow thickness to classify patients as either low risk or high risk for metastasis. Eight genes are included in the GEP: *ITGB3*, *PLAT*, *SERPINE2*, *GDF15*, *TGFBR1*, *LOXL4*, *CXCL8* and *MLANA*. This assay has been proposed to identify which patients at low risk that do not need to undergo SLNB.

The DecisionDx-UM™ test (Castle Biosciences Inc.) is a commercially marketed gene expression profiling test intended for use in assessing metastatic risk in individuals with this condition. It consists of a 15-gene polymerase chain reaction (PCR)-based assay that stratifies individuals with uveal melanoma into two classes based on the molecular signature of tumor tissue. Uveal melanomas cluster into two molecular groups based on their gene expression profile. Tumors with the Class 1 signature rarely metastasize, whereas those with the Class 2

signature metastasize at a high rate. Class 1 tumors have been further distinguished into Class 1a (lowest metastatic risk) and Class 1b (moderate long-term metastatic risk).

According to Castle Biosciences Inc., the DecisionDx-UM™ test results are used for the following:

- To initiate referral to a medical oncologist for treatment planning which may include adjuvant treatment.
- To develop specific monitoring or surveillance plans:
    - More frequent monitoring with advanced imaging procedures may be recommended for those individuals identified as having a high risk of developing metastasis.
    - For individuals at a low risk of developing metastasis, a less intensive surveillance plan may balance the risks of radiation exposure associated with less frequent imaging.
- To improve life-planning.

REGULATORY STATUS

The DecisionDx tests are performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory and do not require U.S. Food and Drug Administration (FDA) clearance.

Note: Microarray-based gene expression analysis of prostate cancer and breast cancer are addressed in separate medical policies (see Cross References).

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Review of the literature focused on identifying evidence related to clinical validity and clinical utility, particularly whether the tests can be used to improve treatment planning compared with the standard of care, and whether their use results in improved health outcomes.

EVALUATION OF SUSPICIOUS PIGMENTED LESIONS

DermTech PLA

Primary care providers evaluate suspicious pigmented lesions to determine who should be referred to dermatology. Factors considered include both a patient's risk for melanoma as well as a visual examination of the lesion. The visual examination assesses whether the lesion has features suggestive of melanoma. Criteria for features suggestive of melanoma have been developed. One checklist is the ABCDE checklist:[3]

- Asymmetry;
- Border irregularities;
- Color variegation;
- Diameter ≥6 mm;
- Evolution.

Another criterion commonly used is the "ugly duckling" sign.[4] An ugly duckling is a nevus that is obviously different from others in a given patient. Primary care providers generally have a low threshold for referral to dermatology.

Melanoma is difficult to diagnose based on visual examination, and the criterion standard for diagnosis is histopathology. There is a low threshold for excisional biopsy of suspicious lesions for histopathologic examination due to the procedure's ease and low risk as well as the high probability of missing melanoma. However, the yield of biopsy is fairly low. The number of biopsies performed to yield one melanoma diagnosis has been estimated to be about 15 for U.S. dermatologists.[5] Therefore a test that could accurately identify those lesions not needing a biopsy (i.e., a rule-out test for biopsy) could be clinically useful. The purpose of gene expression profiling (GEP) in patients who have suspicious pigmented lesions being considered for biopsy is to inform a decision about whether to biopsy.

Clinical Validity

Studies were excluded from the evaluation of the clinical validity of the DermTech PLA test because they reported results of the development cohort,[6] they did not use the marketed version of the test,[6, 7] did not include the reference standard test on PLA-negative patients,[8] did not adequately describe the patient characteristics,[9] or did not adequately describe patient selection criteria.[9]

The validation cohort from the Gerami (2017) publication was included.[10] This was a retrospective study that included lesions that were selected by dermatologists experienced in pigmented lesion management from 28 sites in the United States, Europe, and Australia; therefore, the samples were likely not consecutive or random. Information regarding the previous testing was not provided. The flow of potential and included samples was not clear, and neither was whether the samples were all independent or if multiple samples from the same patient were included. Diagnosis of melanoma was based on consensus among a primary reader and three expert dermatopathologists. The report did not state whether the histopathologic diagnosis was blinded to the results of the PLA test but did state the diagnosis was "routinely" assessed. Interpretation of the PLA result does not depend on a reader, so it is blinded to histopathologic results. In 11% of cases originally selected, a consensus diagnosis was not reached, and these samples were not included in the training or validation cohorts. Dates of data collection were not reported. Sex and anatomic location of biopsy were reported, but other clinical characteristics (e.g., risk factors for melanoma, presenting symptoms) were not. The study training cohort included 157 samples with 80 melanomas and 77 nonmelanomas. The study validation cohort included 398 samples with 87 melanomas (22%) and 311 non-melanomas. The sensitivity and specificity of the test in this group was 91% (95%

confidence interval [CI] 83% to 96%) and 69% (95% CI 64% to 74%), respectively, yielding a positive predictive value (PPV) of 45% (95% CI 38% to 53%) and a negative predictive value (NPV) of 96% (95% CI 93% to 98%).

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence of clinical utility was identified.

A decision-impact study by Ferris (2017) assessed the potential impact of the PLA on physicians' biopsy decisions for patients.[9] Forty-five dermatologists evaluated 60 clinical and dermoscopic images of atypical pigmented lesions (8 melanoma, 52 nonmelanoma). In the first round, dermatologists did not have PLA test results, and in the second round, dermatologists had access to PLA test results with the order of cases being scrambled. The dermatologists were asked whether the lesions should be biopsied after each round. Therefore, the corresponding number of biopsy decisions should be 45×60×2=5,400. Data were collected in 2014 and 2015. Results were reported for 4,680 decisions with no description of the disposition of the remaining decisions. Of the 4,680 reported decisions, 750 correct biopsy decisions were made without PLA results while 1,331 were made with PLA results and 1,590 incorrect biopsy decisions were made without PLA results while 1,009 incorrect biopsy decisions were made with PLA results.

GEP FOR DIAGNOSING LESIONS WITH INDETERMINATE HISTOPATHOLOGY

MyPath

The purpose of GEP testing in patients whose melanocytic lesion is indeterminate after histopathology is to aid in the diagnosis of melanoma and decisions regarding treatment and surveillance. In cases of indeterminate histopathology, long-term follow-up is needed to determine evaluate the clinical outcome, specifically metastasis.

Development of the myPath test was described by Clarke (2015).[11] The myPath test is meant to be used as an add-on test to standard histopathology. Studies have evaluated the performance characteristics of the test when histopathology is used as the reference standard,[11-13] but are not the focus of this evidence review given that the test's potential usefulness is in evaluation of indeterminate lesions.

Studies were excluded from the evaluation of the clinical validity of the myPath test because authors did not use the specified reference standard of long-term (at least five years) follow-up[11-16] and/or did not adequately describe patient characteristics.

The clinical validity study by Ko (2017) met selection criteria.[17] For this study, archived melanocytic neoplasms were submitted for myPath testing from university clinics in the United States and United Kingdom with additional samples acquired from Avaden BioSciences. Stage 1, 2, and 3 primary cutaneous melanomas that produced distant metastases subsequent to the diagnosis and benign lesions with clinical follow-up and no evidence of recurrence of metastases were included. For benign samples, a disease-free time of at least five years was recommended. Information on the previous testing was not provided. It is not clear if any of the samples originally had indeterminate histopathology results. Dates of data collection were not reported. Sex, age, Breslow depth, and anatomic location were described; presenting

symptoms were not reported. A total of 293 samples were submitted; of these 53 did not meet inclusion criteria and 58 (24% of those tested) failed to produce a valid test score. An additional seven samples with indeterminate results were excluded from the calculations of performance characteristics. Of the remaining 175 samples, 54 were diagnosed as melanoma with metastases. The sensitivity and specificity of the test in this group was 94% (95% CI 87% to 98%) and 96% (95% CI 89% to 99%), respectively, with a PPV of 97% (95% CI 91% to 99%) and an NPV of 93% (95% CI 85% to 97%). A limitation of the study is that it was not limited to lesions that were indeterminate following histopathology. In addition, the samples were not consecutive or random, and it is unclear how much time elapsed between the biopsy and the myPath test. A follow-up analysis by Clarke (2020) was limited to lesions with "diagnostic uncertainty" from this study.[18] Of the 125 lesions that met diagnostic uncertainty criteria, 54 were determined to be malignant based on clinical outcomes and 47 (87%) of these had a "likely malignant" test result.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence of clinical utility was identified.

Two decision-impact studies assessed the potential impact of myPath on physicians' treatment decisions in patients with diagnostically challenging lesions.[19, 20] Given the lack of established clinical validity and no reported long-term health outcomes, it is not known whether any treatment changes were clinically appropriate.

CUTANEOUS MELANOMA

Many treatments and surveillance decisions are determined by a patient's prognostic stage group based the American Joint Committee on Cancer tumor, node, metastasis staging system. The prognostic groups are as follows: stage 1, T1a through T2a primary melanomas without evidence of regional or distant metastases; stage 2, T2b through T4b primary melanomas without evidence of lymphatic disease or distant metastases; stage 3: pathologically documented involvement of regional lymph nodes or in transit or satellite metastases (N1 to N3); stage 4: distant metastases. Patients may also SLNB to gain more definitive information about the status of the regional nodes. Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage 1 or 2 (node-negative) melanoma do not generally receive adjuvant therapy. Patients with higher risk melanoma receive adjuvant immunotherapy or targeted therapy. Patients with stage I and IIA disease should undergo an annual routine physical and dermatologic examination. These patients typically do not receive surveillance imaging. Patients with stage 2B – stage 3 melanoma may be managed with more frequent follow-up and imaging surveillance following therapy. However, follow-up strategies and intervals are not based on rigorous data, and opinions vary regarding appropriate strategies.

The purpose of GEP in patients with melanoma is to identify low and high-risk patients classified as stage 1 or 2 according to the American Joint Committee on Cancer (AJCC) criteria. Current guidelines do not recommend adjuvant therapy or imaging surveillance for AJCC stage 1 or 2 patients following surgery. Patients initially staged as 1 or 2 who have positive lymph nodes following SLNB are then eligible to be treated with adjuvant therapy as stage 3 patients.

DecisionDX-Melanoma

Clinical Validity

Several papers were excluded from the evaluation of clinical validity of the DecisionDx test. Hsueh (2017), Podlipnik (2019), Hsueh (2021), and Bailey (2023) were excluded from the evaluation because they did not report five-year outcomes.[21-24] Samples used in Gerami (2015)[25] and Ferris (2017)[26] appear to overlap with the samples from Gerami (2015)[27] and each other and will not be considered independent validation studies for inclusion in the table. They are described briefly following the clinical validity tables. Samples used in both papers by Gastman (2019) are stated to overlap previous validation studies.[28, 29] Vetto (2019) included a retrospective cohort that was used to develop the model and is thus not eligible for inclusion, as well a prospective cohort with some overlapping samples and without report of five-year outcomes.[30] A publication by Marks (2019) describes the development of a cutpoint.[31]

Four independent clinical validity studies meeting eligibility criteria have been conducted. Characteristics and results are summarized in Tables 1 and 2 and briefly in the paragraphs that follow.

Table 1. Clinical Validity Study Characteristics of the DecisionDx-Melanoma Test for Diagnosing Melanoma

Study	Study Population	Design	Outcome Measure	Threshold for Positive Test	Timing	Assessor Blinding
Gerami (2015);[27] Validation subset	Adults Stage I-IV cutaneous melanoma (87% stage I/II) At least 5 y of FU (median, 7.0 y) Median Breslow thickness, 0.8 mm (nonmetastasis) and 3.99 mm (metastasis) SLN positivity NR	Retrospective Not consecutive or randomly selected	5-y RFS	Class 2 is high-risk Risk threshold not provided	Patient diagnosed between 1998 and 2009 Timing of DecisionDx not described	Yes
Zager (2018)[32]	Stage I-III cutaneous melanoma (68% stage I/II) At least 5 y of FU (median, 7.5 y) Median Breslow thickness, 1.2 mm 30% SLN positive	Retrospective Not consecutive or randomly selected	5-y RFS	Class 2 = high risk Class 1 probability score 0-0.49 Class 2 probability score 0.5-1	Patients diagnosed between 2000 and 2014 Timing of DecisionDx not described	Yes

Study	Study Population	Design	Outcome Measure	Threshold for Positive Test	Timing	Assessor Blinding
Greenhaw (2018)[33]	Patients who were treated for primary invasive CM of any Breslow depth within the last 5 years and had had GEP testing (86% stage I, 14% stage II) Mean follow-up of 23 months; only 20 patients had 5-year follow-up	Retrospective Consecutive	5-y MFS	Commercial test cutoffs used	Institution offered DecisionDx testing to newly diagnosed and those treated within the previous five years	Yes
Keller (2019)[34]	Patients had CM (91% stage I/II), opted for GEP testing and underwent SNB and wide excision of primary tumor. Median follow-up time, 3.5 years Median Breslow thickness, 1.4 mm 9% SLN positive	Prospective	3-y MFS	Commercial test cutoffs used	Patients diagnosed between 2013 and 2015 GEP reported to be performed concurrently with SNB	Yes

FU: follow-up; RFS: recurrence-free survival; MFS: metastasis-free survival; GEP: gene expression profiling; CM: cutaneous melanoma; SLN: sentinel lymph node; SNB: sentinel node biopsy

Table 2. Clinical Validity Study Results of the DecisionDx-Melanoma Test for Diagnosing Melanoma

Study	Initial / Final N	Excluded Samples	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Gerami (2015);[27] Validation subset		Samples excluded if melanoma dx not confirmed, dissectible area not acceptable				
Overall	Unclear / 104		89 (73 to 97)[a]	83 (72 to 91)[a]	72 (56 to 85)[a]	93 (84 to 98)[a]
AJCC stage 1 and 2	Unclear / 78		86 (64 to 97)[a]	84 (72 to 93)[a]	67 (46 to 83)[a]	94 (84 to 99)[a]

Study	Initial / Final N	Excluded Samples	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Zager (2018)[32]		Did not meet analytic quality control thresholds				
Overall	601 / 523		70 (62 to 78)	71 (67 to 76)	48 (41 to 55)	87 (82 to 90)
AJCC stage 1	Unclear / 264		35 (14 to 62)[a]	87 (82 to 91)[a]	15 (6 to 31)[a]	95 (91 to 98)[a]
AJCC stage 2	Unclear / 93		77 (61 to 89)[a]	43 (29 to 57)[a]	49 (36 to 62)[a]	72 (53 to 86)[a]
Greenhaw (2018)[33]	256 / 256	None excluded but only 20 had 5-year follow-up	77 (46 to 94)	87 (82 to 91)	24 (13 to 40)	99 (96 to 100)
Keller (2019)[34]	159 / 174	15 patients had insufficient tumor for GEP testing	NR	NR	NR	NR

AJCC: American Joint Committee on Cancer; Dx: diagnosis; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RFS: recurrence-free survival; MFS: metastasis-free survival

[a] Confidence intervals not provided in the report; calculated from data provided.

The validation cohort in Gerami (2015) included patients with stage 0, 1, 2, 3, or 4 disease from six U.S. centers (n=104).[27] A complete disposition of samples received from the institutions and those included in the analysis was not provided. For 78 patients in the validation cohort with AJCC stage 1 or 2 cutaneous melanoma who had either a metastatic event or had more than five years of follow-up without metastasis, five-year disease-free survival was 98% (CIs not reported) for DecisionDx class 1 patients and 37% for DecisionDx class 2 patients. The PPV and NPV were 67% and 94%, respectively. CIs for performance characteristics were calculated in Table 2 based on data provided

Zager (2018) reported results of a second clinical validity study including AJCC stage 1, 2, or 3 primary melanoma tumors from 16 U.S. sites.[32] The samples were independent of the other validation studies. Of the 601 cases submitted from the institutions, 523 were included in the analysis (357 stage 1 and 2). The excluded samples did not meet pre- and post-analytic quality control thresholds. SLNB status was untested in 36% of the patients, negative in 34%, and positive in 30%. The report did not describe any adjuvant therapy that the patients received. Overall, 42 (13%) recurrence events occurred in DecisionDx class 1 patients and 100 (48%) recurrence events occurred in DecisionDx class 2 patients. The five-year recurrence free survival (RFS) estimated by Kaplan-Meier was 88% (95% CI 85% to 92%) in class 1 and 52% (95% CI, 46% to 60%) in class 2. The reported sensitivity and specificity were 70% (95% CI 62% to 78%) and 71% (95% CI 67% to 76%), respectively, with a PPV of 48% (95% CI 41% to 55%) and a NPV of 87% (95% CI 82% to 90%). For comparison, the performance characteristics for five-year RFS for sentinel lymph node status among those with SLNB were: sensitivity 66% (95% CI 57% to 74%); specificity 65% (95% CI 58% to 71%); PPV 52% (95% CI 44% to 60%); and NPV 76% (95% CI 69% to 82%). Estimates stratified by AJCC stage I or II are shown in Table 2. If DecisionDx were used as a triage test such that only class 2

received SLNB, then 159 class 1 patients would not have undergone SLNB. Of the 159 patients in class 1, 56 were SLNB-positive and were therefore eligible for adjuvant therapy. It is not clear if the SLNB-positive patients in this study received adjuvant therapy. Of the 56 patients who were DecisionDx class 1 and SLNB-positive, 22 recurrence events occurred by five years.

Greenhaw (2018) reported results of an independent study of the DecisionDx test using their institution's melanoma registry and including patients who had been treated for cutaneous melanoma within the last five years and undergone DecisionDx testing.[33] Study characteristics and results were reported in the preceeding Tables 1 and 2. Two-hundred fifty-six patients were tested; 84% were categorized as DecisionDx class 1 (low-risk) and 16% were DecisionDx class 2 (high-risk). Of these, 219 (86%) tumors were AJCC stage I and 37 (14%) were AJCC stage II. None of the 18 stage 1/class 2 tumors metastasized but 1 (0.5%) of 201 stage I/class 1 tumors metastasized. Ten (42%) of the stage 2/class 2 tumors metastasized and 2 (15%) of the 13 stage 2/class 1 tumors metastasized.

Keller (2019) reported results of a validity study including 159 patients (ages 26 to 88) diagnosed with melanoma between 2013 and 2015 who underwent SNB and concurrent GEP testing.[34] Study characteristics and results were reported in the preceding Tables 1 and 2. There were 117 patients classified as class 1 (91 subclass 1A and 26 subclass 1B) and 42 classified as Class 2 (12 subclass 2A and 30 subclass 2B); and 78% of the tumors were AJCC stage 1, 13% were stage 2, and 9% were stage 3. Five-year RFS was reported only in a figure and sample sizes at year five and precision estimates were not included. There were six recurrent events (n=117) in class 1 patients by three years (three-year RFS 97%, 95% CI 93% to 100%). There were 23 recurrent events (n=42) in class 2 patients (three-year RFS 47%, 95% CI 34% to 65%). GEP class was significantly associated with RFS in multivariate analysis controlling for age, Breslow thickness, ulceration and SNB results.

In a subsequent analysis of patients with melanoma who had undergone SLNB, Gerami (2015) compared the prognostic accuracy of GEP and biopsy .[25] Patients who had undergone SLNB appear to overlap with patients in Gerami (2015)[27], discussed previously. Most (73%) patients had a negative SLNB, and 27% had a positive SLNB. DecisionDx-Melanoma classified 76 (35%) tumors as low-risk (class 1) and 141 (65%) tumors as high-risk (class 2). Within the group of SLNB-negative patients, the five-year OS rate was 91% in class 1 patients and 55% in class 2 patients. Within the group of SLNB-positive patients, the five-year OS rate was 77% in class 1 patients and 57% in class 2 patients.

A systematic review and meta-analysis by Marchetti (2020) evaluated the performance of GEP tests for prognosis in patients with localized melanoma.[35] Five studies of the DecisionDX-Melanoma were included in the review: the four studies in Tables 1 and 2 as well as the study by Hsueh (2017) that was not included. The review also included two studies of the MelaGenix test, which is not available in the U.S. All studies of DecisionDx-Melanoma were determined to have a high risk of bias. The results of the meta-analysis indicated that there was significant heterogeneity in the performance of the DecisionDX-Melanoma test between patients with stage 1 and stage 2 cancers, with poorer classification seen for stage 1. Limitations of the analysis included heterogeneity in recurrence definitions and lack of individual patient data. The authors also noted that censoring and lack of follow-up could substantially impact the recurrence outcome, with the proportion of recurrences in a mixed stage 1-3 cohort that were correctly classified as high-risk by the DecisionDx test decreasing from 80% at a median event-free follow-up time of 1.5 years to 60% at 3.2 years. Another meta-analysis of the

DecisionDx-Melanoma test was published by Greenhaw (2020).[36] This industry-sponsored analysis reported a sensitivity of 76% (95% CI 71% to 80%) and a specificity of 76% (95% CI 73% to 78%) for five-year RFS, and a sensitivity of 76% (95% CI 72% to 80%) and specificity of 69% (95% CI 66% to 72%) for distant metastasis-free survival. The analysis did not include clinicopathologic factors such as sex, anatomic site, and mitotic index.

Clinical Utility

Several decision-impact studies have been published reporting on the impact of DecisionDx-Melanoma on physicians' management decisions.[37-43] Given the lack of established clinical validity and no reported long-term outcomes of the test used to select patients for active surveillance, it is not known whether any management changes were clinically appropriate.

For the proposed use of the test as a triage for SLNB (to identify patients who can avoid SLNB), performance characteristics are not well-characterized. For the proposed use of the test as a replacement for SLNB (identify patients who are AJCC stage 1 or 2 who should receive adjuvant therapy), performance characteristics are also not well-characterized. In addition, an evidence-based management pathway would be needed to support the chain of evidence. The existing RCTs demonstrating that adjuvant therapy reduces recurrence included node-positive patients.

For the proposed use of the test to identify patients who are AJCC stage 1 or 2 who should receive enhanced surveillance, there is also a lack of evidence that imaging surveillance or increased frequency of surveillance improves outcomes in stage 1 and 2 patients. The National Comprehensive Cancer Network guidelines state that imaging surveillance is not recommended for stage 1-2A and can be 'considered' for 2B-4, but that there is an absence of meaningful data on the association of rigorous routine surveillance imaging with improved long-term outcome for stage 2B-2C and the recommendations regarding consideration of imaging surveillance remain controversial. While earlier detection of recurrence is thought to be beneficial because lower tumor burden and younger age are associated with improved treatment response and survival, this has not been proven and RCTs are needed to assess whether enhanced surveillance improves survival. The optimal frequency and duration of follow-up surveillance are not standardized and how the surveillance would be altered for DecisionDx class 2 patients has not be defined.

No evidence was identified that demonstrated that adjuvant therapy or increased surveillance improves net health outcomes in AJCC stage 1 or 2 patients who are DecisionDx class 2.

Clinicopathological and Gene Expression Profile (CP-GEP)

Clinical Validity

One study of the CP-GEP (also known as the Merlin Assay) was identified that met inclusion criteria. Other studies of this assay were not included because they compared the test to SLNB results and did not assess long-term outcomes.[44, 45]

Eggermont (2020) published a validation study of the CP-GEP that included samples from 580 stage 1-2A cutaneous melanoma patients who had a SLNB within 90 days of their diagnosis.[46] Among this group, 47% were classified as high risk based on the assay. The five-year RFS was 89% (95% CI 84% to 93%) for the CP-GEP low-risk group and 74% (95% CI 67% to 80%) for the CP-GEP high-risk group. Melanoma-specific survival was 97% and 91% for these groups, respectively.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. No direct evidence of clinical utility was identified.

UVEAL MELANOMA

DecisionDX-UM

Clinical Validity

Roelofs (2022) performed a retrospective analysis of 343 patients with uveal melanoma who underwent GEP classification, including 255 patients with class 1 and 88 patients with class 2 results.[47] Patients were classified as being at low (GEP class 1 and tumor thickness <8 mm) or high risk of metastasis (GEP class 2 or tumor thickness ≥8mm); low-risk patients underwent annual surveillance abdominal ultrasound, while high-risk patients underwent alternating surveillance liver ultrasound and abdominal magnetic resonance imaging every six months according to institutional protocol. The mean follow-up was 40 ± 26 months. In univariate Cox proportional hazard regression, enucleation, ciliary body involvement, extraocular extension, tumor thickness, largest basal tumor diameter (as a continuous and categorical [>12mm] variable), and GEP class 2 were associated with future metastasis. Multivariate Cox proportional hazards regression indicated GEP class 2 and longest basal diameter >12mm remained independently predictive of metastasis-free survival, and stratified analysis further indicated longest basal diameter >12mm remained predictive of metastasis-free survival in both GEP class 1 and 2 tumors.

Singh (2022) performed a retrospective analysis of metastasis-free survival in patients with uveal melanoma, with a focused analysis comparing predicted (according to DecisionDx-UM metastasis-free survival prediction for GEP class 2 [i.e., 50% at three years, 28% at five years]), observed (via analysis of a cohort of consecutive patients with uveal melanoma treated at the authors' two institutions), and published (via a meta-analysis of patients with uveal melanoma from seven retrospective or prospective studies utilizing GEP published between 2012 and 2021) metastasis-free survival in GEP class 2 subgroups.[48] The overall retrospective cohort consisted of 343 patients, of whom 121 were GEP class 2, while the meta-analysis pooled data from 667 GEP class 2 patients. In the analysis of GEP class 2 patients, both observed and meta-analysis-derived published metastasis-free survival at three and five years were longer than the corresponding DecisionDx-UM-predicted survival, with point estimate differences ranging from 12% to 19%. The predicted metastasis-free survival estimate was below the lower limit of the 95% confidence interval for both observed and published survival estimates at both time points.

Davanzo (2019) conducted a retrospective review of 107 consecutive uveal melanoma patients, including 39, 31, and 37 patients with unknown, low-, and high-risk GEP results.[49] Low-risk patients were followed with hepatic ultrasonography every six months, whereas high-risk patients were managed with more frequent hepatic imaging. High-risk patients (8/37) were significantly more likely to develop metastasis ($p<0.001$) compared to patients in the low/unknown risk group (0/70) (see Table 3).

Cai (2018) retrospectively evaluated a cohort of 240 patients with uveal melanoma arising from the choroid and/or ciliary body.[50] The study sought to determine whether the prognostic accuracy of combined GEP and PRAME (preferentially expressed antigen in melanoma) status was noninferior to the AJCC tumor-node-metastasis (TNM) staging system for uveal

melanoma. Patients were followed for a median duration of 29 months with metastasis as the primary endpoint. GEP class was the most significant predictor of metastasis ($p=1.5x10^{-8}$). The prognostic accuracy of an optimized GEP/PRAME model ($p=8.6x10^{-14}$) was superior to an optimized TNM model ($p=1.3x10^{-5}$).

Augsburger (2015) reported on the correlation between GEP classifications when samples from two sites from the same tumor were tested.[51] This prospective, single-center study enrolled 80 patients who had uveal melanoma resection. Tumor samples were taken from two different sites and GEP testing was performed independently on both samples. The primary measure reported was the rate of discordance between the two samples on GEP Class. Nine (11.3%) cases were definitely discordant (95% CI 9.0% to 13.6%), and 13 (16.3%) cases were definitely or possibly discordant (95% CI 13.0% to 19.6%). Thus, the heterogeneity of tumor and limitations to sampling may explain cases of misclassification where GEP results do not accurately predict prognosis.

Onken (2010) revalidated the GEP assay when it was migrated from a microarray platform to a polymerase chain reaction–based 15-gene assay comprised of 12 discriminating genes and three endogenous control genes from previously published data sets collected from the same group.[52, 53] Technical performance of the assay was assessed in 609 tumor samples, including 553 fine needle aspiration biopsies and 56 enucleation specimens from the authors' laboratory (n=188) and 11 collaborating sites (n=421). According to the study protocol, sample failure rate due to incorrect specimen handling was low, occurring in 32 of 609 (5.3%) of samples ($p<0.0001$). Preliminary data suggested the potential for increased sensitivity of gene expression profiling compared with cytologic diagnosis, as the assay failed in only one of 51 (2%) of samples with insufficient material for cytological diagnosis; however, point estimates of overall test accuracy (e.g., sensitivity, specificity, or both) were not provided. In a subset of 172 individuals with UM, the relationship between tumor class and metastasis was studied with available clinical data and a median follow-up time of 16 months. Within this group, the assay was reported to correctly identify individuals who went on to develop metastatic disease. Kaplan-Meier analysis showed approximately 24% Class 2 individuals with uveal melanoma surviving at 48 months and close to 100% survival in the Class 1 group, although more specific data was not provided. This study evaluated primarily fine needle aspiration biopsy specimens (553 of 609, or 90.8%) rather than enucleation specimens; however, the data reported on the relationship between tumor class and metastasis are limited, and median follow-up time was reported as a relatively short duration (16 months).

In a prospective, multicenter study by Onken (2012), the prognostic performance of the 15-gene GEP assay was evaluated in 459 patients with posterior uveal melanoma from 12 independent centers.[54] Tumors were classified by GEP as Class 1 or Class 2. The first 260 samples were also analyzed for chromosome 3 status using a single nucleotide polymorphism assay. Net reclassification improvement analysis was performed to compare the prognostic accuracy of GEP with the 7th edition clinical Tumor-Node-Metastasis (TNM) classification and chromosome 3 status. Patients were managed for their primary tumor and monitored for metastasis. The GEP assay successfully classified 446 of 459 cases (97.2%). Metastasis was detected in three Class 1 cases (1.1%) and 44 Class 2 cases (25.9%) (log-rank test, P<10(-14)). At three years follow-up, the net reclassification improvement of GEP over TNM classification was 0.43 (p=0.001) and 0.38 (p=0.004) over chromosome 3 status. The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. The impact of the test results on health outcomes were not identified in the study.

Walter (2016) evaluated two cohorts of patients at two clinical centers who underwent resection for uveal melanoma.[55] This study had similar methodology to Onken (2012) study described above. The primary cohort included 339 patients, of which 132 patients were also included in the Onken study, along with a validation cohort of 241 patients, of which 132 were also included in the Onken study, the latter group of which was used to test a prediction model using the GEP plus pretreatment largest basal diameter. Cox proportional hazards analysis was used in the primary cohort to examine GEP classification and other clinicopathologic factors (tumor diameter, tumor thickness, age, sex, ciliary body involvement, pathologic class). GEP Class 2 was the strongest predictor of metastases and mortality. Tumor diameter was also an independent predictor of outcomes, using a diameter of 12 mm as the cutoff value. In the validation cohort, GEP results were Class 1 (61.4%) in 148 patients and Class 2 (38.6%) in 93 patients.

Similar outcomes were reported by Demirci (2018) in a retrospective review of 293 patients with choroidal melanoma.[56] Class 2 tumors with largest basal diameter ≥ 12 mm and class 2 and 1B tumors with American Joint Committee on Cancer (AJCC) stage III showed significantly worse prognosis. At a median follow-up of 26 months, the probability of metastasis-free survival was lowest in patients with class 2 tumors (HR 0.60, 95% CI 0.44 to 0.72) compared to patients with class 1A (HR 0.99, 95% CI 0.94 to 0.99) or class 1B (HR 0.90, 95% CI 0.77 to 0.96) tumors. The authors subsequently analyzed a scoring system combining AJCC stage and GEP in the same dataset (including three additional patients since the 2018 publication), with results indicating better estimate of prognosis with the combined score than with use of AJCC stage or GEP alone.[57]

Decatur (2016) published a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014.[58] GEP was Class 1 in 35 (43%) patients, Class 2 in 42 (52%) patients, and unknown in four (5%) patients. GEP Class 2 was strongly associated with BAP1 variants (r=0.70, p<0.001). On Cox proportional hazards analysis, GEP Class 2 was the strongest predictor of metastases and melanoma mortality.

Corrêa (2016) performed a single-institution prospective intervention case series to compare the prognostic value of the 15-gene GEP test with other conventional prognostic factors for metastasis and metastatic death, including 299 patients with posterior uveal melanoma evaluated by fine-needle aspiration biopsy at the time of or shortly prior to initial treatment.[59] The cohort in this study had a substantial proportion of patients with smaller tumors compared to previous studies, and this was reflected in the higher proportion of Class 1 to Class 2 cases in this cohort; 211 (70.6%) Class 1 patients and 88 (29.4%) Class 2 patients. Stepwise multivariant analysis determined that although GEP class was the strongest prognostic factor for metastatic death in this series; that tumor large basal diameter was also a significant prognostic indicator of metastatic death. Kaplan-Meier survival curves demonstrated lower survival in GEP Class 2 patients compared with Class 1 patients, but survival and metastasis rates by class were not reported.

Field (2016) published a follow-up study of the Onken (2010) validation cohort, looking at additional biomarkers to complement the DecisionDx-UM GEP test results in 389 consecutive patients.[60] This study analyzed 64 tumor samples previously determined as Class 1 in an effort to find independent markers of metastasis in these samples. The investigators reported that Class 2 GEP was associated with significantly greater metastatic risk than Class 1 GEP, with metastatic disease being detected in 12/216 (6%) Class 1 cases versus 63/173 (36%) Class 2 cases (p<0.0001).

Table 3. Studies of Clinical Validity

Study	Patient Populations	Rates of Metastases		Melanoma Mortality Rates	
		GEP Class 1	GEP Class 2	GEP Class 1	GEP Class 2
Onken (2012)[54]	459 pts with UM from 12 clinical centers	1.1%	25.9%	NR	NR
Walter (2016)[55]	Primary cohort: 339 pts from one clinical center with UM arising in ciliary body or choroid	5.8%	39.6%	3.7%	29.5%
	Validation cohort: 241 pts from one (different) clinical center with UM arising in ciliary body or choroid	2.7%	31.2%	0.7%	17.2%
Decatur (2016)[58]	81 pts from a single center with available tumor samples of UM arising in ciliary body or choroid		9.4 (3.1 to 28.5)		15.7% (3.6 to 69.1)
Field (2016)[60]	389 pts from two clinical centers with UM arising in ciliary body or choroid	6%	36%	NR	NR
Demirci (2018)[56]	293 patients from 2 clinical centers with UM arising from the choroid	3.6%	26.5%	NR	NR
Cai (2018)[50]	240 patients from a single center with UM arising from the choroid and/or ciliary body	10.2% 3.9% (*PRAME*-) 6.3% (*PRAME*+)	41.1% 19.6% (*PRAME*-) 21.4% (*PRAME*+)	NR	NR
Davanzo (2019)[49]	107 consecutive patients from a single-center with UM	0%	21.6%	NR	NR
Roelofs (2022)[47]	343 patients from a single center with non-metastatic UM	4.3%	34%	NR	NR
Singh (2022)[48]	• Observed survival cohort: 343 consecutive patients from two centers with UM, including 121 GEP class 2 patients • Published survival pooled cohort: 667 GEP class 2 patients	• Observed 3-year MFS: 93% (95% CI 89% to 97%) • Observed 5-year MFS: 87% (95% CI 81% to 93%	3-year MFS: • Predicted:[c] 50% • Observed: 67% (95% CI 59% to 77%) • Published: 62% (95% CI 57% to 66%) 5-year MFS: • Predicted:[c] 28% • Observed: 47% (95% CI 37% to 61%) • Published: 40% (95% CI 34% to 46%)	NR	NR

CI: confidence interval; GEP: gene expression profile; MFS: metastasis-free survival; NR: not reported; *PRAME*: preferentially expressed antigen in melanoma; UM: uveal melanoma

Clinical Utility

To date, there are no published studies that address the specificity, sensitivity, or positive- and negative-predictive values, and no studies that compare patient health outcomes as a result of patient management with versus without this testing. However, a chain of evidence based on the clinical validity of the test can be developed.

Khan (2022) conducted a multicenter, single-arm study of crizotinib as adjuvant therapy in adults with localized high-risk uveal melanoma (defined as GEP class 2 and longest basal tumor diameter >12mm).[61] This was the first published clinical trial of crizotinib in uveal melanoma. Patients received crizotinib 250 mg by mouth twice daily for a total of 48 weeks, beginning within 90 days of primary enucleation or radiotherapy. The primary outcome was 32-month relapse-free survival (RFS) rate; planned enrollment was 30 patients to provide 90% power to detect a 75% RFS rate at 32 months relative to a 50% RFS rate based on historical data. The analysis included a comparison of the primary outcome in the study cohort to a 2:1 propensity score-matched historical control. Among the 34 patients enrolled, the median age was 60 years, and all patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The mean relative dose intensity per cycle was 84%; four patients did not complete 48 weeks of treatment with crizotinib due to toxicity despite dose reduction. In 32 evaluable patients, at a median follow-up of 47.1 months, the estimated 32-month RFS rate was 50% (95% CI 23% to 67%). There was no difference in the primary outcome between the study cohort and the propensity score-matched historical control cohort, in whom the estimated 32-month RFS rate was 57% (95% CI 40% to 73%). All patients experienced at least one treatment-related adverse event, the most common of which were nausea, transaminase elevation, diarrhea, fatigue, and sinus bradycardia.

Schefler (2020) reported on risk-appropriate changes in management following testing with DecisionDx-UM in a prospective, multicenter cohort (n=93) enrolled in the Clinical Application of DecisionDx-UM Gene Expression Assay Results (CLEAR II) registry study.[62] Following testing, 44 (98%) of class 2 patients received a referral to another provider, of which 42 (93%) received referrals to medical oncology. For class 1 patients, 55 (59%) received a referral to another provider, of which 47 (51%) were referred to medical oncology. Medical oncology referral was more common for high-risk class 2 patients compared to class 1 ($p<0.001$). Class 2 patients were more 3.3 times more likely to receive high-frequency chest imaging ($p<0.001$) and 4.3 times more likely to received high-frequency abdominal imaging ($p<0.001$). Health outcomes resulting from changes in management were not reported.

Plasseraud (2016) reported metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDx-UM conducted at four centers, which included 70 patients at the time of reporting.[63] Surveillance regimens were documented by participating physicians as part of registry data entry. “High-intensity” surveillance was defined as imaging and/or liver function testing (LFTs) every three to six months and “low-intensity” surveillance was defined as annual imaging and/or LFTs. The method for following patients for clinical outcomes was not specified. Of the 70 enrolled patients, 37 (53%) were Class 1. Over a median follow up of 2.38 years, more Class 2 patients (36%) than Class 1 patients (5%; $p=0.002$) experienced a metastasis. The three-year metastasis-free survival rate was lower for Class 2 patients (63%; 95% CI 43% to 83%) than Class 1 patients (100%, $p=0.003$). Most Class 1 patients (n=30) had low-intensity surveillance and all (n=33) Class 2 patients had high-intensity surveillance. Aaberg (2020) published updated five-year outcomes for 89 patients.[64] Of these 89 patients, 49 (55%) were class 1, of which 39 (80%) received low-intensity management. The five-year metastasis-free survival rate was 90% for class 1 patients compared to 40.7% for class 2 patients ($p<0.0001$). The five-year melanoma-specific survival was 94.3% for class 1 patients compared to 63.4% for class 2 patients ($p=0.0007$). Strengths of this study included a relatively large population given the rarity of the condition, and an association between management strategies and clinical outcomes. However, it is not clear which outcome measures were prespecified or how data was collected, making the risk of bias high.

Aaberg (2014) reported on changes in management associated with GEP risk classification.[1] They analyzed Medicare claims data submitted to Castle BioSciences by 37 ocular oncologists in the United States. Data were abstracted from charts on demographics, tumor pathology and diagnosis, and clinical surveillance patterns. High-intensity surveillance was defined as a frequency of every three to six months and low-intensity surveillance was a frequency of every 6 to 12 months. Of 195 patients with GEP test results, 88 (45.1%) patients had evaluable tests and adequate information on follow-up surveillance, 36 (18.5%) had evaluable tests and adequate information on referrals, and 8 (4.1%) had evaluable tests and adequate information on adjunctive treatment recommendations. Of the 191 evaluable GEP tests, 110 (58%) were Class 1 and 81 (42%) were Class 2. For patients with surveillance data available (n=88), all patients in GEP Class 1 had low-intensity surveillance and all patients in GEP Class 2 had high-intensity surveillance ($p<0.001$ vs. Class 1).

PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines which specifically recommend the use of gene expression assays, specifically the DecisionDx assays, to guide the clinical management of patients with malignant tumors.

NATIONAL COMPREHENSIVE CANCER NETWORK

Cutaneous Melanoma

The National Comprehensive Cancer Network guidelines (v.2.2024) for cutaneous melanoma state the following the use of GEP to evaluate lesions of uncertain malignancy following histology:[65]

> "Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next generation sequencing (NGS). These tests may facilitate a more definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."

The guidelines state the following regarding prognostic testing:

> “Despite commercially available GEP tests being marketed to risk stratify cutaneous melanoma, current GEP platforms do not provide clinically actionable prognostic information when combined or compared with known clinicopathologic (CP) factors (eg, sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status) or multivariable nomograms/risk location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status). Furthermore, the clinical utility of these tests to inform treatment recommendations and improve health outcomes by prompting an intervention has not been established.”
>
> Various studies of prognostic GEP tests suggest their role as an independent predictor of worse outcome. However, GEP studies to date have not demonstrated added benefit beyond comprehensive CP variables, and it remains unclear whether available GEP tests are reliably predictive of outcome across the risk spectrum of cutaneous

melanoma. Validation studies on prospectively collected, independent cohort (similar to those performed in breast cancer) are necessary to define the clinical utility of molecular prognostic GEP testing as an adjunct to AJCC staging and other known prognostically significant CP variables or as part of the multidisciplinary decision-making process to guide surveillance imaging, SLNB, and adjuvant therapy.

Existing and emerging GEP tests and other molecular techniques (ie, circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary models that incorporate readily available CP variables. Prospective study of the utility of predictive GEP for SLNB risk, in conjunction with well-established CP factors, is ongoing."

In addition, the guidelines state:

"Currently, there is insufficient evidence to support incorporation of current GEP tests into melanoma care. The use of GEP according to specific AJCC-8 melanoma stage (before or after SLBN) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP tests to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures and are not recommended outside of the context of a clinical study or trial. Moreover, since there is a low probability of metastasis in stage I melanoma and a high proportion of false-positive results using these tests, GEP testing should not guide clinical decision-making in this subgroup. In addition, the likelihood of a positive SLNB may be informed by the use of multivariable nomograms/risk calculators. Ongoing prospective investigation will further inform the utility of GEP tests and multivariable nomograms/risk calculators for SLNB risk prediction."

Uveal Melanoma

The National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.1.2024)[66] state: "Gene expression profiling (GEP) as described by Onken et al is recommended to determine whether the tumor is Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk) to inform frequency of follow-up."

AMERICAN ACADEMY OF DERMATOLOGY

The American Academy of Dermatology (2019) published guidelines of care for the management of primary cutaneous melanoma.[67] The guidelines state the following regarding GEP tests:

Regarding diagnostic GEP tests:

- "Diagnostic molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not recommended for routine diagnostic use in CM. These include comparative genomic hybridization, fluorescence in situ hybridization, gene expression profiling (GEP), and (potentially) next generation sequencing."
- "Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms."

Regarding prognostic GEP tests:

- "...there is also insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, to provide more accurate prognosis beyond currently known clinicopathologic factors" (Strength of evidence: C, Level of evidence II/III)
- "Going forward, GEP assays should be tested against all known histopathologic prognostic factors and contemporary eighth edition of AJCC CM staging to assess their additive value in prognostication."
- "Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."

MELANOMA PREVENTION WORKING GROUP

The Melanoma Prevention Working Group (2020) published consensus recommendations regarding the use of GEP for cutaneous melanoma.[68] After evaluating the available evidence, the working group concluded that the published evidence is “insufficient to establish that routine use for GEP testing provides additional clinical value for melanoma stating and prognostication beyond available clinicopathologic variables,” and that findings are needed from large, representative patient populations with adequate clinical follow-up to allow comparison with these variables.

SUMMARY

There is enough research to show that the DecisionDX-UM™ genetic test can identify certain patients with uveal melanoma that are at higher risk for their cancer to spread. This information can be used to help determine how often patients should be checked for metastatic disease. Therefore, the DecisionDX-UM™ genetic test may be considered medically necessary for patients with primary, localized uveal melanoma.

There is not enough research to show that the DecisionDX-UM™ genetic test can be useful to measure risk in people with other types of disease, including people with uveal cancer that has spread from another site in the body. Therefore, the DecisionDX-UM™ genetic test is considered investigational in people who do not meet the policy criteria.

There is not enough research to show that any other gene expression tests can help to guide patient management and improve health outcomes for people with cutaneous melanoma or pigmented lesions suspected of being melanoma. Therefore, gene expression assays, including but not limited to DecisionDX-Melanoma™, Pigmented Lesion Assay, PLAplus™, and myPath Melanoma™, are considered investigational in patients with cutaneous melanoma or pigmented lesions.

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CODES

Codes	Number	Description
CPT	0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
	0090U	Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, or malignant)
	0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
	0387U	Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalinfixed paraffin-embedded (FFPE) tissue, report for risk of progression
	81479	Unlisted molecular pathology procedure
	81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
	81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure
	88299	Unlisted cytogenetic study
HCPCS	None	

Date of Origin: *April 2013*

Medical Policy Manual Genetic Testing, Policy No. 41

BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Effective: November 1, 2024

Next Review: July 2025
Last Review: September 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

BRAF and MEK inhibitors are drugs that were originally designed to target a variant in the *BRAF* gene found in some advanced melanoma tumors. This BRAF-variant kinase is believed to be actively involved in oncogenic proliferation, and specific inhibition of the kinase has been shown to slow tumor growth and may improve patient survival.

MEDICAL POLICY CRITERIA

I. Testing for *BRAF* variants in tumor tissue to select targeted therapy may be considered **medically necessary** for patients with advanced, metastatic, or unresectable melanoma.

II. Testing for *BRAF* variants for all other patients with melanoma is considered **investigational**.

III. Testing for *BRAF* variants in tumor tissue to select targeted therapy may be considered **medically necessary** for patients with glioma.

IV. Testing for *BRAF* variants for patients with glioma is considered **investigational** for all other purposes.

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.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes, Genetic Testing, Policy No. 06
2. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83

BACKGROUND

MELANOMA

Overall incidence rates for melanoma have been increasing for at least 30 years. In advanced (stage IV) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are stage IV at diagnosis, prognosis is poor, with a five-year survival of only 15-20%. For several decades since its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has low response rates of only 15-25% and median response durations of five to six months. Less than 5% of responses are complete.[1] Temozolomide has similar efficacy with a greater ability to penetrate the central nervous system. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy[2-6] regardless of *BRAF* status and is now recommended as one potential first-line treatment of metastatic or unresectable melanoma by the National Comprehensive Cancer Network (NCCN).[7]

Variants in the *BRAF* kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway that is associated with oncogenic proliferation. In general, 50 to 70% of melanoma tumors harbor a *BRAF* variant and of these, 80% are positive for *BRAF* V600E and 16% are positive for *BRAF* V600K.[8] Thus,

approximately 45% to 60% of advanced melanoma patients might respond to a BRAF inhibitor targeted to this variant kinase.

BRAF inhibitors (e.g., vemurafenib, dabrafenib) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (e.g., trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (trade name Zelboraf®, also known as PLX4032 and RO5185426) was co-developed under an agreement between Roche (Genentech) and Plexxikon. Vemurafenib was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the BRAF V600E variant kinase and significantly lower potency to inhibit most of many other kinases tested.[9] Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in *BRAF*-variant cells[10-12] and caused regression of *BRAF*-variant human melanoma xenografts in murine models.[9] Paradoxically, preclinical studies also showed that melanoma tumors with the *BRAF* wild-type gene sequence could respond to variant BRAF-specific inhibitors with accelerated growth,[10-12] suggesting that it might be harmful to administer BRAF inhibitors to patients with BRAF wild-type melanoma tumors. Potentiated growth in BRAF wild-type tumors has not yet been confirmed in melanoma patients as the supportive clinical trials were enrichment trials, enrolling only those patients with tumors positive for the *BRAF* V600E variant.

Dabrafenib (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline, now Novartis.[13, 14] Dabrafenib inhibits several kinases, including variant forms of BRAF, with greatest activity against the V600E BRAF variant. In vitro and in vivo studies demonstrated dabrafenib's ability to inhibit growth of *BRAF* V600 variant-positive melanoma cells.[15]

Trametinib (trade name Mekinist™) is an inhibitor of MEK1 and MEK2 developed by GlaxoSmithKline. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2.[16] Trametinib inhibits growth of BRAF V600 variant-positive melanoma cells in vitro and in vivo.[17]

Cobimetinib, formally GDC-0973/XL518 (trade name Cotellic®) was developed by Genentech[18] and Exelixis[19]. It is a MEK inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.

Nivolumab (OPDIVO®), developed by Bristol-Myers Squibb, is not a BRAF or MEK inhibitor, but instead inhibits the PD-1 protein on cells. PD-1 blocks the body's immune system from attacking melanoma tumors. Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express a *BRAF* V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor.

GLIOMA

Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, World Health Organization (WHO) published an update of its classification of gliomas based on both histopathologic appearance and molecular parameters.[20] The classification ranges from grade I to IV corresponding to the degree of

malignancy (aggressiveness) with WHO grade I being least aggressive and grade IV being most aggressive.

Low-grade gliomas were historically those classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, along with additional radiation and chemotherapy following surgery except in the case of pilocytic astrocytoma. The optimal timing of additional therapies is unclear. Many patients will recur following initial treatment with a clinical course similar to high-grade glioma. High-grade gliomas (WHO grade III/IV) include anaplastic gliomas and glioblastoma. Maximal surgical resection is the initial treatment followed by combined adjuvant chemoradiotherapy. Temozolomide, an oral alkylating agent, is considered standard systemic chemotherapy for malignant gliomas. The prognosis for patients with high-grade gliomas is poor: the one-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.[21]

There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, *BRAF* V600E variants have been found in approximately 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma.[22-27] However, it may be rare in adult glioblastoma.[28] There is considerable interest in targeted therapies that inhibit the MAPK pathway, particularly in patients with high-grade glioma and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early phase trials in patients with *BRAF* variant-positive melanoma with brain metastases suggest some efficacy for brain tumor response with vemurafenib and dabrafenib,[29, 30] indicating that these agents might be potential therapies for primary brain tumors.

REGULATORY STATUS

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, released on July 14, 2011,[31] to address the "emergence of new technologies that can distinguish subsets of populations that respond differently to treatment." As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices "when an appropriate scientific rationale supports such an approach." In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

- **Vemurafenib**

  Vemurafenib and a Class III companion diagnostic test, the cobas® 4800 BRAF V600 Mutation Test, were co-approved by the FDA in August 2011.[32] The test is approved as an aid in selecting melanoma patients whose tumors carry the *BRAF* V600 variant for treatment with vemurafenib.[33] Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 variant. The vemurafenib full prescribing information states that confirmation of a *BRAF* V600 variant using an FDA-approved test is required for selection of patients appropriate for therapy.[34]

- **Dabrafenib**

Dabrafenib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variant, as detected by an FDA-approved test.[15] A 2018 updated approval indicates that it may be used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Dabrafenib is specifically not indicated for the treatment of patients with wild-type *BRAF* melanoma.

- **Trametinib**

Trametinib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants, as detected by an FDA-approved test.[17] A 2018 update indicates that it may be used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy.[17]

- **Nivolumab**

Nivolumab was originally FDA-approved December 2014 for the treatment of unresectable or metastatic melanoma.[35] Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express an activating BRAF V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor. Nivolumab may also be used in combination with ipilimumab in patients without a *BRAF* V600 variant.

- **Cobimetinib**

Cobimetinib was FDA-approved November 2015 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib, as detected by an FDA-approved test. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.[36]

- **Binimetinib**

Binimetinib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with encorafenib.

- **Encorafenib**

Encorafenib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with binimetinib.

In 2014, the FDA granted accelerated approval of trametinib and dabrafenib as a combination therapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test.[37] Approval of the combination therapy was based on the demonstration of durable objective responses in a multicenter, open-label, randomized (1:1:1), active-controlled, dose-ranging trial enrolling 162 patients with histologically confirmed Stage IIIC or IV melanoma determined to be *BRAF* V600E or V600K. No more than one prior chemotherapy regimen and/or interleukin-2 were permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

In November 2015, cobimetinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variant, in combination with vemurafenib.[36] Additionally, in 2011, ipilimumab (Yervoy®) was approved by the FDA for the treatment of patients with unresectable or metastatic melanoma. For the first time, a survival advantage was demonstrated in previously treated patients: median survival on ipilimumab of 10 months versus 6.4 months on control medication. However, side effects of ipilimumab can include severe and fatal immune-mediated adverse reactions, especially in patients who are already immune-compromised. Ipilimumab's clinical study did not test metastatic melanoma patients' tumors for *BRAF* status; therefore, it's not known what, if any, clinical relevance *BRAF* status has with respect to ipilimumab.

In 2018, the FDA approved encorafenib and binimetinib together for unresectable or metastatic melanoma with *BRAF* V600 variants.

In 2022, the FDA approved dabrafenib and trametinib together for unresectable or metastatic solid tumors with *BRAF* V600 variants.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on the clinical validity and utility of testing.

BRAF TESTING TO SELECT TREATMENT FOR MELANOMA

For individuals with melanoma who receive *BRAF* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

GLIOMA

For individuals with glioma who receive *BRAF* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

NCCN guidelines for cutaneous melanoma (v.2.2024) includes the following recommendations:[7]

- The panel does not recommend *BRAF* or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation.
- *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future *BRAF*-directed therapy may be an option.
- For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g., larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.
- If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT*, *BRAF* non-V600).

The NCCN guidelines for central nervous system cancers (v.2.2024) state the following:[38]

- The panel encourages molecular testing of glioblastoma because if a driver mutation (such as *BRAF* V600E or *NTRK* fusion) is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial.
- Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.

The NCCN guidelines for pediatric central nervous system cancers (v.1.2024) include a recommendation to test for *BRAF* V600E and *BRAF* fusion for pediatric gliomas, and further recommend that preferred systemic therapy options for recurrent disease include, but are not limited to, dabrafenib/trametinib or vemurafenib for *BRAF* V600E-positive tumors.[39]

SUMMARY

There is enough research to show that *BRAF* variant testing can improve health outcomes for some melanoma patients by helping them to select an FDA-approved targeted treatment. In addition, clinical practice guidelines recommend treatment with these BRAF inhibitors in certain patients with a V600 *BRAF* variant. Therefore, *BRAF* variant testing may be considered medically necessary to select treatment for patients with advanced, metastatic, or unresectable melanoma. Testing for *BRAF* variants for all other patients with melanoma is considered investigational, as there are no FDA-approved *BRAF*-targeted therapies for early-stage melanoma.

There is enough research to show that *BRAF* variant testing can improve health outcomes for some glioma patients by helping them to select an FDA-approved targeted treatment. In addition, clinical practice guidelines recommend treatment with these BRAF inhibitors in certain patients with a V600 *BRAF* variant. Therefore, *BRAF* variant testing may be considered medically necessary to select treatment for patients with glioma. Testing for *BRAF* variants for other purposes is considered not medically necessary.

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CODES

Codes	Number	Description
CPT	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
HCPCS	None	

Date of Origin: *January 2012*

Medical Policy Manual Genetic Testing, Policy No. 42

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Effective: April 1, 2025

Next Review: December 2025
Last Review: February 2025

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 important part of treatment planning for women with early-stage breast cancer involves evaluating the potential benefit from adjuvant therapies. Tests of genetic expression in tumor tissue have been proposed as techniques to determine prognosis (risk of recurrence) thereby providing additional information to guide treatment decisions for patients with breast cancer.

MEDICAL POLICY CRITERIA

Note: This policy does not address the identification of germ-line DNA alterations in genes (*BRCA1* and *BRCA2*) to provide information on future risk of hereditary breast or ovarian cancer. *BRCA1* and *BRCA2* testing is addressed in a separate medical policy (see Cross References).

I. The use of Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, or EndoPredict® to determine recurrence risk, for deciding whether or not to undergo adjuvant chemotherapy, may be considered **medically necessary** when all of the following criteria are met:

   A. Individual has primary breast cancer, stage I, II, or III (see Policy Guidelines);

   B. Individual has had excision of breast mass and full pathologic evaluation of the

specimen has been completed (i.e., the test should not be ordered on a preliminary core biopsy, however biopsy sample testing after full pathologic evaluation may be indicated in rare circumstances when tumor testing is not possible);

C. Primary tumor size greater than 0.5 cm;

D. Hormone receptor positive (that is ER-positive or PR-positive, see Policy Guidelines);

E. HER2-negative (see Policy Guidelines);

F. Individual has negative lymph nodes or 1 to 3 positive lymph nodes (nodes with micrometastases of 2 mm or smaller are considered node negative); and

G. Individual has not already made the decision to undergo or forego chemotherapy.

II. The use of Breast Cancer Index™ to determine recurrence risk, for deciding whether or not to receive extended endocrine therapy (beyond 5 years), may be considered **medically necessary** when all of the following criteria are met:

A. Individual has primary breast cancer, stage I, II, or III (see Policy Guidelines);

B. Individual has had excision of breast mass and full pathologic evaluation of the specimen has been completed (i.e., the test should not be ordered on a preliminary core biopsy, however biopsy sample testing after full pathologic evaluation may be indicated in rare circumstances when tumor testing is not possible);

C. Primary tumor size greater than 0.5 cm;

D. Hormone receptor positive (that is ER-positive or PR-positive, see Policy Guidelines);

E. HER2-negative (see Policy Guidelines);

F. Individual has negative lymph nodes or 1 to 3 positive lymph nodes (nodes with micrometastases of 2 mm or smaller are considered node negative); and

G. Individual has not already made the decision to undergo or forego extended endocrine therapy.

III. Use of Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, or EndoPredict® on surgical tumor specimens to determine recurrence risk in patients with primary breast cancer is considered **not medically necessary** for patients who do not meet Criterion I. or II. above.

IV. All other uses of gene expression assays for breast cancer are considered **investigational**, including but not limited to:

A. Use of Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, or EndoPredict® for predicting response to specific chemotherapy regimens or determining HER2 status.

B. Use of other assays of genetic expression in breast tumor tissue, including but not limited to BluePrint®, Mammostrat®, TargetPrint®, Oncotype Dx Breast DCIS Score, and Prosigna™/PAM50.

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

POLICY GUIDELINES

Ductal carcinoma in situ (DCIS) is considered stage 0 breast cancer and is therefore addressed in criterion III.

Hormone receptor and HER2 status may be determined from needle core biopsy or from the full pathological evaluation.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
    - History and physical exam
    - Conventional testing and outcomes, including full pathological report of excised breast mass

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and/or Ovarian Cancer and Li-Fraumeni Syndrome, Genetic Testing, Policy No. 02
2. Gene Expression-Based Assays for Cancers of Unknown Primary, Genetic Testing, Policy No. 15
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Gene Expression Profiling for Melanoma, Genetic Testing, Policy No. 29
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
6. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46
7. Investigational Gene Expression and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

For patients with early-stage breast cancer, adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk for recurrence. For example, those with the best prognosis have small tumors, are estrogen receptor (ER)-positive, and lymph node-negative. These individuals have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease-free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard, and several common criteria have qualitative or subjective

components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help patients who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Several panels of gene expression markers ("signatures") have been identified that appear to predict the baseline risk of breast cancer recurrence after surgery, radiation therapy, and hormonal therapy (for hormone receptor-positive tumors) in those with node-negative disease. The available gene expression tests include:

- Oncotype DX® Breast Recurrence Score (a 21-gene RT-PCR assay; Genomic Health)
- Oncotype DX® Breast DCIS Score
- 70-gene signature MammaPrint® (also referred to as the "Amsterdam signature"; Agendia)
- Mammostrat® (Clarient Diagnostic Services)
- Molecular Grade Index (Aviara MGI℠; AviaraDx, Inc.)
- Breast Cancer Index™, a combination of the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics)
- BreastOncPx™ (Breast Cancer Prognosis Gene Expression Assay; LabCorp)
- Prosigna™ (NanoString Technologies)
- NexCourse® Breast IHC4 (Geneoptix)
- BreastPRS™ (Signal Genetics)
- EndoPredict® (Myriad Genetics)
- BluePrint® (Agendia)
- TargetPrint® (Agendia)

If these panels are more accurate than current conventional risk classifiers, they could be used to aid chemotherapy decision-making, where current guidelines do not strongly advocate its use, without negatively affecting disease-free and overall survival outcomes.

Oncotype DX® Breast DCIS Score, which uses a slightly different algorithm than the standard Oncotype DX® to calculate results, is marketed for patients with noninvasive, ductal carcinoma in situ (DCIS) to predict the 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision making in patients with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

Of note, gene expression profiling should not be ordered as a substitute for standard ER or progesterone receptor (PR) testing. Gene expression profiles to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy should only be ordered after surgery and subsequent pathology examination of the tumor have been completed. The test should be ordered in the context of a physician-patient discussion regarding risk preferences and when the test result will aid the patient in making decisions regarding chemotherapy.

Gene expression patterns have led to the identification of molecular subtypes of breast cancer, which have different prognoses and responses to treatment regimens. These molecular subtypes are largely distinguished by the differential expression of estrogen receptors, progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) in the tumor, and are classified as luminal, basal or HER2 type. Luminal-like breast cancers are ER positive, basal-like breast cancers correlate best with ER, PR and HER2 negative ("triple negative"), and HER2 type with high expression of HER2.

At present, the methodology for molecular subtyping is not standardized, and breast cancer subtyping is routinely assessed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

- BluePrint® is an 80-gene expression assay which classifies breast cancer into basal type, luminal type or ERBB2-type. The test is marketed as an additional stratification into a molecular subtype following risk assessment with MammaPrint®.
- TargetPrint® is a microarray-based gene expression test which offers a quantitative assessment of ER, PR and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with MammaPrint® and BluePrint®.

EVIDENCE SUMMARY

This evidence review focuses on gene expression profiling (GEP) panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known ER, PR and HER2 status. The proposed clinical utility of these tests varies depending on the clinical context; specific areas of proposed clinical utility are discussed in this evidence review:

1. Prognosis in patients with node-negative, early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.

2. Prognosis in patients with node-positive (one to three nodes), early stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.

3. Prognosis in patients with node-negative, early-stage, HER2-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to five years post-diagnosis, for the purpose of determining whether patients should continue adjuvant hormonal therapy.

4. Prognosis in patients with ductal carcinoma in situ (DCIS) for the purpose of selecting patients for radiation therapy.

Randomized controlled trials (RCTs) comparing health outcomes in women with primary breast cancer, who are managed *with* versus *without* gene expression profiling assays, are necessary to reliably establish the clinical utility of these assays.

In 2014, the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) addressed gene expression profiling in women with lymph node-negative breast cancer to select adjuvant chemotherapy, specifically the use of Oncotype DX®, MammaPrint®, the Breast Cancer Index™, and Prosigna™/PAM50 gene expression assay.[1] This report did not address the use of gene expression profiling in women with lymph node-positive breast cancer to guide adjuvant chemotherapy. The TEC Assessment concluded that the use of Oncotype DX® to assess the risk of recurrence and to determine if a patient should undergo adjuvant chemotherapy in women with unilateral, hormone receptor-positive, lymph node-negative breast cancer, who will receive hormonal therapy, met the BCBSA TEC criteria. The TEC assessment also concluded that use of MammaPrint®, the Breast Cancer Index™, and Prosigna™ to determine recurrence risk in women with unilateral, hormone receptor-positive, lymph node-negative breast cancer who will receive hormonal therapy does not meet TEC criteria.

Since the TEC Assessment above, many studies have been published that have evaluated GEP testing for a variety of indications. This evidence review focuses on studies presenting a minimum of five-year distant disease recurrence rates, as well as recently published prospective studies specifically designed to evaluate the clinical utility of genetic expression profiles. Studies in which the gene expression algorithm was being developed ("training sets"), studies using convenience samples of patients, and observational studies based on registry data were not included.

ONCOTYPE DX® BREAST RECURRENCE SCORE

Oncotype DX® Breast Recurrence Score is available only from the CLIA-licensed Genomic Health laboratory as a laboratory-developed service, as it has not been cleared or approved by the FDA. Results from the Oncotype DX® gene expression profile are combined into a recurrence score (RS). Tissue sampling, rather than technical performance of the assay, is likely to be the greatest source of variability in results. The Oncotype DX® assay was validated in studies using archived tumor samples from subsets of patients enrolled in published RCTs of early breast cancer treatment. Patients enrolled in the trial arms, from which specimens were obtained, had primary, unilateral breast cancer with no history of prior cancer, and were treated with tamoxifen. Tumors were estrogen receptor positive, most were HER2-negative, and in the case of at least one study, multifocal tumors were excluded.[2]

Oncotype DX® RS for Adjuvant Chemotherapy Decisions in Lymph Node-Negative Patients

As described above, the 2014 BCBSA TEC Assessment concluded that the following circumstance meets the TEC criteria: Use of Oncotype DX® to determine recurrence risk in women with unilateral, hormone receptor-positive, lymph node-negative breast cancer, who will receive hormonal therapy, and are deciding whether to undergo adjuvant chemotherapy.[1] In the AHRQ Technology Assessment described above, the 16 studies included in the assessment uniformly examined cohorts with hormone-receptor positive breast cancer, and most were limited to women with node-negative cancers.[3] Additional studies have evaluated the association between RS and recurrence risk in node-negative patients.[4-7] Results indicate strong, independent associations between Oncotype DX® RS results and distant disease recurrence or death from breast cancer.[6, 8]

Sparano (2018) conducted a RCT, Trial Assigning Individualized Options for Treatment (TAILORx), to evaluate risk of recurrence in women with midrange scores.[9] Women with intermediate-risk scores were randomized to receive either endocrine therapy (n=3,399) or chemoendocrine therapy (n=3,312). Women with low-risk scores (≤10) received endocrine therapy (n=1,619) and women with high-risk scores (≥26) received chemoendocrine therapy (n=1,389). Overall disease-free survival (DFS) estimates showed that adjuvant endocrine therapy was noninferior to chemoendocrine therapy in women with intermediate-risk scores (DFS 83.36% vs. 84.3%, respectively). However, subgroup analyses by age showed women younger than 50 may benefit from chemotherapy.

In secondary analyses of data published by Paik (2004), patient risk levels were individually classified by conventional risk classifiers, and then reclassified by Oncotype DX®.[4] Oncotype DX® added additional risk information to the conventional clinical classification of individual high-risk patients, and identified a subset of patients who would otherwise be recommended for chemotherapy, but are actually at lower risk of recurrence (average 7% to 9% risk at 10 years, upper 95% confidence interval [CI] limits 11% to 15%). Thus, a woman who prefers to

avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX® RS value shows that she is at very low risk of recurrence, might reasonably decline chemotherapy. The lower the RS value, the greater the confidence that chemotherapy will not provide net benefit; outcomes are improved by avoiding chemotherapy toxicity.

In another RCT, samples were obtained from ER-positive, node-negative breast cancer patients, who were either treated with tamoxifen or tamoxifen plus chemotherapy, and were tested by Oncotype DX®.[2] RS high-risk patients derived clear benefit from chemotherapy, whereas the average benefit for other patients was statistically not significant.

Because clinical care for breast cancer patients has evolved since the original trials that required archived samples for assay validation, differences in evaluation and treatment regimens were considered. It was concluded that Oncotype DX® meets the TEC criteria for the following women with node-negative breast cancer:

- Those receiving aromatase inhibitor (AI)-based hormonal therapy instead of tamoxifen therapy. AI-based therapy would likely reduce recurrence rates for all RS risk groups. Thus, if a patient declined chemotherapy today on the basis of a low-risk RS (risk categories defined by outcomes with tamoxifen treatment), the even lower risk associated with AI treatment would not change that decision.
- Those receiving anthracycline-based chemotherapy instead of CMF. The type of chemotherapy does not change the interpretation of the Oncotype DX® risk estimate. Additionally, a recent meta-analysis indicates that anthracyclines do not improve disease-free or overall survival in women with early HER2-negative breast cancer[10], and therefore may not be prescribed in this population.
- Lymph nodes with micrometastases are not considered positive for purposes of treatment recommendations.[11] Current practice largely involves a detailed histologic examination of sentinel lymph nodes allowing for the detection of micrometastases (< 2 mm in size).
  Those whose tumors are ER-positive or PR-positive. Only ER-positive women were enrolled in Oncotype DX® validation studies, whereas current clinical guidelines include either ER or PR positivity in the treatment pathway for hormone receptor positive women with early-stage breast cancer. Recent studies show that ER-negative, PR-positive patients also tend to benefit from hormonal therapy.[12, 13] Studies documenting the low incidence (1% to 4%) and instability (lack of reproducibility) of the ER-negative/PR-positive subtype[14] and the reduction in reports of this subtype with improved assay techniques[15] suggest that this subtype may represent a false-negative result.

Several nonrandomized studies reporting on the use of the 21-gene assay in lymph-node negative patients have been published[16, 17], including a prosepective study by Sparano (2015) that assigned women with a recurrence score of 0 to 10 to receive endocrine therapy without chemotherapy.[18] At five-years follow-up, 1,626 women with low recurrence scores were included in the analysis. In this patient population, the rate of invasive disease–free survival was 93.8% (95% CI 92.4 to 94.9), the rate of freedom from distant disease was 99.3% (95% CI 98.7 to 99.6), and the rate of freedom from recurrence of breast cancer at a distant or local–regional site was 98.7% (95% CI 97.9 to 99.2). Kizy (2017) evaluated the use of the of Oncotype DX® in women with invasive lobular carcinoma, using data from the Surveillance, Epidemiology and End Results database from 2004 to 2013.[19] There were 7,316 participants included in the study, the majority with grade I or II tumors (93%) and negative lymph nodes (85%). The RS cutpoints used for most of the analyses were 11 and 25, values used in the Trial Assigning Individualized Options for Treatment (TAILORx) to avoid undertreatment. Using

these conservative cutpoints, 8% of the participants were categorized as high-risk, and 72% as intermediate risk. Adjuvant chemotherapy was not associated with any increased five-year BCSS in these high- and intermediate-risk groups.

Several studies have been published regarding the impact of RS results on chemotherapy recommendations by medical oncologists.[20-28] According to these studies, comparing recommendations made prior to and revised after knowledge of RS results show that decisions change in about 25-61% of patients, most often from endocrine therapy plus chemotherapy to endocrine therapy alone.

Oncotype DX® RS for Adjuvant Chemotherapy Decisions in Lymph Node-Positive Patients

In a systematic review partly funded by Genomic Health, Brufsky (2014) [29] assessed articles and abstracts, that evaluated the 21-gene breast cancer profiling assay (using RT-PCR technology) in patients with ER+ and node-positive early-stage breast cancer. Study results suggested that the RS is an independent predictor of disease-free survival, overall survival, and distant recurrence-free survival. Overall, these studies showed that in 26% of 51% of N+ cases, physicians used results of the RS assay to reassess patient status and ultimately change their treatment recommendations. In 60% to 66% of node-negative and node-positive cases, changes in treatment recommendations resulted in the elimination of chemotherapy.

Despite some favorable results of clinical utility, accompanied by author recommendations supporting the use of RS, the overall quality of the review was hampered by several methodological limitations, for example, study authors did not clearly report the systematic methodology used to conduct the literature search, such as details of the literature search criteria or inclusion and exclusion criteria used during the study selection process. In addition, they did not report assessing the quality of the individual clinical studies nor the body of evidence. Authors included abstracts presented at international congresses for detailed evidence review; however, results of these abstracts have yet to be accepted and published by a peer-reviewed journal. Hence, these various limitations substantially weaken the confidence in the findings that support clinical utility of the 21-gene assay in women with node-positive, early-stage breast cancer.

Kalinsky (2021) reported results from the RxPONDER RCT.[30] Participants with hormone-receptor–positive, HER2-negative breast cancer, one to three positive axillary lymph nodes, and a RS of 25 or lower were randomized to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. The primary objective was to determine the effect of chemotherapy on invasive disease–free survival and whether the effect was influenced by the RS. Secondary end points included distant relapse–free survival.

Among postmenopausal women, estimates of invasive disease–free survival at five years were 91.3% in the chemoendocrine group and 91.9% in the endocrine-only group (hazard ratio [HR] 1.02 for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 95% CI 0.82 to 1.26, p=0.89). In premenopausal women, the rate of invasive disease–free survival at five years among those in the chemoendocrine group was 93.9%, as compared with 89.0% among those in the endocrine-only group (absolute difference, 4.9 percentage points), with a significant chemotherapy benefit (HR 0.60 for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 95% CI 0.43 to 0.83, p=0.002). The study authors concluded that postmenopausal women with one to three positive axillary lymph nodes and a recurrence score of 0 to 25 could “safely forgo adjuvant chemotherapy without

compromising invasive disease–free survival and distant relapse–free survival." In contrast, premenopausal women with one to three positive lymph nodes "had a significant benefit from chemotherapy, even with a very low recurrence score." A follow-up study by Abdou (2024) found that non-Hispanic Black participants in the study had worse clinical outcomes that non-Hispanic White participants, despite having similar RS scores and similar treatment.[31]

Nitz (2017) conducted a phase 3 Plan B trial with a mixed population of women with node-negative and node-positive breast cancer.[32] The trial was initially designed to compare anthracycline-containing chemotherapy with anthracycline-free therapy. An amendment was made to recommend endocrine therapy alone for patients with an RS of 11 or less that were node-negative or had only one positive node. A total of 2,642 patients were included in the trial. Median age was 56 years, 59% were node-negative, 35% had one positive nodes, and 6% had two or three positive nodes. Details of subgroup analyses of node-positive patients were limited. The authors stated that five-year overall survival in patients with an RS between 12 and 25 was significantly higher than in patients with an RS greater than 25 within all nodal subgroups and that five-year overall survival in low RS patients was higher compared with high RS patients in all nodal subgroups, but rates and CIs were not provided. Five-year DFS in patients with one positive node and a RS ≤11 treated with endocrine therapy alone (n=110) was 94.4% (95% CI 89.5 to 99.3%). The final analysis of the Plan B trial reported similar results regarding RS scores and DFS.[33]

Albain (2010) published retrospective analysis of the OncotypeDX® assay.[34] Study results showed that patients with high RS scores appeared to achieve greater benefit from the addition of chemotherapy than patients with low RS scores, regardless of the total number of affected lymph nodes. In the multivariate analysis of RS interaction with disease-free survival, adjusted for number of positive nodes, was significant for the first five years of follow-up (p=0.029) and remained significant after adjusting for age, race, tumor size, PR status, grade, p53, and HER2. However, the interaction was not significant (p=0.15) after adjusting for ER level (ER gene expression is a component of the 21-gene profile). Interaction results were similar for overall survival.

Additional Applications of Oncotype DX®

In 2008, Genomic Health announced that results of Oncotype DX® tests would include not only the overall test results, but also the results of the quantitative ER and PR tests that are included in the Oncotype DX® panel. This is based on a study that compared the Oncotype DX® ER and PR results with traditional immunohistochemistry (IHC) results.[35] The study reported high concordance between the two assays (90% or better), but that quantitative ER by Oncotype DX® was more strongly associated with disease recurrence than the IHC results. However, ER and PR analyses are traditionally conducted during pathology examination of all breast cancer biopsies, whereas Oncotype DX® is indicated only for known ER-positive tumors, after the pathology examination is complete, when the patient meets specific criteria and chemotherapy is being considered. Thus, Oncotype DX® should not be ordered as a substitute for ER and PR IHC. Additionally, accepted guidelines for ER and PR testing outline standards for high quality IHC testing and do not recommend confirmatory testing, so the 21-gene RS should not be ordered to confirm ER/PR IHC results. A subsequent study by Khoury (2015) reported better correlation between IHC and Oncotype DX® for PR (Spearman correlation, 0.91) than for ER (Spearman correlation, 0.65), but worse concordance (at various cutpoints) for PR than for ER (99% vs 88%, respectively).[36]

Similarly, guidelines for HER2 testing specify IHC and/or FISH methods.[37] Although the HER2 component of the 21-gene assay has been shown to strongly correlate with FISH results,[38] the 21-gene assay should not be ordered to determine or confirm HER2.

MAMMAPRINT®

MammaPrint® has received 510(k) clearance for marketing by the FDA as a prognostic test for women younger than 61 years with ER-positive or ER-negative, lymph node-negative breast cancer. It is approved to assist in categorizing these breast cancer patients into high versus low risk for recurrence, but it is not approved for predicting benefit from adjuvant chemotherapy.

Mammaprint® for Adjuvant Chemotherapy Decisions

The Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT trial) published by Cardoso (2016), was a prospective trial that enrolled 6,693 women with early-stage breast cancer and assessed their genomic risk using MammaPrint® and their clinical risk using a modified version of Adjuvant! Online for cancer recurrence.[39] Women at low risk according to both methods did not receive chemotherapy. Women with discordant risks were randomized to chemotherapy or to no chemotherapy. Women at high-risk with both methods received chemotherapy. Although there were randomized components of the study, the primary endpoint was a noninferiority outcome of five-year metastasis-free survival rate in one cohort of the study population: those with high clinical risk and low genomic risk who did not receive chemotherapy. Declaring this to be the main end point implies a clinical strategy of using MammaPrint® only in patients at high clinical risk, and deferring chemotherapy in those tested patients who have low genetic risk scores. In this strategy, patients at low clinical risk are not tested with MammaPrint®.

While trial entry criteria included patients with node-positive, estrogen receptor-negative, or *HER2*-positive breast cancer, these patients constituted a minority of those in the study. The main results included these patients. The authors conducted supplemental analyses of various subgroups, including the subset who were node-negative, estrogen receptor-positive, or *HER2*-negative, which were qualitatively similar to the published main results.

In the main article, the principal objective of the study was met. The group at high clinical risk and low genomic risk who did not receive chemotherapy had a distant recurrence rate of 5.3% (95% CI 3.8% to 7.5%). In the node-negative, estrogen receptor-positive, or *HER2*-negative subgroup analysis, this group had a distant recurrence rate of 4.5% (95% CI, 3.8% to 8.4%). Piccart (2021) reported updated results from MINDACT with a median follow-up of 8.7 years.[40] In the updated analysis, five-year distant metastasis-free survival rate for individuals with high clinical risk and low genomic risk receiving no chemotherapy (primary test population, n=644) was 95.1% (95% CI 93.1% to 96.6%), supporting the previous analysis.

In the group with clinical low-risk and high genomic risk, who were not considered in the main outcome, in both the main analysis and in the node-negative, estrogen receptor-positive, or *HER2*-negative subgroup, the results would indicate that the risk of distant recurrence is not low enough to avoid chemotherapy (main analysis distant recurrence 5%, 95% CI 3% to 8.2%, subgroup distant recurrence HR 6.1%, 95% CI 3.9% to 9.4%). In the testing strategy implied in this study, by not testing for genomic risk in the low clinical risk group, these patients would not be identified.

The groups randomized to chemotherapy showed no significant difference in five-year distant recurrence, but the CIs were wide and thus less informative regarding whether chemotherapy is or is not beneficial in these patient groups. In the main study, the HR for chemotherapy in the high clinical risk/low genomic risk was 0.78 (95% CI 0.5 to 1.21). The HR for chemotherapy in the low clinical risk/high genomic risk group was 1.17 (95% CI 0.59 to 2.28).

To assess the impact of MammaPrint® on treatment decision-making, Cusumano (2014) distributed clinical information on 194 patients to multidisciplinary teams initially without and then with MammaPrint® gene signatures.[41] Eighty-six percent of patients were ER-positive, 88% were HER2-negative, and 66% were lymph node-negative. With the addition of MammaPrint® signatures, treatment recommendations changed in 27% of patients: 22% from chemotherapy to no chemotherapy and 35% from no chemotherapy to chemotherapy. In the subset of 453 ER-positive, HER2-negative patients, treatment advice changed in 32% of patients, with similar proportions changing from chemotherapy to no chemotherapy and vice versa.

Mammaprint® for Extended Endocrine Therapy Decisions

Esserman (2017) conducted a secondary analysis on data from women who were node-negative, in the Stockholm tamoxifen trial, which randomized patients with node-negative breast cancer to two years of tamoxifen, followed by an optional randomization for an additional three years to tamoxifen or no treatment.[42] A total of 652 tissue samples from the trial underwent MammaPrint® risk classification, 313 from the tamoxifen arm and 339 from the no therapy arm. The primary outcome was 20-year breast cancer-specific survival (BCSS). Initial classification by MammaPrint® identified 58% of the patients as low risk for distant recurrence and 42% as high risk. Twenty-year BCSS rates were 85% and 74% ($p<0.001$), respectively. Analysis was conducted on a subgroup of the low-risk group, considered ultralow risk. The tamoxifen-treated ultralow-risk group did not experience any deaths at 15 years. Survival rates were high for all patients in the ultralow-risk group, 97% for those treated with tamoxifen and 94% for those untreated.

BREAST CANCER INDEX™ (BCI)

The Breast Cancer Index™ is a simultaneous assessment of the HOXB13:IL17BR (H/I) ratio and the MGI (Molecular Grade Index). The H/I ratio indicates estrogen-mediated signaling; MGI assesses tumor grade by measuring the expression of five cell-cycle genes and provides prognostic information in ER-positive patients regardless of nodal status.

Breast Cancer Index™ for Adjuvant Chemotherapy Decisions

The 2014 TEC Assessment reviewed available studies for the original component assays.[1] There was insufficient evidence to determine whether the H/I ratio is better than conventional risk assessment tools in predicting recurrence. The ten-year recurrence estimates for patients classified as low risk were 17% to 25%, likely too high for most patients and physicians to consider forgoing chemotherapy.

Schroeder (2017)[43] calculated distant recurrence-free survival rates following five years of endocrine therapy among the subset of patients with clinically low-risk (T1N0) breast cancer from the two populations studied by Zhang (2013), described below. The Stockholm trial had 237 patients, and the U.S. medical center cohort contributed 210 patients that were T1N0. BCI classified 68% (160/237) and 64% (135/210) of the Stockholm population and the medical

center population as low risk, respectively. Median follow-up was 17 years for the Stockholm study and 10 years for the medical center cohort. Among the BCI high-risk, HER2-negative participants, the 5- to 15-year distant recurrence-free survival rates in the Stockholm trial and the multi-institutional study were 86.9% (95% CI 78.8% to 95.9%) and 87.5% (95% CI 79.1% to 96.9%), respectively. The rates in the low-risk, HER2-negative groups were 95.2% (95% CI 91.9% to 98.8%) and 98.4% (95% CI 96.1% to 100%), respectively.

A retrospective study by Sgroi (2016) evaluated the use of the BCI in samples from the NCIC MA.14 clinical trial of tamoxifen alone vs. tamoxifen plus octreotide in postmenopausal women with early breast cancer.[44] A total of 292 samples from banked tumor blocks were assayed: 146 from each treatment arm. BCI was categorized as high-risk (BCI ≥ 6.4), intermediate risk (5 ≤ BCI < 6.4), and low risk (BCI < 5). These risk groups were associated with adjusted 10-year relapse-free survival, which was 87.5% in the low-risk group, 83.9% in the intermediate-risk group, and 74.7% in the high-risk group. There was no significant interaction between BCI and treatment group. Because most lymph node-positive patients received chemotherapy, the prognostic utility of BCI could not be assessed for those patients.

Zhang (2013) evaluated a continuous risk model derived from the H/I ratio and MGI in tumor samples from the Stockholm tamoxifen cohort; n=317), along with additional samples from a multi-institutional registry of ER-positive, lymph node-negative patients (n=358), 32% of whom received adjuvant chemotherapy.[45] An optimized continuous recurrence risk model, the Breast Cancer Index™ model, was built using patients from the untreated arm of the Stockholm cohort as a training set. Samples from the endocrine therapy arm of the Stockholm trial and from the multi-center registry were used for the validation studies. The Stockholm validation set included 7% HER2-positive samples and the multicenter registry included 12% HER2-positive samples. The overall 10-year distant recurrence rates for the BCI low, intermediate, and high risk groups in the Stockholm cohort were 4.8% (95% CI 1.7% to 7.8%), 11.7% (95% CI 3.1% to 19.5%), and 21.1% (95% CI 15.3% to 32.0%), respectively, while the 10-year distant recurrent rates for these groups in the multi-center registry were 6.6% (95% CI 2.9% to 10%), 23.3% (95% CI 12.3% to 33%), and 35.8% (95% CI 24.5% to 45.5%), respectively.

Breast Cancer Index™ for Endocrine Therapy Decisions

Sgroi (2013) examined 665 lymph node-negative, ER-positive, postmenopausal women receiving endocrine therapy but no chemotherapy in the ATAC trial.[46] In this group, approximately 10% of samples were HER2+. Two versions of the Breast Cancer Index (BCI) score were generated in the study: the BCI-C, based on cubic combinations of the variables, and the BCI-L, based on linear combinations of the variables. The BCI-L, which is the model used in the development studies by Zhang (2013) described above and represents the commercial version of the BCI, was more effective than the BCI-C at risk discrimination. The overall 10-year distant recurrence rates for the BCI-L low, intermediate, and high-risk groups were 4.8% (95% CI 3.0% to 7.6%), 18.3% (95% CI 12.7% to 25.8%), and 29.0% (95% CI 21.1% to 39.1%), respectively. For patients in the low- and intermediate-risk groups, 10-year distant recurrence risks were similar, regardless of endocrine treatment (tamoxifen, anastrozole, or both).[46] In the high-risk group, recurrence risk was lowest (22%) for patients taking anastrozole only and highest for patients taking tamoxifen only (37%), although these groups were small (54 and 55 patients, respectively).

Sgroi (2013) conducted a prospective-retrospective, nested case-control study within the

MA.17 trial that compared extended endocrine therapy (letrozole) with placebo in postmenopausal women who had hormone receptor-positive cancers.[47] The trial randomized 5,157 women recurrence-free at five years to letrozole or placebo. A case-control design was adopted owing to challenges in obtaining archived tumor samples. An eligible case (319 of which 83 were examined) was one that experienced a local, regional, or distant recurrence and had an available tumor sample. Two controls free of recurrence longer than cases were matched to each case based on age, tumor size, node status, and prior chemotherapy. Any recurrence (locoregional or distant) was used as the endpoint; patients with contralateral or unknown recurrences were excluded. Using the BCI H/I ratio, there was a 42% relative risk reduction in the low-risk group vs. a 77% reduction in the high-risk group. Although statistical significance was lacking in the low-risk group, the CIs were wide and included values consistent with those observed in the high-risk group. The Zhang (2013) study described above,[45] as well as studies by Bartlett (2019)[48] and Noordhoek (2021)[49] also reported a larger potential relative risk reduction with extended endocrine therapy in the H/I high-risk group, with similar uncertainty reflected in the CIs (HR 0.35, 95% CI 0.19 to 0.65; HR 0.35, 95% CI 0.15 to 0.86; and HR 0.34, 95% CI 0.16 to 0.73, respectively).

ONCOTYPE DX® DCIS

Ductal carcinoma in situ (DCIS) is the presence of abnormal cells inside a milk duct in the breast. DCIS is considered the earliest forms of breast cancer and is noninvasive. DCIS requires treatment to prevent the condition from becoming invasive and most women diagnosed with DCIS are effectively treated with breast-conserving surgery and radiation. DCIS diagnosis accounts for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy with or without radiation treatment; post-surgical tamoxifen treatment is recommended for ER-positive DCIS, especially if excision alone is used. The overall rate recurrence following DCIS diagnosis is less than 30% and usually occurs within 5 to 10 years after initial diagnosis.

The Oncotype DX® DCIS test uses information from 12 of the 21 genes assayed in the standard Oncotype DX® test for early breast cancer. Scaling and category cut-points are based on an analysis of DCIS Score results from a separate cohort of patients with DCIS; this study has not yet been published and is available only as a meeting abstract.[50]

In a retrospective analysis, Rakovitch (2015) evaluated 571 tumor specimens with negative margins from a convenience cohort of patients with DCIS treated by breast-conserving surgery (lumpectomy) alone.[51] Patients were drawn from a registry of 5752 women in Ontario, Canada, who were diagnosed with DCIS between 1994 and 2003. Median follow-up of the 571 women was 9.6 years. There were 100 local recurrence events (18% prevalence); 43 were DCIS (8% prevalence), and 57 were invasive cancer (10% prevalence). Oncotype DX® DCIS score was significantly associated with local recurrence outcomes (HR 2.15, 95% CI 1.43 to 3.22). Sixty-two percent of patients were classified as low-risk, 17% as intermediate risk, and 21% as high risk. Corresponding 10-year local recurrence estimates were 13% (95% CI 10% to 17%), 33% (95% CI 24% to 45%), and 28% (95% CI 20% to 38%), respectively. Corresponding 10-year estimates for DCIS recurrence (5%, 95% CI 3% to 9%; 14%, 95% CI 8% to 24%; 14%, 95% CI 9% to 22%; respectively) and for invasive breast cancer recurrence (8%, 95% CI 6% to 12%; 21%, 95% CI 13% to 33%; 16%, 95% CI 9% to 25%; respectively) were based on small numbers of events. It is unclear whether estimated recurrence risks for patients classified as low risk are low enough to forgo radiotherapy.

In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study by Solin (2013), the Oncotype DX® Score for DCIS was compared with the 10-year recurrence risk in a subset of DCIS patients treated only with surgery and some with tamoxifen (n=327).[52] Oncotype DX® DCIS Score was significantly associated with recurrence outcomes (HR 2.31, 95% CI 1.15 to 4.49, p=0.02) whether or not patients were treated with tamoxifen. The standard Oncotype DX® Score for early breast cancer was not associated with DCIS recurrence outcomes. The standard Oncotype DX® Score for early breast cancer was not associated with DCIS recurrence outcomes.

Rakovitch (2018) combined the populations from the two studies described above (Solin [2013] and Rakovitch [2015]) and calculated 10-year local recurrence rates by DCIS category (low, intermediate, and high), age, tumor size, and year of diagnosis.[53] Ten-year recurrence rates in the low risk score group ranged from 7.2% (95% CI 5.3% to 10.0%) for those age 50 and above with tumors ≤1 cm to 11.6% (95% CI 7.7% to 15.5%) for those with tumors > 2.5 cm.

DCISIONRT®

The DCISionRT test combines seven monoclonal protein markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with four clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies individuals with DCIS into three risk groups: low risk, elevated risk with good response, and elevated risk with poor response. The purpose of the test is to predict radiation benefit in individuals with DCIS following breast conserving surgery.

Warnberg (2021) analyzed the association of DCIS RT score with risk of recurrence in 504 individuals with DCIS enrolled in the SweDCIS randomized trial.[54] This study is Simon Category B. Using a cutoff of DS >3, 52% of participants were categorized as elevated risk and 48% as low risk. In the low-risk group, there was no significant difference in risk of recurrence observed with radiotherapy. In contrast, radiotherapy was associated with reduced risk of total and invasive ipsilateral recurrence in the elevated-risk group.

PROSIGNA™/ PAM50 BREAST CANCER INTRINSIC SUBTYPE CLASSIFIER

PAM50 Breast Cancer Intrinsic Classifier, a qRT-PCR test based on a panel of 50 genes, was developed to identify the breast cancer intrinsic subtypes known as luminal A, luminal B, HER2-enriched, and basal-like, and to generate risk-of-relapse scores in node-negative patients who had not had systemic treatment for their cancer. Prosigna™ evolved from the PAM50 test and uses NanoString's nCounter platform[55] in place of qRT-PCR to assay 46 genes instead of the original 50. The 2014 TEC Assessment reviewed development and validation studies of the PAM50 intrinsic subtype classifier and Prosigna™.[1]

In a study that supported FDA clearance of Prosigna™, Gnant (2014) evaluated tumor samples from 1,047 lymph node-negative patients who participated in the Austrian Breast and Colorectal Cancer Study Group's trial 8 (ABCSG-8); this represented 28% of the original trial sample.[56] ABCSG-8 randomized hormone receptor-positive, postmenopausal women with early-stage breast cancer to five years of endocrine adjuvant therapy, either tamoxifen for five years or tamoxifen for two years followed by anastrozole for three years. Adjuvant or neoadjuvant chemotherapy was not allowed. Both PAM50 subtype and Prosigna™ ROR class were associated with 10-year distant recurrence-free survival, with CIs that overlapped slightly or not at all. Lower confidence limits for women in the luminal A and low-risk groups were

around 94%, and upper confidence limits for luminal B and high-risk groups were approximately 90%. That is, the risk distinction seemed clinically useful.

Dowsett (2013) reported on groups from the ATAC trial stratified by subtype (luminal A or B) and by PAM50 ROR class, both with and without consideration of clinicopathologic factors.[57] Among 739 lymph node-negative patients, 10-year distant recurrence-free survival was 94% in 529 luminal A patients and 75% in 176 luminal B patients, and was comparable with low- and high-risk ROR groups with or without clinical factors: 95%, 85%, and 70% in low-, intermediate-, and high-risk groups, respectively. An ROC analysis in 649 lymph node-negative, HER2-negative patients showed that PAM50 plus clinical factors had greater discriminatory ability than either risk predictor alone. In this study, the commercial assay was performed on 46 of the PAM50 genes (ROR46). Because proliferation-associated genes are given special weighting to produce the Prosigna™ ROR score, it is unclear how closely ROR46 approximated the marketed test; the authors reported a correlation of 0.9989 between ROR50, which incorporated all PAM50 genes, and ROR46 risk classifications.

Two studies published in 2015 presented combined analyses of pretreatment FFPE tumor specimens from ABCSG-8 and ATAC trial monotherapy arms (TransATAC).[58, 59] Median follow-up was 10 years. Sestak (2015) examined the association between ROR score and late distant recurrence (5 to 10 years after diagnosis) in 2,137 postmenopausal women (60% from ABCSG-8).[58] Patients had HR–positive invasive breast cancer treated with only endocrine therapy (anastrozole or tamoxifen; no chemotherapy) for five years without recurrence. The majority of patients (74%) had node-negative disease (87% of patients with node-positive disease had one to three positive lymph nodes), and 92% were HER2-negative. ROR score was determined using a 46-gene subset of the PAM50 genes plus tumor size. Cutpoints differed from cutpoints used in the FDA-approved version of the test, designed to assess recurrence risk in the first 10 years after diagnosis (years 0 to 10). In this study, ROR score less than 26 identified patients with low risk of distant recurrence (<10% risk); ROR score 26 to 68 identified patients with intermediate risk (10% to 20% risk); and ROR score greater than 68 identified patients with high risk (>20% risk) in both node-negative and node-positive patients. Fifty-five percent of women were categorized as low risk, 25% as intermediate risk, and 20% as high risk. Kaplan-Meier estimated risks for late distant recurrence (between five and 10 years) in node-negative patients were 2.3% (95% CI 1.3 to 3.5), 8.5% (95% CI 5.9 to 12.1), and 9.3% (95% CI 5.5 to 15.5), respectively. In node-positive patients, estimated risks were 3.3% (95% CI 1.2 to 8.6), 7.8% (95% CI 4.4 to 13.8), and 20.9% (95% CI 16.1 to 26.9) in low-, intermediate-, and high-risk groups, respectively. It is worth noting that prediction of 10-year survival contingent on five-year survival without recurrence is not informative for treatment decisions at the time of diagnosis.

The other study, by Gnant (2015), evaluated FFPE tissue specimens from 543 patients in the ABCSG-8 and ATAC trials who had one to three positive lymph nodes.[59] The primary endpoint was distant recurrence-free survival, defined as the interval from randomization until distant recurrence or death due to breast cancer. Investigators developed a Clinical Treatment Score (CTS) that integrated nodal status, tumor size, histopathologic grade, patient age, and type of endocrine therapy received (anastrozole or tamoxifen) into a summary score.[60] Risk classification by CTS was compared with and without ROR in subsets of patients with one positive lymph node (n=331) and with two to three positive lymph nodes (n=212). ROR cutpoints for defining risk groups differed from cutpoints used in the FDA-approved version of the test, which were defined by Gnant (2014),[56] discussed below. Among patients with one positive node, 40% were categorized as low risk, 32% as intermediate risk, and 28% as high

risk. Kaplan-Meier estimates for 10-year distant recurrence or death from breast cancer were 6.6% (95% CI 3.3% to 12.8%), 15.5% (95% CI 9.5% to 25.0%), and 25.5% (95% CI 17.5% to 36.0%), respectively. Because the upper bound of the 95% CI for patients categorized as low risk exceeded 10%, usefulness of these risk distinctions is uncertain. For patients with two or three positive nodes, low and intermediate risk groups were combined due to small numbers of patients and events in the low-risk group; 39% of patients were categorized as low/intermediate risk, and 61% were categorized as high risk. The 10-year distant RFS estimates were 12.5% (95% CI 6.6% to 22.8%) and 33.7% (95% CI 25.5% to 43.8%), respectively. When ROR, either as a continuous or a categorical variable, was added to CTS, prognostic information was improved (changes in likelihood ratios were statistically significant) compared with CTS alone for all nodal subgroups, including node-negative patients.

Sestak (2013) reported on the prognostic ability of PAM50 ROR score in 940 (16%) of 5880 patients from the ATAC trial.[61] Thirty percent of patients were lymph node positive. Investigators modified the ROR scoring algorithm to exclude tumor size and defined cutpoints by the median for each outcome; patients were segregated into two rather than three risk classes. These modifications have not been validated and may increase considerably the risk of misclassification bias. Two outcomes were examined, distant recurrence during the first five years after completion of hormone therapy and after five years (up to 10 years). For the latter, the number of patients at risk at the start of the interval was not reported; in the first five years, 71 distant recurrences occurred. Finally, estimated uncertainty (e.g., variance) was not reported for either outcome. Although distant recurrence-free survival was longer in the low-risk than in the high-risk group, given the methodological flaws of the study, the meaning of these results is uncertain.

Hequet (2017)[62] and Martin (2015)[63] evaluated the impact of ROR on treatment decision making in patients with ER-positive, HER2-negative, node-negative breast cancer. Because survival or recurrence outcomes were not reported, these studies are considered uninformative for assessing clinical utility of Prosigna™.

The majority of PAM50/Prosigna™ studies suffered from confounding due to heterogeneous patient samples. It is therefore difficult to estimate outcomes for the patients of interest: ER-positive, HER2-negative, lymph node-negative patients not receiving chemotherapy. In addition, studies reporting 10-year outcomes have not consistently used the commercially available version of the test or used standardized cutpoints for risk category determination. This inconsistency limits the conclusions that can be drawn regarding the potential clinical utility of this test.

BLUEPRINT® AND TARGETPRINT®

Gene expression patterns have led to the identification of molecular subtypes of breast cancer, which have different prognoses and responses to treatment regimens. These molecular subtypes are largely distinguished by differential expression of ER, PR, and HER2 in the tumor, and are classified as luminal, basal, or HER2 type. Luminal type breast cancers are ER-positive; basal type breast cancers correlate best with ER-, PR-, and HER2-negative (“triple negative”) tumors, and HER2 type, with high expression of HER2.

BluePrint® is an 80-gene expression assay that classifies breast cancer into basal type, luminal type or HER2 type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint®. BluePrint® classifies breast cancer into basal type, luminal type or ERBB2 type. TargetPrint® is a microarray-based gene expression

test that offers a quantitative assessment of ER, PR and HER2 overexpression in breast cancer. Both BluePrint® and TargetPrint® are intended for use with MammaPrint®. Wesseling (2016) compared TargetPrint® to IHC and in situ hybridization (ISH) testing for ER, PR, and HER2 in samples from 806 patients at 22 hospitals. The positive/negative agreement between IHC and TargetPrint® was 96%/87% for ER, 84%/74% for PR, and 74%/98% for HER2.[64] The authors noted substantial discord in IHC/ISH results between different hospitals and indicated that TargetPrint® might improve the reliability of these discordant results by prompting retesting in a reference laboratory.

Gran (2015) compared HER2 testing results by IHC, FISH, and TargetPrint® in 127 tumor specimens from patients with early-stage breast cancer in South Africa.[65] Tumor specimens were fresh frozen (32%) or FFPE (68%). Only specimens with IHC-positive results (n=23) underwent FISH testing, except for one IHC-negative specimen that had a positive TargetPrint® result, subsequently confirmed by reflex FISH. TargetPrint® improved HER2 testing compared with IHC/FISH in four (17%) of 24 cases that underwent both IHC and FISH testing. TargetPrint® performance in this study cannot be fully characterized in the absence of FISH testing of IHC-negative samples.

The BluePrint® molecular subtyping profile was developed using 200 breast cancer specimens that had concordant ER, PR and HER2 protein levels by immunohistochemistry and TargetPrint® mRNA readout.[66] Using a threefold cross validation procedure, the 80 genes thought to best discriminate the three molecular subtypes were identified. BluePrint® was confirmed on four independent validation cohorts (n=784), which included patients from a consecutive series of patients seen at Netherlands Cancer Institute and treated with adjuvant tamoxifen monotherapy (n=274), a group of patients from the RASTER trial (n=100), and two publicly available data sets (n=410). In addition, in 133 patients treated with neoadjuvant chemotherapy, the molecular subtyping profile was tested as a predictor of chemotherapy response. The authors concluded that use of BluePrint® classification showed improved distribution of pCR among molecular subgroups compared with local pathology: 56% of the patients had a pCR in the basal-type subgroup, 3% in the MammaPrint® low-risk, luminal-type subgroup, 11% in the MammaPrint® high-risk, luminal-type subgroup, and 50% in the HER2-type subgroup.

Whitworth (2014) reported reclassification of 94 (22%) of 426 patients with breast cancer who were classified by both IHC/FISH and BluePrint® and treated with neoadjuvant chemotherapy.[67] Six percent of BluePrint® luminal-type patients achieved pCR compared with 10% of IHC/FISH hormone receptor–positive/HER2-negative patients; 53% of BluePrint® HER2-positive patients achieved pCR compared with 38% of IHC/FISH HER2-positive patients (the majority of HER2-positive patients by either method received trastuzumab); and 35% of BluePrint® basal-type patients achieved pCR compared with 37% of IHC/FISH “triple negative” patients.

Wuerstlein (2019) conducted a prospective evaluation of how MammaPrint® and BluePrint® influence clinical therapy decisions in patients with luminal early breast cancer.[68] About 72% (309 out of 430) of patients had node-negative disease. Specifically focusing on the impact of BluePrint® testing, the investigators found that there was a 65% concordance rate between IHC assessment and BluePrint® subtyping for Luminal A or B-like tumors. Notably, BluePrint® reclassified two clinically identified Luminal A-like tumors and four Luminal B-like tumors as Basal type. Additionally, BluePrint® reclassified 46% (80 out of 173) of Luminal B-like tumors to Luminal A, and 24% (62 out of 256) of Luminal A-like tumors to Luminal B. This led to an

overall discordance rate of 34% in subtype classification. The study also highlighted the strong association between chemotherapy recommendations and molecular subtype: 94% (143 out of 152) of patients with molecular Luminal B tumors received a recommendation for chemotherapy, whereas 92% (251 out of 272) of patients with molecular Luminal A tumors were advised to omit chemotherapy.

ENDOPREDICT®

EndoPredict® is a gene expression test that uses reverse transcription polymerase chain reaction (RT-PCR) of 12 genes.

Filipits (2011) reported on the validation of EndoPredict® using tumor samples from women receiving endocrine treatment in the ABCSG-6 and ABCSG-8 trials.[69] The test was successful in 378 out of 395 tumors from ABCSG-6 and 1,324 out of 1,330 tumors from ABCSG-8. All tumors were HER2-negative. Prespecified cutoff points were used to classify the patients into EP and EPclin high- and low-risk groups (5 for EP, 3.3 for EPclin). The EPclin score combines the EP risk score with two clinical parameters, tumor size and nodal status. The 10-year distant recurrence rates for the EP low- and high-risk groups from ABCSG-6 were 8% (95% CI 3% to 13%) and 22% (95% CI 15% to 29%), respectively, and the rates for the EP low- and high-risk groups from ABCSG-8 were 6% (95% CI 2% to 9%) and 15% (95% CI 11% to 20%), respectively. The EPclin score outperformed the EP score in this study, with 10-year distant recurrent rates of 4% (95% CI 1% to 8%) and 28% (95% CI 20% to 36%) in the ABCSG-6 low and high-risk groups, respectively, and 4% (95% CI 2% to 5%) and 22% (95% CI 15% to 29%) in the ABCSG-8 low- and high-risk groups. Filipits (2019) published a follow-up to this study, which reported outcomes for 1,702 patients and reported that patients with low-risk EPclin scores (62.6%) had increased distant recurrence-free rates compared with patients that had high-risk scores (HR 4.77, 95% CI 3.37 to 6.67), and that the EPclin scores were significantly associated with this rate regardless of nodal status.[70]

Sestak (2019) reported results of an analysis of the performance of EndoPredict® to predict chemotherapy benefit.[71] The analysis included 3,746 women; 2,630 patients received five years of endocrine therapy alone (from ABCSG-6/8, TransATAC trials) and 1,116 patients received endocrine therapy plus chemotherapy (from GEICAM 2003-02/9906 trial). There was a significant positive interaction between EPclin as a continuous measure and treatment group for the outcome of the ten-year recurrence rate (interaction p=0.022). Although the comparison is indirect, it may suggest that a high EPclin score can predict chemotherapy benefit in women with ER-positive, HER2-negative disease.

Buus (2016) evaluated EndoPredict® as a prognostic indicator for breast cancer recurrence in women treated endocrine therapy.[72] This study was performed with 928 ER-positive, HER2-negative tumors samples from the TransATAC trial, which randomized post-menopausal women with localized disease to either tamoxifen or anastrozole for five years. High and low risk groups for both EP and EPclin were determined using pre-specified cutpoints. The 10-year recurrence rate for node-negative patients was 3.0% (95% CI 1.5 to 6.0) for the EP low group and 14.5% (95% CI 11.3 to 18.8) for the EP high group. For the node-negative EPclin low and high groups, the 10-year recurrence rates were 5.9% (95% CI 4.0 to 8.6) and 20.0% (95% CI 14.6 to 27.0), respectively. The 10-year recurrence rates were also determined for node-positive patients: 21.3% (95% CI 13.9 to 31.9) for the EP low group, 36.4% (95% CI 29.6 to 40.1) for the EP high group, 5.0% (95% CI 1.2 to 18) for the EPclin low group, and 36.9% (95% CI 30.2 to 44.5) for the EPclin high group.

Martin (2014) assessed tumor samples from 566 ER-positive, HER2-negative patients who participated in the GEICAM 9906 RCT.[73] GEICAM 9906 compared two adjuvant chemotherapy regimens in 1,246 women who had lymph node-positive disease: six 21-day cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) or four 21-day cycles of FEC followed by eight weekly courses of paclitaxel (FEC-P). EP was successfully assayed in 555 (98%) of 566 tumor samples. There were 25% (n=141) of the samples classified as low-risk by EP score, and 75% (n=414) were high-risk; 10-year metastasis-free survival was 93% in the low-risk group and 70% in the high-risk group (HR for metastasis or death in the high- vs low-risk group, 4.8 (95% CI 2.5 to 9.6, log-rank test p<0.001). Thirteen percent (n=74) of samples were classified as low-risk by EPclin score, and 87% (n=481) were classified as high-risk; 10-year metastasis-free survival was 100% in the low-risk group and 72% in the high-risk group.

EndoPredict® for Endocrine Therapy Decisions

Dubsky (2013) examined predictive ability of EP and EPclin for early (within five years) and late (more than five years post-diagnosis) disease recurrence.[74] Tumor samples from chemotherapy-untreated, ER-positive, HER2-negative patients who participated in one of two RCTs (ABCSG-6 or ABCSG-8) were assayed (total n=1,702). In the trials, patients received either tamoxifen for five years or tamoxifen for two years followed by anastrozole for three years. Forty-nine percent (n=832) of patients were classified as low risk by EP score, and 51% (n=870) were classified as high-risk. Only relative estimates (i.e., HRs) of distant recurrence were reported. In comparison with low-risk patients, high-risk patients had an almost three-fold increase in the risk of recurrence in the first five years after diagnosis (HR 2.80, 95% CI 1.81 to 4.34, log-rank test p<0.001) and a slightly increased risk after five years in those who survived five years (HR 3.28, 95% CI 1.48 to 7.24, log-rank test p=0.002). By EPclin, 1,066 (63%) of 1,702 patients were classified as low-risk, and 636 (37%) were classified as high-risk. In comparison with low-risk patients, high-risk patients had an almost five-fold risk of recurrence within the first five years (HR 4.82, 95% CI 3.12 to 7.44, log-rank test p<0.001) and a more than six-fold increased risk of recurrence after five years (HR 6.26, 95% CI 2.72 to 14.36, log-rank test p<0.001).

EP and EPclin appear to be able to identify a group at low-risk of distant recurrence from years 5 to 10 in this prospective-retrospective study of patients untreated with adjuvant chemotherapy enrolled in the ABCSG-6 and -8 trials. However, in the Filipits (2019) study, the lower-bound of the 95% CI for the distant recurrence rate in the high-risk group falls within a range that may be clinically meaningful for decision-making about avoiding extended ET both at 5-10 years (5.9%, 95% CI 2.2% to 9.5%) and at 5 to 15 years (15.1%, 95% CI 4.0% to 24.9%).[70] These results suggest the possibility that a proportion of high-risk patients may still have been unnecessarily treated with extended ET endocrine therapy based on a gene expression profiling result. ROC statistics (area under the receiver operating characteristic curve) were reported to support incremental improvement with the EP or EPclin over Adjuvant! Online or nodal status, tumor size, or grade. However, they appeared to include EP and EPclin as continuous variables and not threshold cutoffs for those tests that would inform decisions.

TEST COMPARISON STUDIES

Sestak (2018) compared Breast Cancer Index®, Oncotype DX®, Prosigna®, and Endopredict® using samples from the TransATAC RCT.[75] The low-risk categories of all four tests exhibited both low overall 10-year distant recurrence rates and low 5- to 10-year distant recurrence rates (within the threshold of <10%). Comparatively, among those who are

considering adjuvant chemotherapy (n=591), EPclin classified the most women as low risk (n=429) compared with the other three tests which classified 318 to 365 women as low risk. Among those who are considering extended endocrine therapy (n=535), EPclin classified the most women as low risk (n=393) compared with the other three tests, which classified 292 to 351 women as low risk.

Bosl (2017) compared MammaPrint® with EndoPredict® in 48 tumor samples - 29 were node-negative and 19 were node-positive.[76] For the MammaPrint test, RNA quality was low for three samples. Of the 45 tested by MammaPrint, 17 (38%) were classified as low-risk and 28 (62%) were classified as high-risk for recurrence. Four samples were excluded from the EndoPredict® analysis because the tumors were estrogen receptor-positive or HER2-positive, which are not part of the inclusion criteria of this test. Based on the EP molecular score, eight (18%) were classified as low-risk and 36 (82%) were classified as high-risk. Based on the EPclin score, 17 (39%) were considered low-risk and 27 (61%) were considered high-risk. There was no statistically significant agreement between MammaPrint® and molecular EP (overall concordance, 63%) or between MammaPrint® and EPclin (overall concordance, 66%).

Sgroi (2013) compared the Breast Cancer Index™ and Oncotype DX® in 665 lymph node-negative women receiving endocrine therapy but not chemotherapy in the ATAC trial.[46] The distribution of patients across risk groups was similar. For patients receiving tamoxifen alone or in combination with anastrozole, 10-year distant recurrence risk estimates by the two tests were similar within risk groups. In the anastrozole group, the Breast Cancer Index™ was a better predictor of risk: 5% of Breast Cancer Index™ low-risk patients had distant recurrence compared with 9% of Oncotype DX® low-risk patients, and 22% of Breast Cancer Index™ high-risk patients had distant recurrence compared with 13% of Oncotype DX® high-risk patients. Importantly, these values were reported without 95% CIs; it is therefore not possible to assess the degree of overlap between risk groups.

Sestak (2016)[77] examined cross-stratification between the Breast Cancer Index™ and Oncotype DX® RS using the same data as Sgroi (2013). Gene expression analyses for both scores were conducted, and risk categories were determined based on prespecified cutoff points (RS <18: low risk, 18 to 31: intermediate risk, >31: high risk; BCI <5.0825: low risk, 5.0825 to 6.5025: intermediate risk, >6.5025: high risk). Each gene expression score was combined with the CTS an algorithm of nodal status, tumor size, grade, age, and treatment. In a multivariate analysis, when BCI was added to RS plus CTS, there was a significant effect on prognostic information. When RS was added to BCI plus CTS, no additional prognostic information was added.

Dowsett (2013) compared the PAM50 ROR score to the Oncotype DX® RS, four immunohistochemical markers (IHC4) for ER, PR, Ki67 and HER2, and a CTS.[57] Patients had ER-positive, primary breast disease treated with anastrozole or tamoxifen in the ATAC trial, a double-blinded, phase three clinical trial that was designed to compare the ability of anastrozole, tamoxifen, and the two drugs in combination to prevent breast cancer recurrence in postmenopausal women with hormone receptor-positive tumors. Lymph node-negative and positive patients were included. mRNA from 1,017 patients was assessed for ROR, and likelihood ratio tests and concordance indices were used to assess the prognostic information provided beyond that of a CTS, RS, ROR or IHC4. The CTS integrated prognostic information from nodal status, tumor size, histopathologic grade, age and anastrozole or tamoxifen treatment. The authors concluded that the ROR added significant prognostic information beyond CTS in all patients (p<0.001), and in all four subgroups: lymph node negative, lymph

node positive, HER2 negative and HER2 negative/node-negative, and that more information was added by ROR than RS. More patients scored as high risk of recurrence and fewer as intermediate risk by ROR than RS. Prognostic information provided by ROR score and IHC4 was similar.

The study by Buus (2016) described earlier, compared EndoPredict® with Oncotype DX® RS in hormone receptor-positive, HER2-negative tumor samples from the TransATAC study.[72] The EP assay was used to generate an EPclin value that incorporated information about nodal status and tumor size. In this study, EP, EPclin, and RS had similar predictive power for distant recurrence in within five years in node-negative disease, while EP and EPclin had more prognostic value than RS for distant recurrence in 5 to 10 years, regardless of nodal status. Classification as low-risk by EPclin was associated with significantly lower 10-year risk of recurrence than a low-risk classification by RS (EPclin 5.8%, 95% CI 4.0 to 8.3, RS 10.1%, 95% CI 7.7 to 13.1). EPclin classification as high-risk was also more highly associated with cases of recurrence than non-low-risk RS classification. However, for this analysis, both intermediate risk and high-risk RS categories were grouped together to allow comparison between the two risk categories of EPclin and the three risk categories of the RS.

PRACTICE GUIDELINE SUMMARY

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (v.1.2025)[11] recommend that the 21-gene (Oncotype DX® Breast Recurrence Score) assay be strongly considered in node-negative, HR-positive, HER2-negative disease when the tumor is >0.5 cm, and of ductal/NST, lobular, mixed, or micropapillary histology (category 1), if the patient is a candidate for chemotherapy. They note that “other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.” This test is also the preferred test for postmenopausal patients with one to three positive nodes (category 1).

MammaPrint® is also considered a category 1 option based on the results of the randomized MINDACT trial, which “demonstrated that the 70-gene assay can identify a subset of patients who have a low likelihood of distal recurrence despite high-risk clinical features (based on tumor size, grade, nodal status).” However, they note that the test is not useful for guiding chemotherapy decisions in those with low clinical risk, as no difference in outcomes with and without chemotherapy were seen in the trial for this group.

Regarding node-positive, HR-positive, HER2-negative disease, the guidelines recommend considering a multigene assay to assess prognosis and determine chemotherapy benefit for patients that are candidates for chemotherapy, The guidelines additionally state:

> “The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. A secondary analysis of the prospective SWOG 8814 trial using the 21-gene assay demonstrated no benefit for chemotherapy for patients with 1-3 involved axillary lymph nodes and a low RS, and a significant benefit for the addition of adjuvant chemotherapy in those with high-RS (≥ 31). […] Other multigene assays have not proven to be predictive of chemotherapy benefit.”

Oncotype DX® is listed as the preferred multigene assay by the NCCN for node-negative disease, and predictive of chemotherapy response as well as prognostic, while the Breast Cancer Index™, Endopredict®, Prosigna®, and MammaPrint® tests were listed as prognostic only. Oncotype DX®, MammaPrint®, Prosigna®, and Endopredict® are listed as multigene assays that may be considered for individuals with one to three positive nodes, as well as those who are node negative.

The Breast Cancer Index™ is listed as being predictive of benefit of extended endocrine therapy, with evidence indicating that patients that have BCI (H/I) Low test results do not have improved survival with extending endocrine therapy beyond five years.

The guidelines do not recommend the use of multigene or mRNA assays for assignment of HER2 status.

The guidelines do not address the use of assays such as Oncotype DX® DCIS Score or DCISionRT® to guide decisions about radiation therapy in individuals with DCIS.

American Society of Clinical Oncology

In June 2022, the American Society of Clinical Oncology (ASCO) published updated clinical practice guidelines on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer.[78] The recommendations related to the interventions and populations included in this evidence opinion include the following:

Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer

1.1 If a patient has node-negative breast cancer, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Evidence Quality [EQ]: High, Recommendation Strength [RS]: Strong)

1.2. In the group of patients in Recommendation 1.1 with Oncotype DX score greater than or equal to 26, the clinician should offer chemoendocrine therapy (EQ: High, RS: Strong)

1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX score 16 to 25, the clinician may offer chemoendocrine therapy. (EQ: Intermediate, RS: Moderate)

1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (EQ: High, RS: Strong)

1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX score is greater than or equal to 26 (EQ: High, RS: Strong)

1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy (EQ: High, RS: Moderate)

1.7. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for

adjuvant endocrine and chemotherapy is insufficient to recommend its use (EQ: Insufficient, RS: Moderate)

1.8. If a patient is older than 50 and has high clinical risk breast cancer, that is node-negative or node-positive with 1-3 positive nodes, the clinician may use MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (EQ: Intermediate, RS: Strong)

1.9. If a patient is 50 years of age or younger and has high clinical risk, node negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (EQ: High, RS: Strong)

1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (EQ: Intermediate, RS: Moderate)

1.11. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (EQ: Insufficient, RS: Strong)

1.12. If a patient is postmenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician may use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (EQ: Intermediate, RS: Moderate)

1.13. If a patient is premenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician should not use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (EQ: Insufficient, RS: Moderate)

1.14. If a patient has breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient (EQ: Intermediate, RS: Moderate)

1.15. If a patient is postmenopausal and has breast cancer that is node negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (EQ: Intermediate, RS: Moderate)

1.16. If a patient is premenopausal, and has node-negative or node-positive breast cancer the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (EQ: Insufficient, RS: Moderate)

1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy (EQ: Intermediate, RS: Moderate)

1.18. If a patient has node-positive breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (EQ: Insufficient, RS: Strong)

Extended Endocrine Therapy for ER Receptor-Positive HER2-Negative Breast Cancer

1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 tests to guide decisions about extended endocrine therapy (EQ: Intermediate, RS: Moderate)

1.24. If a patient has node-negative or node-positive with 1-3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI (EQ: Intermediate, RS: Moderate)

1.25. If a patient has node-positive breast cancer with more than 3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI (EQ: Intermediate, RS: Strong)

HER2-Positive Breast Cancer or Triple-Negative Breast Cancer

1.27. If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (EQ: Intermediate, RS: Strong)

The guidelines do not address the use of assays such as Oncotype DCIS or DCISionRT to guide decisions about radiation therapy in individuals with DCIS.

ASCO 2019 guidelines on the role of patient and disease factors in adjuvant systemic therapy decision-making for early-stage, operable breast cancer state:[79]

- Shared decision making between clinicians and patients is appropriate for adjuvant systemic therapy for breast cancer. For patients older than age 50 years and whose tumors have Oncotype DX recurrence scores less than 26, and for patients age 50 years or younger whose tumors have Oncotype DX recurrence scores less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone for these patients. For patients age 50 years or younger with recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy. Patients with recurrence scores greater than 30 should be considered candidates for chemoendocrine therapy. Based on informal consensus, the Panel recommends that oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30.
- The MammaPrint assay could be used to guide decisions on withholding adjuvant systemic chemotherapy in patients with hormone receptor–positive lymph node–negative breast cancer and in select patients with lymph node–positive cancers. In both patients with node-positive and node-negative disease, evidence of clinical utility of the MammaPrint assay was only apparent in those determined to be at high clinical risk; the Panel thus did not recommend use of MammaPrint assay in patients determined to be at low clinical risk. Remaining recommendations from the 2016 ASCO guideline endorsement are unchanged.

American Society of Clinical Oncology/College of American Pathologists

In 2010, ASCO and the College of American Pathologists (CAP) issued recommendations on immunohistochemical testing for ER and PR, and issued recommendations in 2007[37, 80] (updated in 2014)[81] for HER2 testing by immunohistochemical and FISH methods. Recommendations do not address the use of gene expression assays to test for ER, PR or HER2 expression.

SUMMARY

ONCOTYPE DX®, BREAST CANCER INDEX™, AND ENDOPREDICT®

Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, and EndoPredict® Assay in Node-Negative Patients and Patients with One to Three Positive Lymph Nodes

There is enough research to show that the Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, and EndoPredict® test can help identify patients with certain types of breast cancer that may be at low risk for disease recurrence and can be useful when making decisions about chemotherapy treatment. In addition, the Breast Cancer Index™ may provide information to help make decisions regarding extended endocrine therapy. Clinical guidelines based on research consider these tests to be an option to help in making treatment decisions for individuals with breast cancer who do not have lymph node involvement, and those with 1-3 positive lymph nodes. Therefore, this testing may be considered medically necessary in patients when policy criteria are met.

Oncotype DX®, Breast Cancer Index™, MammaPrint®, and EndoPredict® Assay in Preliminary Biopsy Samples

There is not enough research to show that the use of the Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, and EndoPredict® test on preliminary biopsy samples (prior to pathological evaluation) may improve health outcomes in breast cancer patients. The large studies that have validated these tests have primarily used surgical specimens. Full pathologic evaluation is important to determine the cellular and molecular features of a cancer, including lymph node status, prior to chemotherapy decision making. In addition, these tests have not been validated for use in making decisions for pre-surgical (neoadjuvant) therapy. Therefore, the use of these tests on preliminary biopsy samples is considered not medically necessary.

Oncotype DX®, Breast Cancer Index™, MammaPrint®, and EndoPredict® Assay in Patients with More than Three Positive Lymph Nodes

There is enough research to show that the use of the Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, MammaPrint®, and EndoPredict® test may not improve health outcomes in breast cancer patients with more than three positive lymph nodes. For these patients, the risk of cancer recurrence without additional recommended therapy may be high. Therefore, testing in node-positive patients with more than three positive lymph nodes is considered not medically necessary.

Gene Expression Testing for DCIS

There is not enough research to show that gene expression tests for ductal carcinoma in situ (DCIS), including but not limited to the Oncotype DX® DCIS or DCISionRT, helps patients make treatment decisions that improve health outcomes. Clinical practice guidelines for breast cancer do not recommend this type of testing. Therefore, gene expression testing for DCIS is considered investigational.

Oncotype DX® Assay to Determine or Confirm HER2 Status

Guidelines based on research recommend using other methods and not Oncotype DX® to confirm HER2 status. Therefore, use of the Oncotype DX® assay to determine or confirm HER2 status is considered investigational.

Other Uses of Oncotype DX®, Breast Cancer Index™, MammaPrint®, or EndoPredict®

There is not enough research to show that using the Oncotype DX® Breast Recurrence Score, Breast Cancer Index™, or Endopredict® tests for purposes other than helping to decide whether to undergo adjuvant chemotherapy can improve survival and other health outcomes for patients with breast cancer. This includes using test results to make decisions about endocrine therapy, to predict response to specific chemotherapy regimens, or to evaluate response to treatments. In addition, there are no clinical guidelines based on research that recommend testing for these purposes. Therefore, the use of these tests for purposes other than helping to decide whether to undergo adjuvant chemotherapy is considered investigational.

BLUEPRINT® AND TARGETPRINT®

There is not enough research to show that BluePrint® and TargetPrint® improve health outcomes in individuals with breast cancer. There are no clinical guidelines based on research that recommend using BluePrint® or TargetPrint® to help determine the risk of cancer recurrence for breast cancer patients. Therefore, the gene expression assays BluePrint® and TargetPrint® are considered investigational for all indications.

OTHER GENE EXPRESSION ASSAYS

There is not enough research to show that other gene expression assays for breast cancer, including the Molecular Grade Index (Aviara MGISM), Prosigna™, or BreastPRS™ tests can help breast cancer patients make treatment decisions that improve health outcomes. Therefore, these tests are considered investigational.

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CODES

Codes	Number	Description
CPT	0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified
	0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
	0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
	0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffinembedded (FFPE), algorithm reported as gene pathway activity score

Codes	Number	Description
	0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin- embedded (FFPE) tissue, algorithm reported as a recurrence risk score
	81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
	81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
	81520	Oncology (breast), MRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
	81521	Oncology (breast), MRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
	81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
	81523	Oncology, mRNA, next-generation sequencing gene expression profiling
HCPCS	S3854	Gene expression profiling panel for use in the management of breast cancer treatment

Date of Origin: *October 2004*

Regence

Medical Policy Manual Genetic Testing, Policy No. 43

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

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

Fragile X syndrome (FXS), caused by expansion of the *FMR1* gene, is characterized by intellectual disability. FXS is also associated with certain physical and behavioral characteristics, including typical facial features, connective tissue anomalies, autism spectrum disorder, and seizures. Fragile XE (FRAXE) syndrome is caused by expansion of the *AFF2* gene (also known as *FMR2*) and is associated with mild intellectual disability without consistent physical features.

MEDICAL POLICY CRITERIA

Note: This policy applies to diagnostic testing only. Reproductive carrier screening is addressed separately (see Cross References).

I. Diagnostic genetic testing for *FMR1* variants may be considered **medically necessary** when one or more of the following criteria are met:

   A. Individuals with intellectual disability, developmental delay, or autism spectrum disorder.

   B. Individuals diagnosed with primary ovarian insufficiency before the age of 40.

C. Prenatal testing of fetuses of known carrier mothers.

D. Individuals with neurologic symptoms consistent with fragile X syndrome, including but not limited to ataxia and intention tremor.

II. Diagnostic genetic testing for *FMR1* variants is considered **not medically necessary** in all other circumstances, including but not limited to children with isolated attention-deficit/hyperactivity.

III. Genetic testing for *AFF2* (*FMR2*) variants is considered **investigational** for fragile XE (FRAXE) syndrome.

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

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Policy No. 58
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Fragile X Syndrome

Fragile X syndrome (FXS) is the most common cause of heritable intellectual disability, characterized by mild to moderate intellectual disability. In addition to the intellectual impairment, patients present with typical facial characteristics such as an elongated face with a prominent forehead, protruding jaw, and large ears. Connective tissue anomalies include hyperextensible finger and thumb joints, hand calluses, velvet-like skin, flat feet, and mitral valve prolapse. The characteristic appearance of adult males includes macroorchidism. Patients may show behavioral problems including autism spectrum disorders, sleeping problems, social anxiety, poor eye contact, mood disorders and hand-flapping or biting. Another prominent feature of the disorder is neuronal hyperexcitability manifested by hyperactivity, increased sensitivity to sensory stimuli, and a high incidence of epileptic seizures.

Current approaches to therapy are supportive and symptom-based. Psychopharmacologic intervention to modify behavioral problems in a child with fragile X syndrome may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, special educational services, and behavioral interventions. Medication management may be indicated to modify attention deficits, problems with impulse control, and hyperactivity. Anxiety-related symptoms, including obsessive compulsive tendencies with perseverative behaviors, also may be present and require medical intervention. Emotional lability and episodes of aggression and self-injury may be a danger to the child and others around him or her; therefore, the use of medication(s) to modify these symptoms also may significantly improve an affected child's ability to participate more successfully in activities in home and school settings.

DNA studies are used to test for fragile X syndrome (FXS). Genotypes of individuals with symptoms of FXS and individuals at risk for carrying the pathogenic variant can be determined by examining the size of the CGG trinucleotide repeat segment and the methylation status of the *FMR1* gene on the X chromosome. There are no known forms of fragile X mental retardation protein (FMRP) deficiency that do not map to the *FMR1* gene. Two main testing approaches are used: polymerase chain reaction (PCR) and Southern blot analysis. In fragile X testing, the high fraction of GC bases in the repeat region makes it extremely difficult for standard PCR techniques to amplify beyond about 100-150 CGG. As a result, Southern blot analysis is commonly used to determine the number of triplet repeats in FXS and methylation status.

CGG-repeat expansion full mutations account for more than 99% of cases of fragile X syndrome (FXS). Therefore, tests that effectively detect and measure the CGG repeat region of the *FMR1* gene are more than 99% sensitive. Positive results are 100% specific. The patient is classified as normal, intermediate (or "gray zone"), premutation, or full mutation based on the number of CGG repeats.

- Full mutation: >200-230 CGG repeats (methylated)

  Patients with a full mutation are associated with FXS, which is caused by expansion of the *FMR1* gene CGG triplet repeat above 200 units in the untranslated region of *FMR1*, leading to a hypermethylation of the promoter region followed by transcriptional inactivation of the gene. The FXS is caused by a loss of the fragile X mental retardation protein (FMRP). Approximately 1% to 3% of children ascertained on the basis of autism diagnosis are shown to have fragile X syndrome.

Full mutations are typically maternally transmitted. The mother of a child with an *FMR1* mutation is almost always a carrier of a premutation or full mutation. Men who are premutation carriers are referred to as transmitting males. All of their daughters will inherit a premutation, but their sons will not inherit the premutation. Males with a full mutation usually have intellectual disability and decreased fertility.

- Premutation: 55-200 CGG repeats (unmethylated)

  Patients with a premutation are carriers and are at small risk for developing a *FMR1*-related disorder, fragile X-associated tremor/ataxia syndrome (FXTAS). This disorder is a late onset, progressive development of intention tremor and ataxia often accompanied by progressive cognitive and behavioral difficulties including memory loss, anxiety, reclusive behavior, deficits of executive function and dementia, or premature ovarian insufficiency (FXPOI).

  Premutation alleles in females are unstable and may expand to full mutations in offspring. Premutations of less than 59 repeats have not been reported to expand to a full mutation in a single generation. Premutation alleles in males may expand or contract by several repeats with transmission; however, expansion to full mutations has not been reported. A considerable number of children being evaluated for autism have been found to have *FMR1* premutations (55-200 CGG repeats).[2]

- Intermediate: 45-54 CGG repeats (unmethylated)
- Normal: 5-44 CGG repeats (unmethylated)

Fragile XE Syndrome

Fragile XE syndrome (FRAXE) is much rarer than FXS, and affects an estimated 1 on 25,000 to 100,000 males.[3] This disorder is characterized by mild intellectual disability, though some affected individuals may have borderline cognitive function that is not severe enough to be classified as a disability.

Similar to FXS, FRAXE is caused by a trinucleotide repeat expansion – nearly all cases are due to the presence of more than 200 repeats of CCG in the *AFF2* gene (sometimes referred to as *FMR2*). Individuals with 50 to 200 CCG repeats are said to have a premutation, which is not associated with impaired cognition.

Regulatory Status

No FDA-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Asuragen offers the Xpansion Interpreter™ test which analyzes AGG sequences that interrupt the CGG repeats which have been suggested to stabilize alleles and protect against expansion in subsequent generations.

Note: An additional test for developmental delays, Lineagen FirstStepDxPLUS, offers sequencing of *FMR1* in combination with a chromosomal microarray genetic test. When *FMR1*

analysis is bundled with CMA analysis or any other genetic test, additional plan medical policies may apply. For the plan's medical policy on CMA analysis, see Cross References in the section above.

EVIDENCE SUMMARY

The focus of this review is on evidence related to the clinical utility of the testing, which is the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

FMR1

The conditions caused by abnormal CGG repeats in the *FMR1* gene, FXS, FXTAS, and FXPOI, do not have specific treatments that alter the natural history of the disorders. However, because they represent relatively common causes of conditions that are often difficult to diagnose and involve numerous diagnostic tests, the capability of *FMR1* testing to obtain an accurate definitive diagnosis and avoid additional diagnostic testing supports its clinical utility. Knowledge that the condition is caused by fragile X provides important knowledge to offspring and the risk of disease in subsequent generations.

Since there is no specific treatment for FXS, a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. However, there are several potential ways in which adjunctive management might be changed following genetic testing after confirmation of the diagnosis.[4, 5] Although not related specifically to *FMR1* testing, the American Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN)/Child Neurology Society (CNS) guidelines, described in more detail below, noted the following more immediate and general clinical benefits of achieving a specific genetic diagnosis:

- limit additional diagnostic testing;
- anticipate and manage associated medical and behavioral comorbidities;
- improve understanding of treatment and prognosis;
- allow counseling regarding risk of recurrence in future offspring and help with reproductive planning;
- early diagnosis and intervention in an attempt to ameliorate or improve behavioral and cognitive outcomes over time.

In a 2012 review by Abrams, the importance of early diagnostic and management issues, in conjunction with the identification of family members at risk for or affected by FMR1 variants is discussed.[6] The expanded CGG repeat in the *FMR1* gene, once thought to have clinical significance limited to fragile X syndrome, is now well established as the cause for other fragile X-associated disorders including fragile X-associated primary ovarian insufficiency and fragile X-associated tremor ataxia syndrome in individuals with the premutation (carriers).

Also, FXS is associated with a number of medical and behavioral comorbidities.[7] Behavioral comorbidities may include attention problems, hyperactivity, anxiety, aggression, poor sleep, and self-injury. Individuals with FXS are also prone to seizures, recurrent otitis media, strabismus, gastrointestinal disturbances, and connective tissue problems. A correct diagnosis can lead to the appropriate identification and treatment of these comorbidities.

Hersh (2011) reported on families with an affected male and whether an early diagnosis would have influenced their reproductive decision making.[4] After a diagnosis in the affected male was made, 73% of families reported that the diagnosis of FXS affected their decision to have another child, and 43% of the families surveyed had had a second child with a full mutation.

The feasibility of newborn screening is being investigated.[8] However, there is currently no treatment for FXS that would reduce mortality or morbidity if given in infancy. Also, there are a number of ethical concerns with newborn screening for FXS, including the need for informed consent from both parents, the need for genetic counseling for both full mutation and premutation status, and the detection of carriers in infants.[9]

AFF2

As with FXS, there are no specific treatments available for people diagnosed with FRAXE. In addition, FRAXE is a far less common disorder with a variable presentation ranging from relatively normal cognition to mild intellectual disability. There is limited evidence regarding the clinical utility of testing for *AFF2*. Several studies have screened for FRAXE in populations with intellectual disability[10-13], but only one identified a patient with this disorder.[14]

PRACTICE GUIDELINE SUMMARY

THE AMERICAN COLLEGE OF MEDICAL GENETICS

The purpose of the following American College of Medical Genetics (ACMG) guideline[15] recommendations is to provide aid to clinicians in making referrals for testing the repeat region of the *FMR1* gene:

- Individuals of either sex with intellectual disability, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed intellectual disability
- Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed intellectual disability
- Fetuses of known carrier mothers
- Affected individuals or their relatives in the context of a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. The cytogenetic test was used prior to the identification of the *FMR1* gene and is significantly less accurate than the current DNA test. DNA testing on such individuals is warranted to accurately identify premutation carriers and to distinguish premutation from full mutation carrier women.

In the clinical genetics evaluation in identifying the etiology of autism spectrum disorders, the ACMG recommends testing for FXS as part of first tier testing.[16]

In 2021, the ACMG released a revised technical standard on laboratory testing for fragile X.[17] The authors noted that the new laboratory standards "are in general agreement" with the 2005 ACMG policy statement summarized above.

THE AMERICAN ACADEMY OF PEDIATRICS

In 2011, the American Academy of Pediatrics (AAP) published consensus guidelines which suggested that, because children with FXS may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities or intellectual disability, or has a diagnosis of autism without a specific etiology should undergo molecular testing for FXS to determine the number of CGG repeats.[4]

In 2014, the AAP updated their consensus guidelines which recommend Fragile X testing in patients with global developmental delay (GDD) or intellectual disability (ID).[18] Specifically, the AAP guideline recommended, “fragile X testing should be performed in all boys and girls with GDD/ID of unknown cause. Of boys with GDD/ID of uncertain cause, 2% to 3% will have fragile X syndrome (full mutation of *FMR1*, >200 CGG repeats), as will 1% to 2% of girls (full mutation).”

THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

The 2017 American College of Obstetricians and Gynecologists (ACOG) committee opinion recommended prenatal testing for fragile X syndrome for known carriers of the fragile X premutation or full mutation and for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome.[19] They additionally recommended *FMR1* premutation testing for women younger than 40 with unexplained ovarian insufficiency or failure, or an elevated follicle-stimulating hormone level.

SUMMARY

There is enough research to show that testing the *FMR1* gene can improve the diagnostic process for individuals with fragile X-related symptoms and help in informed reproductive decision making. Also, clinical guidelines based on research from several U.S. professional associations recommend this testing for certain people. Therefore, genetic testing for *FMR1* may be considered medically necessary for patients when criteria are met.

For all other situations, *FRM1* gene testing provides no benefit in directing medical management and is therefore considered not medically necessary.

There is not enough research to show that testing for *AFF2* (*FMR2*) variants can help improve health outcomes for patients or inform reproductive decision making. In addition, there are no clinical guidelines based on research that recommend *AFF2* testing. Therefore, genetic testing for *AFF2* is considered investigational.

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CODES

Codes	Number	Description
CPT	81171	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81172	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
	81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
HCPCS	None	

Date of Origin: *February 2013*

Regence

Medical Policy Manual Genetic Testing, Policy No. 44

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

Effective: October 1, 2024

Next Review: January 2025
Last Review: September 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

Fetal cell-free DNA fragments and fetal cells present in the plasma of pregnant women can be used for fetal screening, including testing for fetal sex chromosome aneuploidies (e.g., Turners, Klinefelter syndrome), fetal sex determination, twin zygosity, and microdeletion syndromes (e.g., Prader-Willi/Angelman syndrome).

MEDICAL POLICY CRITERIA

Note: This policy does not address reproductive carrier screening (see Cross References).

I. Genetic testing of maternal plasma for fetal trisomies 13, 18, and 21 may be considered **medically necessary**.

II. For *member contracts subject to Washington's State Board of Health Rule* (WAC 246-680), genetic testing of maternal plasma for fetal sex chromosome aneuploidies (e.g., sex chromosome aneuploidy (SCAs) or sex chromosome aneuploidy panel (SCAP) testing) may be considered **medically necessary**.

III. For *all other member contracts*, genetic testing of maternal plasma for fetal sex chromosome aneuploidies (e.g., sex chromosome aneuploidy (SCAs) or sex chromosome aneuploidy panel (SCAP) testing) is considered **investigational.**

IV. Genetic testing of maternal plasma for fetal sex determination is considered **not medically necessary**.

V. Genetic testing of maternal plasma for fetal microdeletion syndromes is considered **investigational**.

VI. Genetic testing of maternal plasma for twin zygosity is considered **investigational.**

VII. Genetic testing of maternal plasma for diagnosing fetal single-gene disorders, including but not limited to the Vistara™ test, is considered **investigational**.

VIII. Combination tests that include microdeletion, twin zygosity, and/or single-gene disorder testing are considered **investigational** (see Policy Guidelines).

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

POLICY GUIDELINES

COMBINATION TESTS

Combination tests that include investigational test components (such as microdeletion or single-gene testing) in addition to the standard trisomy testing include, but are not limited to the following tests:

- MaterniT® 21 PLUS (Labcorp)
- Panorama™ (Natera)
- Unity™ (BillionToOne)

TESTING RESULTS

Karyotyping would be necessary to exclude the possibility of a false-positive, nucleic acid sequencing– based test. Before testing, women should be counseled about the risk of a false-positive test. In a 2015 committee opinion, the American College of Obstetricians and Gynecologists recommended that all patients receive information on the risks and benefits of various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing.

Studies published to date on noninvasive prenatal screening for fetal aneuploidies have reported rare but occasional false positives. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. Diagnostic testing is necessary to confirm positive cell-free fetal DNA tests, and management decisions should not be based solely on the results of cell-free fetal DNA testing. The American College of Obstetricians and Gynecologists further recommended that patients with indeterminate or uninterpretable (i.e., “no call”) cell-free fetal DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because “no call” findings have been associated with an increased risk of aneuploidy.

Cell-free fetal DNA screening does not assess risk of neural tube defects. Patients should continue to be offered ultrasound or maternal serum α-fetoprotein screening.

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.

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The analyses included in the test (e.g., trisomies, sex chromosome aneuploidies, etc.)
- Relevant billing codes
- Blood draw date
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test

CROSS REFERENCES

1. Evaluating the Utility of Genetic Panels, Genetic Testing Policy No. 64
2. Fetal RHD Genotyping Using Maternal Plasma, Genetic Testing No. 74
3. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
4. Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss, Genetic Testing, Policy No. 79
5. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81
6. Maternal Serum Analysis for Risk of Adverse Obstetric Outcomes, Laboratory, Policy No. 75

BACKGROUND

Historically, karyotype testing was an optional test used to examine chromosomes in a sample of fetal cells to help identify genetic disorders. Karyotype testing is an invasive and requires either an amniocentesis or a chorionic villi sampling test (CVS). Newer non-invasive prenatal screening tests have been developed that analyzes fetal cell-free DNA (cfDNA) or fetal cells circulating in maternal blood. Most DNA is contained within cells, but a small amount circulates freely in the bloodstream, called cfDNA. This non-invasive prenatal screening test (NIPT) analyzes the maternal serum for fetal trisomy aneuploidies and can also include testing for fetal sex chromosomes aneuploidies, microdeletions, twin zygosity, and fetal sex determination.

FETAL TRISOMY ANEUPLOIDY TESTING

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, the majority of which are aneuploidies (an abnormal number of chromosomes). Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. The trisomy syndromes are aneuploidies involving three copies of one chromosome. Trisomies 21 (Down syndrome, T21), 18 (Edwards syndrome, T18) and 13 (Patau syndrome, T13) are the most common forms of fetal aneuploidy that survive to birth. The most important risk factor for Down syndrome is maternal age, with an approximate risk of 1/1500 in young women that increases to nearly 1/10 by age 48.[1]

Standard aneuploidy screening involves combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of noninvasive testing ranges from 60% to 96% when the false-positive rate is set at 5%. When tests indicate a high risk of a trisomy syndrome, direct karyotyping of fetal tissue obtained by amniocentesis or CVS is required to confirm that T21 or another trisomy is present. Both

amniocentesis and CVS are invasive procedures and have procedure-associated risks of fetal injury, fetal loss and infection. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures or increases detection of T21, T18, and T13 could improve outcomes. Confirmation of positive noninvasive screening tests with amniocentesis or CVS is recommended; with more accurate tests, fewer women would receive positive screening results.

SEX CHROMOSOME ANEUPLOIDY

Some of the NIPT prenatal tests also include testing for sex chromosome aneuploidies (SCAs) or sex chromosome aneuploidy panel (SCAP) testing. Abnormalities in the number of X or Y chromosomes result in the following syndromes:

- Turner syndrome (Monosomy X or 45, X)
- Klinefelter syndrome (47, XXY)
- Triple X syndrome (47, XXX)
- Jacob syndrome (47, XYY)
- XXYY syndrome (48, XXYY)

Sex chromosome aneuploidies occur in approximately 1 in 400 live births. These aneuploidies are typically diagnosed postnatally, sometimes not until adulthood, such as during an evaluation of diminished fertility. Alternatively, sex chromosome aneuploidies may be diagnosed incidentally during invasive karyotype testing of pregnant women at high risk for Down syndrome. Potential benefits of early identification (e.g., the opportunity for early management of the manifestations of the condition), must be balanced against potential harms that can include stigmatization.

MICRODELETION SYNDROMES

Microdeletion syndromes are defined as a group of clinically recognizable disorders characterized by a small (< 5Mb) deletion of a chromosomal segment spanning multiple disease genes, each potentially contributing to the phenotype independently. The phenotype is defined as the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. Microdeletion testing can include, but is not limited to the following conditions or syndromes:

- 22q deletion syndrome (DiGeorge)
- 22q11 deletion syndrome (Shprintzen syndrome)
- 15q11.2 (Prader-Willi/Angelman syndromes)
- 5p deletion (Cri du chat syndrome)
- 1p36 deletion syndrome
- 4p deletion (Wolf-Hirschhorn syndrome)

Clinical implications of prenatal testing for microdeletions are not well defined. It is unclear whether prenatal diagnosis is appropriate given the inherent difficulty in accurately predicting the phenotype for the myriad of microdeletion syndromes. Though laboratories may offer screening for microdeletion syndromes, screening for these microdeletion syndromes is not currently the main intent of NIPT screening tests.

SINGLE-GENE DISORDERS

Single-gene disorders (also known as monogenic disorders) are caused by a variation in a single gene. Individually, single-gene disorders are rare, but collectively are present in approximately 1% of births. The Vistara Single-Gene Disorder Test panel screens for 25 conditions that result from variants across 30 genes, which have a combined incidence of 1 in 600 (0.17%).[2] These include Noonan syndrome and other Noonan spectrum disorders, skeletal disorders (e.g., osteogenesis imperfecta, achondroplasia), craniosynostosis syndromes, Cornelia de Lange syndrome, Alagille syndrome, tuberous sclerosis, epileptic encephalopathy, *SYNGAP1*-related intellectual disability, CHARGE syndrome, Sotos syndrome, and Rett syndrome. The clinical presentation and severity of these disorders can vary widely. Some, but not all, can be detected by prenatal ultrasound examination.

FETAL SEX DETERMINATION

Sequencing-based testing of maternal serum for determination of fetal sex in the first trimester of pregnancy is possible. However, the current standard of care for fetal sex is ultrasound. Fetal sex includes:

- Male (XX)
- Female (XY)

TWIN ZYGOSITY TESTING

Twin gestations occur in approximately 1 in 30 live births in the United States and have a 4- to 10-fold increased risk of perinatal complications.[3] Dizygotic or "fraternal" twins occur from ovulation and fertilization of two oocytes, which results in dichorionic placentation and two separate placentas. In contrast to dichorionic twins, monochorionic twin pregnancies share their blood supply. Monochorionic twins account for about 20% of twin gestations and are at higher risk of structural defects, miscarriage, preterm delivery, and selective fetal growth restriction compared to dichorionic twins.[3] Up to 15% of monochorionic twin pregnancies are affected by twin-to-twin transfusion syndrome (TTTS), a condition characterized by relative hypovolemia of one twin and hypervolemia of the other.[4] According to estimates from live births, TTTS occurs in up to 15% of monochorionic twin pregnancies. In these twin pregnancies, serial fetal ultrasound examinations are necessary to monitor for development of TTTS as well as selective intrauterine growth restriction because these disorders have high morbidity and mortality and are amenable to interventions that can improve outcomes.[4] NIPT using cell-free fetal DNA to determine zygosity in twin pregnancies could potentially inform decisions about early surveillance for TTTS and other monochorionic twin-related abnormalities. In particular, determining zygosity with NIPT could potentially assist in the assessment of chorionicity when ultrasound findings are not clear.

REGULATORY STATUS

None of the commercially available sequencing assays listed above have been submitted to or reviewed by the U.S. Food and Drug Administration (FDA). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories offering LDTs must be licensed by CLIA for high-complexity testing. The NIPT panels vary significantly in the base components and additional options a provider may choose on the requisition form. Commercial tests include, but are not limited to, the following:

- **Harmony**™ Prenatal Test (Ariosa Diagnostics, now Roche).

  Tests for fetal trisomies.

  Additional options for testing fetal sex chromosome aneuploidies, fetal sex, monosomy X, and 22q11.2 microdeletion.

- **InformaSeq**SM **Prenatal Test** (Integrated Genetics, a division of LabCorp)

  Tests for fetal trisomies.

  Optional testing includes fetal sex chromosome and fetal sex.

- **MaterniT Genome** (Sequenom Laboratories, now LabCorp)

  Tests for genome wide aneuploidies

- **MaterniT21™ Plus** (Sequenom Laboratories, now LabCorp).

  Tests for fetal trisomies and fetal sex.

  Additional items to include microdeletions, other chromosomes (T16, T22), and sex chromosomes aneuploidies.

- **Panorama**™ (Natera).

  Tests for fetal trisomies, fetal sex chromosome aneuploidies, triploidy, microdeletions, and fetal sex.

- **Prequel™ Prenatal Screen** (Myriad)

  Tests for fetal trisomies, with options for sex chromosome and microdeletion testing.

- **Progenity Innatal® Prenatal Screen** (Progenity)

  Tests for fetal trisomies, may include fetal sex chromosome aneuploidies and fetal sex.

- **Verifi**® Prenatal Test (Illumina, formerly Verinata Health).

  There are two options for these tests which may include fetal trisomies, fetal sex chromosomes aneuploidies, microdeletions, and fetal sex.

- **Vistara™** Single Gene NIPT (Natera)

  Tests for 25 autosomal dominant and X-linked conditions across 30 genes.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[5] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Assessment of a diagnostic technology such as maternal plasma DNA sequencing tests typically focuses on three parameters:

1. Analytic validity;
2. Clinical validity (includes calculations of sensitivity and specificity in appropriate populations of patients); and
3. Clinical utility (demonstration that the diagnostic information can be used to improve patient health outcomes).

The focus of this evidence summary below is on the clinical validity and utility of these tests.

The evidence regarding these three questions was addressed in the 2012 and 2014 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessments.[6, 7] The initial Assessment, published in 2012, focused on detection of T21/Down syndrome because the majority of published data at the time was concentrated on this trisomy. Additionally, large numbers of cases were included in several publications, and all companies had published data regarding the detection of T21. The subsequent Assessment, published in 2014, reviewed the available data for detection of T18, T13, and sex chromosome aneuploidies (SCAs). The scope of both TEC Assessments was limited to the evaluation of tests that are available in the United States. Additional literature published after publication the TEC Assessments is also addressed in the analysis below.

CLINICAL VALIDITY

Multiple Conditions

Gil (2017) published a systematic review with meta-analysis which evaluated the performance of screening for fetal trisomies 21, 18 and 13 and sex chromosome aneuploidies.[8] This summary will only focus on the results for sex chromosome aneuploidies. There were 36 total cases of monosomy X and 7,677 unaffected singleton pregnancies. The pooled weighted detection rate and false positive rate were 95.8% (95% confidence interval [CI] 70.3 to 99.5%) and 0.14% (95% CI 0.05 to 0.38%), respectively. Also, there were 17 cases of sex chromosome abnormalities that were not monosomy X and 5,383 unaffected singleton pregnancies. The pooled weighted detection rate and false positive rate were 100% (95% CI 83.6 to 100%) and 0.003% (95% CI 0 to 0.07%), respectively. The authors concluded that the number of cases for sex chromosome aneuploidy was too small to calculate overall screening performance.

Norton (2016) conducted a high-quality systematic review and meta-analysis which evaluated cohort studies comparing sequential screening to cell free DNA detection rates for fetal chromosomal abnormalities.[9] A total of 452,901 women underwent sequential screening and out of those women, 2575 (0.57%) had a fetal chromosomal abnormality. Of those abnormalities, the detection rate was 81.6% (total of 2,101). Additionally, 19,929 euploid fetuses had positive sequential screening resulting in a detection rate of 4.5%. The authors concluded that cfDNA testing has good performance for fetal sex and the detection rate of sequential screening for all aneuploidies was significantly greater than cfDNA ($p<0.0001$).

Mackie (2016) conducted a systematic review with meta-analysis evaluating the performance of cell free fetal DNA testing for all conditions (singleton pregnancies only).[10] A total of 117 studies addressing 18 conditions were included. The meta-analysis showed that for fetal sex (60 studies with 11,179 tests), the sensitivity and specificity were 0.989 (95% CI 0.980 to 0.994) and 0.996 (95% CI 0.989 to 0.998), respectively. For monosomy X (80 studies and 6,712 tests), the sensitivity was 0.929 (95% CI 0.741 to 0.984) and specificity 0.999 (95% CI

0.995 to 0.999). The authors concluded that fetal sex can be considered diagnostic but that testing for aneuploidies should only be considered as screening.

Fetal Sex Chromosome Aneuploidies

A Cochrane review by Badeau (2017) evaluated diagnostic accuracy of NIPT for sex chromosome anomalies.[11] Twelve studies were identified on the 45,X chromosome with sensitivities of 91.7% to 92.4% and specificities of 99.6% to 99.8%. Reviewers calculated that of 100,000 pregnancies, 1,039 would be affected by 45,X. Of these, 953 tested with massively parallel shotgun sequencing and 960 tested with targeted massively parallel sequencing would be detected and 86 and 79 cases, respectively, would be missed. Of the 98,961 unaffected women, 396 and 198 pregnant women would undergo an unnecessary invasive test. The authors were unable to perform meta-analyses of NIPT for chromosomes 47,XXX, 47,XXY, and 47,XYY due to insufficient evidence.

A systematic review published after the Cochrane review had similar results, showing high sensitivity (94.1%, 95% CI 90.8% to 96.3%) and specificity (94.1%, 95% CI 90.8% to 96.3%), but more false positives (235 per 100,000) than tests for the common trisomies.[12] Subgroup analyses showed variation in positive predictive value (PPV) by type of sex chromosome aneuploidy, from 32% (95% CI 27.0% to 37.4%) for monosomy X to 70% (95% CI 63.9% to 77.1%) for XYY syndrome, explained by higher sensitivity and specificity for the Y chromosome and high risk of false-positive results for aneuploidies involving the X chromosome only.

Gil (2015) published results from a systematic review and meta-analysis that examined the analysis of cfDNA in maternal blood in screening for fetal aneuploidies between January 2011 and January 2015.[13] Thirty-seven articles were included in the review; however, just 28 of these studies reported on sex chromosome aneuploidy testing. Sixteen of the 28 studies addressed the detection of monosomy X (Turner syndrome). The authors found, that of the 177 singleton pregnancies with fetal monosomy X, the detection rate varied between 66.7% and 100% and the false-positive rate varied between 0% and 0.52%. The pooled weighted detection rate was 90.3% (95% CI 85.7 to 94.2%), and the false-positive rate was 0.23% (95% CI 0.14 to 0.34%). The remaining 12 studies reported on the performance of sex chromosome abnormalities other than monosomy X (i.e., 47XXX, 47XXY, 47XYY), in a combined total of 56 affected and 6,699 non-sex chromosome aneuploidy singleton pregnancies. The pooled detection rate was 93.0% (95% CI 85.8 to 97.8% and the false-positive rate was 0.14% (95% CI 0.06 to 0.24%). This study has significant methodological limitations, which include but are not limited to, very small sample sizes, high risk of bias in relation to flow and timing (i.e., consecutive cases), testing performed in selected populations, and a lack of clarity about karyotyping, and the studies did not clearly define the patient's risk category.

The 2014 BCBSA TEC Assessment included a meta-analysis of sequencing-based studies published through April 15, 2014 that included a report on sex chromosome anomalies.[7] The largest number of studies (14 studies, total of 152 cases) published on sex chromosome aneuploidies addressed detection of monosomy X. Pooled sensitivity for detecting monosomy X was 83% (95% CI 74% to 90%) and pooled specificity was 100% (95% CI 100% to 100%). In addition, 11 studies with a total of 51 cases were identified on the performance of sequencing-based tests in identifying other sex chromosome anomalies. Pooled sensitivity was 89% (95% CI 50% to 98%) and pooled specificity was 100% (100% to 100%). The meta-

analysis of studies on sex chromosome aneuploidies did not differentiate between high and low-risk populations.

A study published by Wang (2015), which was not included in the above systematic reviews, examined the concordance of NIPT results among 109 consecutive cases with positive or negative NIPT results and compared those findings with the cytogenetic prenatal and/or postnatal karyotype results.[14] Sixteen of these cases were tested for fetal sex chromosome aneuploidies. The authors found that of these, the true positive rate was 38% (6/16 cases), and the false positive rate to be 62% (10/16 cases). This study has methodological limitations, including small sample size and the design, which was limited to testing at just one of the four main laboratories performing NIPT in the U.S., all of which use different methodologies or algorithms.

A larger study by Guy (2019) reported results for NIPT testing from a large laboratory testing company.[15] Of the 75,658 samples received (from 72,176 women), 69,794 had successful testing. Approximately 87% represented “high risk” pregnancies. The reported PPV was 69% for SCAs and 75% for microdeletions.

A study by Yang (2021) evaluated the performance of NIPT for SCA detection in a cohort of 47,800 patients in Southern China.[16] Of the 238 high-risk cases that were detected by NIPT, 170 patients had available information on subsequent prenatal diagnostic testing, such as karyotyping and CMA. These included 137 cases of 45X, 27 cases of 47XXX, and 74 cases of 47XYY/47XXY. The PPV of the NIPT testing was reported to be 30.00% for 45X, 70.58% for 47XXX, and 81.13% for 47XYY/47XXY.

Reiss (2017) compared NIPT to nuchal translucency screening for SCA among patients at a single prenatal diagnosis center. Of the 2,851 patients, 18 were positive for an SCA by NIPT. There were no false positives among the five cases that screened positive for 47XXX or the two cases that screened positive for 47XXY. Among the 11 positive screens for monosomy X, only one was a true positive. Four additional cases of monosomy X were identified due to cystic hygromas, one of which had a negative NIPT result.

Microdeletion syndromes

In a systematic review of NIPT using cfDNA in general risk pregnancies conducted for ACMG, Rose (2022) included 17 studies of screening for copy number variants (microdeletions and microduplications).[17] Meta-analyses were not conducted due to study heterogeneity. Although screening identified a small number of copy number variants (CNVs), confirmatory testing was frequently unavailable and complete ascertainment of cases was lacking. Sample sizes in each study were relatively small and sensitivities varied greatly. Additionally, it was often difficult to distinguish between low- and high-risk cohort in individual studies. The study authors concluded that the performance of NIPT was significantly poorer when targeting CNVs than the common trisomies and additional outcome studies are needed to understand the unique clinical value of NIPT for CNVs when compared with other approaches.

Zaninović (2022) conducted a systematic review of NIPT for CNVs and microdeletions.[18] A total of 32 studies were identified with literature searches conducted through February 2022. Of these, 21 studies concerned screening for microdeletion syndromes. Meta-analyses were not conducted due to study heterogeneity. Although a comprehensive quality assessment of studies was not conducted, the study authors described notable limitations of the included studies. Most studies did not define indications for screening, and some included only high-risk

pregnancies. Negative predictive values could not be determined because none of the studies performed systematic confirmatory analysis by chromosomal microarray analysis for negative/low-risk cases, mostly relying on clinical follow-up. The study authors concluded that given the limited follow-up and validation data available, NIPT for microdeletions and CNVs should be used with caution.

Familiari (2021) conducted a systematic review of the literature on screening for fetal microdeletions and microduplications using cfDNA.[19] A total of seven studies met inclusion criteria, representing 210 cases of microdeletions or microduplications. The overall pooled PPV was 44.1% (95% CI 31.49 to 63.07, range 28.9% to 90.6%). Limitations in the individual studies included retrospective design, low number of cases for each condition, lack of a standardized confirmation of the disease, low detail regarding the presence of absence of ultrasound anomalies and sonographic protocol used, different gestational ages at the time of the test, and variation in background risk. The authors noted that confirmatory testing was seldom reported in studies, under the assumption that all anomalies would have been identified in the newborn by physical exam. However, because many newborns with microdeletion and microduplication syndromes will not demonstrate phenotypical anomalies, standard neonatal examination cannot be considered a reliable ascertainment method and the detection rate and negative predictive value could not be determined from this body of evidence.

Additional non-randomized studies from companies offering microdeletion testing have been published evaluating data from clinical samples submitted for screening. Dar (2022) conducted a prospective analysis of 20,887 women who underwent NIPT testing at 21 centers in six countries.[20] A genetic outcome result was available for 18,289 women (87.6%), and 12 cases of 22q11.2 deletion syndrome were confirmed in the cohort. Limitations of the study include the low number of overall confirmed cases, wide confidence intervals for sensitivity, positive and false positive values, and varied indications for testing.

Soster (2021) conducted a retrospective analysis of 55,517 samples submitted for genome-wide cfDNA screening at a commercial laboratory between 2015 and 2018.[21] Diagnostic testing results were available in 42.5% (n=1,142) of screen-positive samples, and 0.82% of screen-negative samples, with overall 2.98% of samples with diagnostic outcomes. Microdeletion syndromes included 1p36 deletion, Wolf–Hirschhorn, Cri-du-chat, Langer–Giedion, Jacobsen, Prader–Willi, Angelman, and DiGeorge syndrome. Test performance characteristics were based on the 1,569 patients who had diagnostic testing performed, and an overall PPV of 72.6% was reported.

Wang (2021) conducted a prospective analysis of 39,002 pregnant women who received NIPT in a single center between 2018 and 2020.[22] There were 473 (1.21%) pregnancies that tested positive for fetal chromosome abnormalities, of which 95 were microdeletion/microduplication syndrome cases. Limitations of this study include variable types of diagnostic testing and specimen types, a large number of patients who refused to receive a prenatal diagnosis (n=135) and then were lost to follow-up (n=128), and low percentage of overall specimens that had diagnostic testing results available.

Fetal Sex Determination

The current standard of care for fetal sex determination is ultrasound.

Three reviews report on the use of cfDNA for fetal sex determination. Davaney (2011) published results from a systematic review and meta-analysis to determine if noninvasive prenatal determination of fetal sex using cfDNA provides an alternative to invasive techniques for some heritable disorders.[23] From 57 selected studies, 80 data sets (representing 3524 male-bearing pregnancies and 3,017 female-bearing pregnancies) were analyzed. Authors reported that despite inter-study variability, performance was high using maternal blood. Sensitivity and specificity for detection of Y chromosome sequences was greatest using RT-qPCR after 20 weeks' gestation. Tests using urine and tests performed before seven weeks' gestation were unreliable.

Wright (2012) published results from a review and meta-analysis of the published literature to evaluate the use of cfDNA for prenatal determination of fetal sex.[24] The authors reviewed 90 studies, incorporating 9,965 pregnancies and 10,587 fetal sex results. Overall mean sensitivity was 96.6% (95% CI 95.2% to 97.7%) and mean specificity was 98.9% (95% CI 98.1% to 99.4%). The authors identified one limitation of their study as the inability to properly evaluate the proportion of inconclusive or uncertain results, which is known to be problematic with this technique and may vary with gestational age. Further, literature-based reviews are at risk of publication bias due to the suppression of unwanted findings. The authors concluded that fetal sex can be determined with a high level of accuracy by analyzing cfDNA.

Colmant (2013) published a review of the published literature evaluating the use of cfDNA and ultrasound for prenatal determination of fetal sex during the first trimester of pregnancy.[25] The authors identified 16 reports of the determination of fetal sex in maternal blood and 13 reports of the determination by ultrasound. Authors determined a sensitivity and specificity of nearly 100% from eight weeks of gestation for cfDNA and from 13 weeks of gestation for ultrasound respectively. Authors concluded that fetal sex can be determined with a high level of accuracy by analyzing cfDNA and at an earlier gestation than ultrasound.

Twin Zygosity

Norwitz (2019) conducted a validation study of a single-nucleotide polymorphism-based NIPT in twin pregnancies.[3] The study included 95 samples with confirmed zygosity: 30 monozygotic and 65 dizygotic. Two of the 95 samples did not receive results due to low fetal fraction. Among the 93 pregnancies that yielded results, monozygotic sensitivity was 100% (29/29) and monozygotic specificity was 100% (64/64). A major limitation of this study was a lack of information on timing of the index test and the use of different methods to confirm zygosity.

Single-Gene Disorders

The performance characteristics of the Vistara NIPT were evaluated in a retrospective validation study conducted by Zhang (2019).[26] Most of the study participants were high risk due to prenatal ultrasound findings or a family history of genetic disease. The validation cohort included 76 cases (3 positive and 73 negative) and the clinical study included 422 samples (32 positive and 390 negative). Pathogenic or likely pathogenic variants were confirmed using a secondary NGS assay. Sanger sequencing was used to confirm positive findings if an invasive specimen (e.g., amniotic fluid) or a postnatal sample was available. Of the 35 positive results, 20 had a confirmed diagnosis. Pregnancy outcome data were obtained for 26 of 35 (74.2%) positive tests and 198 of 463 (42.7%) negative tests from both the validation and clinical studies.

Mohan (2022) reported on the clinical experience of Vistara NIPT in a series of 2,208 pregnancies.[2] Of 2,416 initial tests, 132 (5.5%) tests were ineligible and 76 (3.1%) did not pass quality control. Indications for NIPT included family history (6.0%), abnormal ultrasound finding (23.3%), advanced paternal age (41.3%), and unspecified/other/advanced maternal age (29.4%). In cases without abnormal ultrasound findings or family history, the test positive rate was 6 of 52 (0.4% (6/52). Positive variants were confirmed by a secondary NGS assay using deeper sequencing, and variants of unknown significance were not reported. Confirmatory prenatal or postnatal diagnostic testing was recommended for all screen-positive patients. Overall, the test positive rate was 125 of 2,208 (5.7%), and of these, follow-up information was available for 67 (53.6%), with none classified as false positive. Positive tests in cases without abnormal ultrasound findings or family history were found for 6/52 (0.4%).

Major limitations of these studies include a lack of confirmatory testing and selection bias. Because of missing data, it is not possible to determine accurate estimates of true positive and true negative tests. In addition, a large proportion of participants in both studies had a previous screening with findings suggestive of a potential disorder. It is unclear if single-gene NIPT is intended to be an adjunct to or replacement for other screening tests such as ultrasound. More clarity on the proposed use of the testing would be needed to adequately evaluate performance characteristics.

CLINICAL UTILITY

Fetal Sex Chromosome Aneuploidies

The impact of screening for sex chromosome aneuploidies has not been modeled in published studies. Fetal sex chromosome aneuploidies were not included in the decision analysis of the 2014 BCBSA TEC Assessment because the implications of a screen-positive finding and diagnostic confirmation were considered to differ significantly when compared to T13 and T18.[7] Finally, fetal sex aneuploidies are generally diagnosed postnatally in association with specific health problems, such as delayed puberty, or diminished fertility or infertility. Therefore, the balance of benefits and harms of cfDNA prenatal screen and subsequent diagnosis of sex chromosome fetal aneuploidies, each of which has variable and uncertain prognosis, is unclear.

Microdeletion syndromes

The clinical utility of testing for any specific microdeletion or any panel of microdeletions is uncertain.

There is a potential that prenatal identification of individuals with microdeletion syndromes could improve health outcomes due to the ability to allow for informed reproductive decision making, and/or to initiate earlier treatment; however, data demonstrating improvement are unavailable. Given the variability of expressivity of microdeletion syndromes and the lack of experience with routine genetic screening for microdeletions, clinical decision making based on genetic test results is not well defined. It is not clear what follow-up testing or treatments might be indicated for screen-detected individuals. Routine prenatal screening may identify a small percentage of fetuses with microdeletion variants earlier in pregnancy than would otherwise have occurred (e.g., by ultrasound evaluation and diagnostic testing). At the same time, routine prenatal screening for microdeletions would also result in false-positive tests and a larger number of invasive confirmatory tests. The large number of confirmatory tests could lead to a net harm because of pregnancy loss.

Most treatment decisions would be made after birth, and it is unclear whether testing in utero will lead to earlier detection and treatment of clinical disease after birth. Moreover, clinical decision making when a maternal microdeletion is detected in a pregnant woman without previous knowledge of a genetic variant is unclear.

Single-Gene Disorders

No studies were identified that evaluated whether cfDNA testing for single-gene disorders improves outcomes compared with standard care. There is a potential that prenatal identification of pregnancies with single-gene disorders could improve health outcomes due to the ability to allow for informed reproductive decision making and/or initiate earlier treatment; however, data demonstrating improvement are unavailable. Given the variability of single-gene disorders identified by this testing and the lack of experience with routine genetic screening for single-gene disorders, clinical decision-making based on this testing is not well defined.

Twin Zygosity

No studies were identified that evaluated whether cfDNA testing for twin zygosity improves outcomes compared with standard care.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS AND SOCIETY FOR MATERNAL-FETAL MEDICINE (ACOG/SMFM)

Noninvasive Prenatal Screening for Fetal Aneuploidies

In 2020, ACOG and SMFM released a practice bulletin summary (No. 226) on screening for fetal aneuploidy.[27] The following recommendations are based on “good and consistent” scientific evidence:

- “Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing.”
- “Patients with a positive screening test result for fetal aneuploidy should undergo genetic counseling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results.”
- “Patients with a negative screening test result should be made aware that this substantially decreases their risk of the targeted aneuploidy but does not ensure that the fetus is unaffected. The potential for a fetus to be affected by genetic disorders that are not evaluated by the screening or diagnostic test should also be reviewed. Even if patients have a negative screening test result, they may choose diagnostic testing later in pregnancy, particularly if additional findings become evident such as fetal anomalies identified on ultrasound examination.”
- “Patients whose cell-free DNA screening test results are not reported by the laboratory or are uninterpretable (a no-call test result) should be informed that test failure is associated with an increased risk of aneuploidy, receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing.”

The following recommendations are based on “limited or inconsistent” scientific evidence:

- “The use of cell-free DNA screening as follow-up for patients with a screen positive serum analyte screening test result is an option for patients who want to avoid a diagnostic test. However, patients should be informed that this approach may delay definitive diagnosis and will fail to identify some fetuses with chromosomal abnormalities.” “No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies; this information should be incorporated into pretest counseling for patients with multiple gestations.”
- “Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13.”

The following recommendations are based primarily on based “primarily on consensus and expert opinion:

- “In multifetal gestations, if a fetal demise, vanishing twin, or anomaly is identified in one fetus, there is a significant risk of an inaccurate test result if serum-based aneuploidy screening or cell-free DNA is used. This information should be reviewed with the patient and diagnostic testing should be offered.
- “Patients with unusual or multiple aneuploidies detected by cell-free DNA should be referred for genetic counseling and maternal–fetal medicine consultation.”

Cell-free DNA Screening for Single-Gene Disorders

In a practice advisory on cell-free DNA screening for single-gene disorders published in 2019 and reaffirmed in 2021,[28] ACOG stated, "Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy.”

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS

In 2023, the American College of Medical Genetics and Genomics (ACMG) published a position statement on noninvasive prenatal screening (NIPS) for fetal aneuploidy for fetal chromosome abnormalities in a general-risk population.[29] Relevant recommendations are as follows:

- ACMG recommends NPS over traditional screening methods for all pregnant patients with singleton gestation for fetal trisomies 21, 18, and 13 (strong recommendation based on high certainty of evidence)
- ACMG recommends NIPS over traditional methods for trisomy screening in twin gestations (strong recommendation, based on high certainty of evidence)

- ACMG recommends that NIPS be offered to patients with a singleton gestation to screen for fetal SCA (strong recommendation, based on high certainty of evidence)
- ACMG suggests that NIPS for 22q11.2 deletion syndrome be offered to all patients (conditional recommendation, based on moderate certainty of the evidence)
- At this time, there is insufficient evidence to recommend routine screening for CNVs other than 22q11.2 deletions (no recommendation, owing to lack of clinically relevant evidence and validation)
- At this time, there is insufficient evidence to recommend or not recommend NIPS for the identification of RATS [rare autosomal trisomies] (no recommendation, owing to lack of clinically relevant evidence)

SUMMARY

FOR MEMBER CONTRACTS SUBJECT TO WASHINGTON'S STATE BOARD OF HEALTH RULE (WAC 246-680)

For member contracts subject to Washington's State Board of Health Rule, criteria for sex chromosome aneuploidy testing are based on the Rule. Therefore, for member contracts subject to Washington's State Board of Health Rule (WAC 246-680), sex chromosome aneuploidy testing using cell-free DNA may be considered medically necessary.

FOR MEMBER CONTRACTS *NOT* SUBJECT TO WASHINGTON'S STATE BOARD OF HEALTH RULE (WAC 246-680)

There is not enough research to show an improvement in health outcomes for non-invasive screening using fetal DNA to detect fetal sex chromosome aneuploidies. The current research shows mixed results for detection of abnormalities, including high false-positive rates. Therefore, non-invasive prenatal testing (NIPT) for fetal sex chromosome aneuploidies is considered investigational.

FOR ALL MEMBER CONTRACTS

Testing for Fetal Trisomies 13, 18, and 21

There is enough research to show that non-invasive prenatal testing (NIPT) for fetal trisomies 13, 18, and 21 are important for informing patient management and reproductive decision making. This testing is recommended by evidence-based clinical practice guidelines. Therefore, NIPT testing for trisomies 13, 18, and 21 may be considered medically necessary.

Fetal Sex Determination Testing

Research does not show that the use of nucleic acid sequencing-based testing for fetal sex determination is more beneficial than fetal ultrasound, which is the current clinical standard for determining fetal sex. Therefore, non-invasive prenatal testing (NIPT) for fetal sex determination is considered not medically necessary.

Microdeletion Testing

There is not enough research to show an improvement in health outcomes for non-invasive screening using fetal DNA to detect fetal microdeletion syndromes. The current research shows mixed results for detection of abnormalities. In addition, there are no evidence-based practice guidelines that recommend testing for fetal microdeletions. Therefore, non-invasive prenatal testing (NIPT) for fetal microdeletion syndromes is considered investigational.

Twin Zygosity Testing

There is not enough research to show that non-invasive screening using fetal DNA to detect twin zygosity leads to improvements in health outcomes. The current research for this type of testing is very limited. In addition, there are no evidence-based practice guidelines that recommend this testing. Therefore, non-invasive prenatal testing (NIPT) for twin zygosity is considered investigational.

Single-gene Disorder Testing

There is not enough research to show that non-invasive screening using fetal DNA to detect single-gene disorders leads to improvements in health outcomes. The current research for this type of testing is very limited. In addition, there are no evidence-based practice guidelines that recommend this testing. Therefore, non-invasive prenatal testing (NIPT) for single gene disorders (e.g., Vistara™) is considered investigational.

Combination Testing

There is not enough research to show that certain components of combination tests, including microdeletion testing, twin zygosity testing, and/or single-gene disorder testing, leads to improvements in health outcomes. In addition, there are no evidence-based practice guidelines that recommend this testing. Combination tests that include investigational components (microdeletion, twin zygosity, and/or single-gene disorders) are considered investigational.

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CODES

NOTE: There are specific CPT codes for trisomy testing and for microdeletion testing. It is inappropriate to use nonspecific molecular pathology CPT codes (i.e., 81400-81408) for trisomy or microdeletion testing.

Codes	Number	Description
CPT	0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
	0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid
		Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (*CFTR*, *SMN1*, *HBB*, *HBA1*, *HBA2*)

Codes	Number	Description
	0489U	Obstetrics (single-gene noninvasive prenatal test), cell free DNA sequence analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants, and relative mutation-dosage analysis based on molecular counts to determine fetal inheritance of maternal mutation, algorithm reported as a fetal risk score for the condition (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia)
	81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
	81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
	81408	Molecular pathology procedure, Level 9
	81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *January 2013*

Regence

Medical Policy Manual Genetic Testing, Policy No. 51

Genetic Testing for CADASIL Syndrome

Effective: June 1, 2024

Next Review: April 2025
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

Variants in the *NOTCH3* gene have been causally associated with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Genetic testing is available to determine if pathogenic variants exist in the *NOTCH3* gene for patients with suspected CADASIL and their family members.

MEDICAL POLICY CRITERIA

I. Genetic testing of *NOTCH3* for the diagnosis of CADASIL may be considered **medically necessary** when one or more of the following criteria are met:
   A. Clinical signs and symptoms are consistent with CADASIL (subcortical ischemic events, cognitive impairment, migraine with aura, mood disturbances, and/or apathy); or
   B. In adults when there is a first- or second-degree family member with a diagnosis of CADASIL syndrome**.**

II. Genetic testing for CADASIL syndrome for all other situations, including but not limited to testing in children, is considered **investigational.**

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

POLICY GUIDELINES

CLINICAL SIGNS AND SYMPTOMS

The clinical presentation of CADASIL varies among and within families. The disease is characterized by five main symptoms: subcortical ischemic events, cognitive impairment, migraine with aura, mood disturbances, and apathy.

FAMILY MEMBERS

- First-degree relatives are parents, siblings, and children of an individual; and
- Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing. Medical records related to this genetic test, if available:
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an uncommon, autosomal dominant disease, although it is the most common cause of hereditary stroke and hereditary vascular dementia in adults. The CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

The clinical presentation of CADASIL is variable and may be confused with multiple sclerosis, Alzheimer dementia, and Binswanger disease. The specific clinical signs and symptoms, along with family history and brain magnetic resonance imaging (MRI) findings, are important in determining the diagnosis of CADASIL. The clinical features and mode of inheritance (autosomal dominant versus autosomal recessive) help to distinguish other inherited disorders in the differential diagnosis from CADASIL.

When the differential diagnosis includes CADASIL, various other tests are available for diagnosis:

- Genetic testing by direct sequencing of selected exons or of exons 2-24 of the *NOTCH3* gene (see Scientific Evidence section below). Identification of a *NOTCH3* pathogenic variant definitively establishes a diagnosis of CADASIL without the need for additional testing (eg, skin biopsy).
- Immunohistochemistry assay of a skin biopsy sample, using a monoclonal antibody with reactivity against the extracellular domain of the NOTCH3 receptor. Positive immunostaining reveals the accumulation of NOTCH3 protein in the walls of small blood vessels.[1] Lesnick Oberstein (2003) estimated sensitivity and specificity at 85-90% and 95-100%, respectively, for two observers of the test results in a population of patients and controls correlated with clinical, genetic and MRI parameters.[2]
- Detection of granular osmiophilic material (GOM) in the same skin biopsy sample by electron microscopy. The major component of GOM is the ectodomain of the *NOTCH3* gene product.[3] GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease. [4] However, GOM may not be present in all biopsy samples. Sensitivity has been reported as low as 45% and 57%, but specificity is generally near or at 100%.[5-7]
- Examination of brain tissue for the presence of GOM. GOM was originally described as limited to brain vessels.[8] Examination of brain biopsy or autopsy after death was an early gold standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain vessels.

NOTCH3 VARIANTS

Variants in *NOTCH3* have been identified as the underlying cause of CADASIL. In almost all cases, the variants lead to loss or gain of a cysteine residue that could lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.[9]

The *NOTCH3* gene is found on chromosome 19p13.2-p13.1 and encodes the third discovered human homologue of the Drosophila melanogaster type I membrane protein NOTCH. The NOTCH3 protein consists of 2,321 amino acids primarily expressed in vascular smooth muscle cells and plays an important role in the control of vascular transduction. It has an extracellular ligand-binding domain of 34 epidermal growth factor-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.[10]

Variants in the *NOTCH3* gene have been differentiated into those that are causative of the CADASIL syndrome (pathogenic variants) and those that are of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein.[10, 11] More than 150 pathogenic variants have been reported in at least 500 pedigrees. *NOTCH3* has 33 exons, but all CADASIL variants reported to date have been found in exons 2–24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGFR 2–5 (>40% of variants in >70% of families occur in these exons).[12]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). *NOTCH3* genetic testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has not chosen to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[13] is used to describe variants found in DNA and serves as an international standard. It was implemented for genetic testing medical evidence review updates in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

ANALYTICAL VALIDITY

Limited data on analytic validity of *NOTCH3* testing were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

Fernandez (2015) described the development of a next-generation sequencing (NGS) protocol for *NOTCH3* and *HTRA1* genes in 70 patients referred for clinical suspicion of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), all of whom had previously undergone Sanger sequencing of exons 3 and 4 of the *NOTCH3* gene.[14] *NOTCH3* variants were detected in six patients on NGS, including two variants previously detected with Sanger sequencing and four variants in exons 6, 11, and 19.

CLINICAL VALIDITY

Several retrospective and prospective studies have examined the association between *NOTCH3* genes and cerebral autosomal dominant arteriopathy with CADASIL, as shown in Table 1. These studies have been divided into two categories:

- Part 1, diagnostic studies, in which the patients enrolled were suspected, but not confirmed to have CADASIL; and
- Part 2, clinical validity studies, in which the patients had already been diagnosed with the disease by some method other than genetic testing. The diagnostic studies are more likely to represent the target population in which the test would be used.

Table 1. Studies of the association of NOTCH3 with CADASIL

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
Part 1 Diagnostic Studies			**Diagnostic Yield**	**Specificity**
Maksemous 2016[15]	Patients: 44 patients with suspected CADASIL previously screened for standard sequencing exons (3 and 4, and/or 2, 11, 18, 19) by Sanger sequencing and classified as negative for known pathogenic variants	Custom NGS panel	Patients: six typical CADASIL variants were identified in 7/44 patients.	NR
Yin 2015[16]	Patients: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL Patient diagnosis/selection: MRI abnormalities and the presence of more than one typical symptom (eg, migraine, stroke, cognitive deficits, psychiatric symptoms) or the presence of atypical symptoms with a positive family history	Testing method: exons 3 and 4 screened first; if no variants detected, remaining exons analyzed	Patients: six known variants were identified in eight families and two novel variants were identified in two families (exons 3 and 4), and one VUS was identified in one family (exon 2). Overall NOTCH3 variant prevalence: 29.4%	NR
Choi 2011[8]	Patients: 151 consecutive Korean patients with acute ischemic stroke. Patient Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography or MRI.	Bidirectional sequencing of exons 3, 4, 6, 11 and 18.	Patients: six patients (4%) were found with the identical *NOTCH3* variant (R544C; exon 11). Of these, all had pre-existing lacunar infarction, five (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; a history of stroke and dementia was higher in patients with variants. Family Members: No data for additional family members	NR
Mosca 2011[9]	Patients: 140 patients with clinical suspicion of CADASIL (Italian and Chinese). Patient Selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; a consistent family history; or a combination of the above criteria.	Direct sequencing of exons 2-8, 10, 14, 19, 20, and 22.	Patients: 14 patients with causative variants located in 10 different exons. 126 patients free of pathogenic variants. Family Members: Analysis of 15 additional family members identified 11 of the same causative variants.	NR
Lee 2009[17]	Patients: 39 patients with suspected CADASIL (China).	Direct sequencing of exons 2-23.	Patients: nine different single nucleotide variants identified in 21/39 patients.	100% No variants found in 100 healthy

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
	100 healthy elderly controls 80 years or older. Patient Selection: Suggestive MRI findings and at least one of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history.		Family members: No data for additional family members	elderly controls.
Markus 2002[7]	Patients: 83 patients with suspected CADASIL (UK). Patient Selection: Patients were younger than 60 years of age with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential.	Direct sequencing of exons 3-4; SSCP of exons 2, 5-23.	Patients: 15 different single nucleotide variants identified in 48 families with a total of 116 symptomatic patients, 73% in exon 4, 8% in exon 3, and 6% in exons 5 and 6. Family Members: No data for additional family members	NR
Part 2 Clinical Validity Studies			**Sensitivity**	**Specificity**
Choi 2013[18]	Patients: 73 unrelated patients diagnosed with CADASIL between 2004-2009. Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI, and stroke history.	Bidirectional sequencing of R544C (exon 11).	Patients: 65 of 73 Patients (90.3%) had the same R544C genotype.	NR
Tikka 2009[19]	Patients: 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, and French). Patient Diagnosis/Selection: EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families.	Direct sequencing of exons 2-24.	Sensitivity: 100% Patients: 131 CADASIL patients were variant positive. Family Members: No data for additional family patients. No variant reporting per family or per unrelated individual.	100% No variants were found in the 26 negative controls.
Dotti et al. 2005[20]	Patients: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian). Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI.	DHPLC, followed by confirmatory sequencing of identified variants.	Sensitivity: 100%. Patients: All 28 patients had variants.	NR

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
Peters 2005[21]	Patients: 125 unrelated patients diagnosed with CADASIL. Patient Diagnosis/Selection: Skin biopsy-proven CADASIL pts referred between 1994 and 2003 (German).	Bidirectional sequencing of all exons.	Sensitivity: 96% Patients: 54 distinct variants in 120 (96.0%) of the 125 patients. In five patients (4.0%), no variant was identified. Family Members: No data for additional family patients	NR
Joutel 1997[22]	Patients: 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls. Patient Diagnosis/Selection: History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and a consistent familial history.	SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified variants.	Sensitivity: 90% Patients: 45 of 50 CADASIL patients had variants.	100% No variants were found in 100 healthy controls.

Key: MRI, magnetic resonance imaging; SSCP, single-stranded conformational polymorphism; EM, electron microscope; DHPLC, denaturing high-performance liquid chromatography

The results of the clinical validity studies demonstrate that a *NOTCH3* variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90-100%. Limited data on specificity is from testing small numbers of healthy controls, and no false positive *NOTCH3* variants have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10-54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

CLINICAL UTILITY

Genetic testing may have clinical utility in several situations. The clinical situations addressed in herein are:

- Confirmation of a clinical diagnosis of CADASIL in an individual with signs and symptoms of the disease; and
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing or altering reproductive planning decisions when a *NOTCH3* pathogenic variant is present in a parent.

Confirmation of a CADASIL Diagnosis

The clinical specificity of genetic testing for CADASIL is high, and false-positive results have not been reported in studies of clinical validity. Therefore, a positive genetic test in a patient with clinical signs and symptoms of CADASIL is sufficient to confirm the diagnosis with a high degree of certainty. The clinical sensitivity is also relatively high, in the range of 90% to 100%

for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However, because false-negative tests do occur, a negative test is less definitive in ruling out CADASIL. Whether a negative test is sufficient to rule out CADASIL depends on the pretest likelihood that CADASIL is present.

Hack (2023) published a three-tiered risk stratification system for individualized *NOTCH3*-small vessel disease prediction based on *NOTCH3* genotype.[23] The frequency of cysteine-altering missense variants in each EGF repeat domain was assessed in the CADASIL literature, cohorts, and population databases among 2,574 CADASIL patients and 1,657 individuals from population databases. EGF repeat domains were classified as either low, medium, or high risk. The three risk categories were validated with comparisons to small vessel disease imaging markers and clinical outcomes using a genotype-phenotype dataset of 434 CADASIL patients and 1,003 individuals with *NOTCH3* cysteine-altering variants. CADASIL patients and individuals with *NOTCH3* cysteine-altering variants had 379 unique *NOTCH3* cysteine-altering variants. Nine EGF repeat domains were classified as high risk, 10 were classified as medium risk, and 11 were classified as low risk. In the population genotype-phenotype dataset, individuals with high risk EGF repeat variants had the highest risk of stroke (odds ratio [OR]=10.81, 95% confidence interval [CI]: 5.46 to 21.37) followed by medium risk individuals (OR=1.81, 95% CI: 0.84 to 3.88), and low risk individuals (OR=1). In the CADASIL genotype-phenotype group, patients with high risk EGF repeat domain variants had a significantly higher risk of stroke (p=0.002) and disability (p=0.041).

Chen (2021) published a study in 45 patients with young-onset cognitive impairment with leukodystrophy in which a custom panel of 200 neurodegeneration-associated genes was performed.[24] The frequency of gene variants was evaluated along with study participants' brain magnetic resonance imaging (MRI) findings to inform the diagnostic utility of combining the two approaches. In more than half (19/37, 51.4%) of patients with MRI changes consistent with vascular cognitive impairment secondary to small vessel disease (VCI-SVD), a pathogenic variant was identified, including all patients with pathogenic NOTCH3 (17/19, 89.5%) and HTRA1 variants (2/19, 11.5%). Anterior temporal white matter involvement was specific to patients with pathogenic NOTCH3 variants (6/17, 35.3%) in this cohort. No pathogenic variant was identified in 26/45 (57.8%) patients evaluated. The impact of genetic testing on health care decision making or on clinical outcomes was not evaluated in this study.

Pescini (2012) published a study that attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present and therefore might be helpful in selecting patients for testing.[25] The authors first performed a systematic review to determine the frequency with which clinical and radiologic factors are associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. Table 2 summarizes the pooled frequency of clinical and radiologic features.

Table 2. Clinical and Radiological Features in Patients with NOTCH3 Variants

Features	No. With NOTCH3 Variant	Percent With NOTCH3 Variant, %
Clinical features		
Migraine	239/463	52%
Migraine with aura	65/85	76%
Transient ischemic attack/stroke	380/526	72%
Psychiatric disturbance	106/380	28%
Cognitive decline	188/434	43%
Radiologic features		

Features	No. With NOTCH3 Variant	Percent With NOTCH3 Variant, %
LE (leukoencephalopathy)	277/277	100%
LE extended to temporal pole	174/235	74%
LE extended to external capsule	228/303	75%
Subcortical infarcts	210/254	83%

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with *NOTCH3* variants, and in 54 patients with phenotypic features of CADASIL who were *NOTCH3*-negative. With the addition of family history and age at onset of transient ischemic attack (TIA)/stroke, a scoring system was developed with the following point values: migraine (1); migraine with aura (3); TIA/stroke (1); TIA/stroke 50 years old or younger (2); psychiatric disturbance (1); cognitive decline (3); leukoencephalopathy (3); leukoencephalopathy extended to temporal pole (1); leukoencephalopathy extended to external capsule (5); subcortical infarcts (2); family history, one generation (1); and family history, two generations or more (2). The authors recommended that a total score of 14 be used to select patients for testing, because this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

A 2017 study reported by Mizuta analyzed clinical features of Japanese patients suspected for CADASIL to determine new diagnostic criteria for CADASIL.[26] Criteria were developed and validated with two separate groups of genetically diagnosed CADASIL patients, with 37 patients in the first group and 65 in the second. Controls groups were young stroke patients (n = 67) and CADASIL-like patients without *NOTCH3* variants (n = 53). Clinical criteria were as follows:

1. Age at onset less than or equal to 55 years
2. At least two of the following clinical findings:
    a. Either subcortical dementia, long tract signs, or pseudobulbar palsy.
    b. Stroke-like episode with a focal neurological deficit.
    c. Mood disorder.
    d. Migraine.
3. Autosomal dominant inheritance.
4. White matter lesions involving the anterior temporal pole by MRI or CT.
5. Exclusion of leukodystrophy

Genetic and pathological criteria were:

- *NOTCH3* variants localized in exons 2–24 and result in the gain or loss of cysteine residues in the epidermal growth factor-like repeat domain. Cysteine-sparing variants should be carefully evaluated by skin biopsy and segregation studies.
- The pathological hallmark of CADASIL is granular osmiophilic material (GOM) detected by electron microscopy. Immunostaining of NOTCH3 extracellular domain is also useful.

CADASIL diagnosis was considered definite when white matter lesions were detected by MRI or CT, clinical criteria #5 was met, and genetic or pathological criteria were met. Diagnosis was considered probable when the subject met all five clinical criteria and possible when the subject had abnormal white matter lesions and either was less than or equal to 55 years old or had at least one of the symptoms in clinical criteria number two. The sensitivity and specificity of the new criteria were 97.1% and 7.5%, respectively, when calculated using both control

groups. Sensitivity and specificity of the scale proposed by Pescini (above) using this cohort was also calculated. Sensitivity and specificity were 52.1% and 64.1%, respectively.

Currently, no specific clinical treatment for CADASIL has established efficacy. Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families.[3] Studies that addressed the efficacy of potential treatments for CADASIL are summarized below.

De Maria (2014) reported the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL.[27] Sapropterin is a synthetic analog of tetrahydrobiopterin, which is an essential cofactor in nitric oxide synthesis in endothelial cells. Given nitric oxide's role in cerebrovascular function, the authors hypothesized that sapropterin supplementation would improve cerebral endothelium-dependent vasodilation in CADASIL patients. Endothelial dysfunction was assessed using the reactive hyperemia peripheral arterial tonometry (RH-PAT) response, which has been shown to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry (PAT) is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia (RH) and evaluates the endothelial function of resistance arteries and nitric oxide–mediated changes in microvascular response. The study randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In intention-to-treat analysis, there was no significant difference in change in RH-PAT response (mean difference in RH-PAT change, 0.19: 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in RH-PAT values over the course of the study, but, after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

Another study published by Huang (2010) evaluated the efficacy and tolerance of a 24-week treatment with acetazolamide 250 mg/d to improve cerebral hemodynamics in CADASIL patients (n=16)..[28] Treatment with acetazolamide resulted in a significant increase of mean blood flow velocity (MFV) in the middle cerebral artery (MCA) compared with MFV in the MCA at rest before treatment (57.68±12.7 cm/s vs 67.12±9.4 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients (e.g., headaches, dizziness) were relieved. A double-blind, placebo-controlled trial evaluating the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL was published in 2008 by Dichgans.[29] The study showed donepezil HCl had no effect on the primary cognitive endpoint, the Cognitive subscale of the Vascular AD Assessment Scale score in patients with CADASIL and cognitive impairment.

Peters (2007) evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for eight weeks.[30] Treatment was started at 40 mg, followed by a dosage increase to 80 mg after four weeks. Transcranial Doppler sonography measuring MFV in the MCA was performed at baseline and at the end of treatment. There was no significant treatment effect on MFV (p=0.5) or cerebral vasoreactivity, as assessed by hypercapnia (p=0.5) or intravenous L-arginine (p=0.4) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO2- and L-arginine–induced vasomotor response (both p<0.05). Short-term treatment with atorvastatin resulted in no significant improvement of hemodynamic parameters in the overall cohort of CADASIL subjects.

Genetic Testing of *NOTCH3* in Relatives of Patients with CADASIL

For individuals that have family members with CADASIL syndrome who receive genetic testing, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For family members of an individual with known CADASIL, knowledge of the presence of a familial variant may lead to changes in lifestyle decisions for the affected individual (eg, reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent the onset of disease. A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 familial variant predicts future development of CADASIL in asymptomatic individuals, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning and helps determine the likelihood of an affected offspring.

It has been suggested that asymptomatic family members follow the guidelines for presymptomatic testing for Huntington disease. Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired.[4] For an asymptomatic individual, knowledge of variant status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be one factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing.

PRACTICE GUIDELINE SUMMARY

In a 2023 scientific statement, the American Heart Association reviewed the current clinical, genetic, and imaging aspects of CADASIL to provide prevention, management, and therapeutic considerations to support future treatment recommendations.[31] In consideration of when to test for *NOTCH3* mutations, the statement recommends to "consider gene testing in patients with small vessel stroke before 55 years of age with a paucity of vascular risk factors (eg, normotensive, nondiabetic, nonsmoker) or positive family history of CADASIL."

SUMMARY

There is enough research to show that testing for *NOTCH3* variants can help diagnose CADASIL in patients with signs and symptoms consistent with CADASIL. Therefore, genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary when the policy criteria are met.

There is enough evidence to show that testing for *NOTCH3* variants associated with CADASIL in individuals who have a family member with the disease can help patients make reproductive planning decisions and avoid unnecessary diagnostic testing. Therefore, genetic testing for *NOTCH3* variants in adults that have a first- or second-degree family member with a diagnosis of CADASIL syndrome may be considered medically necessary.

There is not enough research to show that genetic testing for CADASIL improves health outcomes or decision-making in patients that do not meet the policy criteria. Therefore, genetic testing for CADASIL syndrome in all other situations, including but not limited to testing in children, is considered investigational.

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CODES

Codes	Number	Description
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Codes	Number	Description
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Medical Policy Manual Genetic Testing, Policy No. 52

Diagnostic Genetic Testing for α-Thalassemia

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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

Alpha-thalassemia represents a group of clinical syndromes of varying severity characterized by hemolytic anemia and ineffective hematopoiesis. Genetic defects in any or all of four α-globin genes are causative of these syndromes.

MEDICAL POLICY CRITERIA

Note: This policy applies to diagnostic testing only. Reproductive carrier screening is addressed separately (see Cross References).

I. Diagnostic prenatal (fetal) genetic testing for α-thalassemia may be considered **medically necessary**.

II. Diagnostic genetic testing to confirm a diagnosis of α-thalassemia is considered **not medically necessary**.

III. Diagnostic genetic testing for α-thalassemia in other clinical situations is considered **investigational**, including in patients with hemoglobin H disease (alpha-thalassemia intermedia) to determine prognosis.

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

POLICY GUIDELINES

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

Alpha-thalassemias include:

- Thalassemia trait (α-thalassemia minor)
- Hemoglobin H Disease (α-thalassemia intermedia)
- Hemoglobin Bart's (α-thalassemia major, hydrops fetalis)

BIOCHEMICAL TESTING

Biochemical testing to determine whether α-thalassemia is present should be the first step in evaluating the presence of the condition. Biochemical testing consists of complete blood count (CBC), microscopic examination of the peripheral blood smear, and hemoglobin electrophoresis. In silent carriers and in α-thalassemia trait, the hemoglobin electrophoresis will most likely be normal. However, there should be evidence of possible α-thalassemia minor on the CBC and peripheral smear.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - History and physical exam including any relevant diagnoses related to the genetic testing
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
3. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

ALPHA-THALASSEMIA

Alpha-thalassemia is a common genetic disorder, affecting approximately 5% of the world's

population.[1] The frequency of variants is highly dependent on ethnicity, with the highest rates seen in Asians, and much lower rates in Northern Europeans. The carrier rate is estimated to be 1 in 20 in Southeast Asians, 1 in 30 for Africans, and between 1 in 30 and 1 in 50 for individuals of Mediterranean ancestry. By contrast, for individuals of northern European ancestry, the carrier rate is less than 1 in 1000.

Physiology

Hemoglobin, which is the major oxygen-carrying protein molecule of red blood cells (RBCs), consists of two α-globin chains and two β-globin chains. Alpha-thalassemia refers to a group of syndromes that arise from deficient production of α-globin chains. Deficient α-globin production leads to an excess of β-globin chains, which results in anemia by a number of mechanisms[2]:

- Ineffective erythropoiesis in the bone marrow.
- Production of nonfunctional hemoglobin molecules.
- Shortened survival of RBCs due to intravascular hemolysis and increased uptake of the abnormal RBCs by the liver and spleen.

The physiologic basis of α-thalassemia is a genetic defect in the genes coding for α-globin production. Each individual carries four genes that code for α-globin (two copies each of *HBA1* and *HBA2*, located on chromosome 16), with the wild genotype (normal) being aa/aa. Genetic variants may occur in any or all of these four α-globin genes. The number of genetic variants determines the phenotype and severity of the α-thalassemia syndromes. There are four different syndromes, which are classified below.

Silent Carrier

Silent carrier (α-thalassemia minima) arises from one of four abnormal α genes (αα/α-), and is a silent carrier state. A small amount of abnormal hemoglobin can be detected in the peripheral blood, and there may be mild hypochromia and microcytosis present, but there is no anemia or other clinical manifestations.

Thalassemia Trait

Thalassemia trait (α-thalassemia minor), also called α-thalassemia trait, arises from the loss of two α-globin genes, resulting in one of two genotypes (αα/--, or α-/α-). Mild anemia is present, and RBCs are hypochromic and microcytic. Clinical symptoms are usually absent and, in most cases, the hemoglobin electrophoresis is normal.

Hemoglobin H Disease

Hemoglobin H (HbH) disease (α-thalassemia intermedia) results from three abnormal α-globin genes (α-/--), resulting in moderate-to-severe anemia. In HbH disease, there is an imbalance in α- and β-globin gene chain synthesis, resulting in the precipitation of excess β chains into the characteristic hemoglobin H, or β-tetramer.[2]

HbH has marked phenotypic variability, but most individuals have mild disease.[3] Splenomegaly is common and can lead to the need for splenectomy, for which transfusion support may be required.[1] Iron chelation therapy may be indicated for increased iron deposition. Inappropriate iron therapy and oxidant drugs that can exacerbate hemolysis should

be avoided in patients with HbH disease. A minority of people with HbH develop jaundice, hepatomegaly, and mild to moderate skeletal changes associated with thalassemia (e.g., hypertrophy of the maxilla, bossing of the skull).[3]

There is an association between genotype and phenotype among patients with HbH disease. Individuals with a nondeletion variant typically have an earlier presentation, more severe anemia, jaundice, and bone changes, and more frequently require transfusions.

Hemoglobin Bart's

Hemoglobin Bart's (α-thalassemia major) results from variants in all four α-globin genes (--/--), which prevents production of α-globin chains. This condition causes hydrops fetalis, which often leads to intrauterine death or death shortly after birth. There are also increased complications during pregnancy for a woman carrying a fetus with hydrops fetalis. They include hypertension, preeclampsia, antepartum hemorrhage, renal failure, premature labor, and abruption placenta.[1]

Genetic Testing

A number of different types of genetic abnormalities on the *HBA1* and *HBA2* genes are associated with α-thalassemia. Deletion of one or more of the α-globin chains is the most common genetic defect. This type of genetic defect is found in approximately 90% of cases.[3] Large genetic rearrangements can also occur from defects in crossover and/or recombination of genetic material during reproduction. Point mutations in one or more of the α genes that impair transcription and/or translation of the α-globin chains.

Testing is commercially available through several genetic labs. Targeted variant analysis for known α-globin gene variants can be performed using Gap polymerase chain reaction (Gap-PCR) or sequence analysis. Newer testing methods used to detect α-thalassemia variants include multiplex amplification methods and next generation sequencing (NGS).[3]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for α-thalassemia is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[4] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

GENETIC TESTING FOR ALPHA-THALASSEMIA

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The published literature on genetic testing for α-thalassemia consists primarily of reports describing the molecular genetics of testing, the types of variants encountered, and genotype-phenotype correlations.[5-11]

Analytic Validity

A variety of testing methods can be used to evaluate the two genes related to α-globin production, *HBA1* and *HBA2*, including sequence analysis of the entire coding region, targeted variant analysis via polymerase chain reaction (PCR), and deletion/duplication analysis. Therefore, the analytic validity depends on the method used, but would generally be expected to be high.

One 2016 study identified evaluated the reproducibility and accuracy of a PCR-based multicolor melting curve analysis method for detecting common nondeletional variants in the *HBA2* gene from 700 whole blood samples.[12] Reproducibility of the assay was high. In the clinical samples, there was 100% concordance between the 20 genotypes identified and the genotyping method. Petropoulou (2015) evaluated a PCR-based high-resolution melting curve analysis of duplicated areas of the *HBA1 and HBA2* genes with novel nondeletion variants.[13] The study included 62 samples with previously identified novel variants and 18 normal controls; the melting curve analysis was able to distinguish at least 80% of novel homozygote samples detected by earlier generation tests.

Clinical Validity

Clinical validity is expected to be high when the causative variant is a large deletion of one or more α-globin gene, as PCR testing is generally considered highly accurate for this purpose. When a point variant is present, the clinical validity is less certain.

Henderson (2016) reported on a retrospective study of genotype and phenotype correlations of the novel thalassemia and abnormal hemoglobin variants identified after adoption of routine DNA sequencing of α- and β-globin genes for all U.K. samples referred for evaluation of hemoglobinopathy for the preceding 10 years.[14] Of a total of approximately 12,000 samples, 15 novel α-thalassemia variants, 19 novel β-thalassemia variants, and 11 novel β-globin variants were detected.

Clinical Utility

There are several potential areas for clinical utility. Genetic testing can be used to determine the genetic abnormalities underlying a clinical diagnosis of α-thalassemia. It can also be used to define the genetics of α-globin genes in relatives of patients with a clinical diagnosis of α-

thalassemia. Prenatal (in utero) testing can also be performed to determine the presence and type of α-thalassemia of a fetus. Prenatal testing is not addressed in this evidence review.

Confirming a Diagnosis

The diagnosis of α-thalassemia can be made without genetic testing. This is first done by analyzing the complete blood count (CBC) and peripheral blood smear, in conjunction with testing for other forms of anemia. Patients with a CBC demonstrating microcytic, hypochromic red blood cell (RBC) indices who are not found to have iron deficiency, have a high likelihood of thalassemia. On peripheral blood smear, the presence of inclusion bodies and target cells is consistent with the diagnosis of α-thalassemia.

Hemoglobin electrophoresis can distinguish between the asymptomatic carrier states and α-thalassemia intermedia (HbH disease) by identifying the types and amounts of abnormal hemoglobin present. In the carrier states, greater than 95% of the hemoglobin molecules are normal (hemoglobin A), with a small minority of hemoglobin A_2 present (1%-3%).[15] Alpha-thalassemia intermedia is diagnosed by finding a substantial portion of hemoglobin H (1%-30%) on electrophoresis.[15] In α-thalassemia major, the majority of the hemoglobin is abnormal, in the form of hemoglobin Bart's (85%-90%).[15]

However, biochemical testing, including CBC and hemoglobin electrophoresis, cannot always reliably distinguish between the asymptomatic carrier state and α-thalassemia trait, because the hemoglobin electrophoresis is typically normal in both conditions. Genetic testing can differentiate between the asymptomatic carrier state (α-thalassemia minima) and α-thalassemia trait (α-thalassemia minor) by measuring the number of abnormal genes present. This distinction is not important clinically because both the carrier state and α-thalassemia trait are asymptomatic conditions that do not require specific medical care treatment. Alpha-thalassemia trait may overlap in RBC indices values with iron deficiency states, so it is important that iron supplementation not be continued unnecessarily in patients with α-thalassemia trait. However, it would be reasonable to make a diagnosis of α-thalassemia trait in a patient with microcytic, hypochromic RBC indices without evidence of iron deficiency, either before or after a trial of iron supplementation. Because the diagnosis of clinically relevant α-thalassemia conditions can usually be made without genetic testing, there is little utility to genetic testing of a patient with a clinical diagnosis of thalassemia to determine the underlying genetic abnormalities.

Prognostic Testing in Patients with HbH Disease

Among patients with HbH disease, there is heterogeneity in the nature of the variant (i.e., deletional vs. nondeletional), with differences across geographic areas and ethnic groups.[16] Patients with deletional variants may have a less severe course of illness than those with nondeletional variants.[16] In a cohort of 147 Thai pediatric patients with HbH disease, those with nondeletional variants were more likely to have pallor after fever, hepatomegaly, splenomegaly, jaundice, short stature, need for transfusions, and gallstones.[17]

The evidence suggests that different genetic variants leading to α-thalassemia are associated with different prognoses.[18] However, clinical diagnosis can be made based on red cell indices to guide therapy, and no evidence was identified to indicate that patient management or outcomes would be changed by prognostic testing.[19]

Section Summary: Clinical Utility

The clinical utility of genetic testing for α-thalassemia may occur in several settings. For confirming a diagnosis of α-thalassemia, because the diagnosis of clinically actionable types can generally be made on the basis of nongenetic testing, there is little utility to genetic testing. For patients with HbH disease, there may be a genotype-phenotype correlation for disease severity; however, no studies were identified that suggested patient management or outcomes would be altered by genetic testing. Therefore, genetic testing for determining the prognosis of HbH disease is not associated with improved clinical utility.

SUMMARY OF EVIDENCE

For individuals who have suspected α-thalassemia who receive genetic testing for α-thalassemia, the evidence includes case reports and case series documenting the association between pathogenic variants and clinical syndromes. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and quality of life. For the α-thalassemia syndromes that have clinical implications, diagnosis can be made based on biochemical testing without genetic testing. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have hemoglobin H disease (α-thalassemia intermedia) who receive genetic testing for α-thalassemia, the evidence includes case series that correlate specific variants with prognosis of disease. Relevant outcomes are overall survival, disease-specific survival, symptoms, and quality of life. There is some evidence for a genotype-phenotype correlation with disease severity, but no current evidence indicates that patient management or outcomes would be altered by genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUMMARY

There is enough research to show that prenatal testing for α-thalassemia can improve health outcomes. Prenatal fetal testing informs reproductive decision making, including decisions regarding continuation of the pregnancy, birthing decisions, and enabling for timely treatment of a condition that could be treated either in utero or immediately after birth. Therefore, prenatal testing for α-thalassemia may be considered medically necessary.

There is enough research to show that diagnosis of α-thalassemia syndromes can be made based on biochemical testing without genetic testing. Therefore, genetic testing to confirm a diagnosis of α-thalassemia is considered not medically necessary.

There is not enough research to show that genetic testing for α-thalassemia can improve health outcomes for patients with any other conditions, including people who have hemoglobin H disease (α-thalassemia intermedia). In addition, there are no clinical guidelines based on research that recommend this testing. Therefore, genetic testing is considered investigational for patients with hemoglobin H disease or for other clinical situations.

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CODES

Codes	Number	Description
CPT	81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
	81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	;full gene sequence
	81269	;duplication/deletion variants
	81404	Molecular pathology procedure level 5
HCPCS	None	

Date of Origin: *January 2018*

Regence

Medical Policy Manual Genetic Testing, Policy No. 54

Genetic Testing for Primary Mitochondrial Disorders

Effective: January 1, 2024

Next Review: January 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

Primary mitochondrial disorders are caused by variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that directly affect the function of the oxidative phosphorylation complex in mitochondria. They often manifest as progressive, multisystem disorders. There are currently no effective treatments for mitochondrial disorders, but genetic testing may allow patients to avoid more invasive laboratory testing and provide information for reproductive decision-making.

MEDICAL POLICY CRITERIA

Notes: This policy applies only to diagnostic testing for primary mitochondrial disorders (see Policy Guidelines). It does not apply to reproductive carrier screening of asymptomatic individuals or testing for other disorders that affect mitochondria, such as fatty acid oxidation disorders (see Cross References).

I. Genetic testing for the diagnosis of primary mitochondrial disorders (see Policy Guidelines), including single-gene testing, panel testing and/or whole mitochondrial genome sequencing, may be considered **medically necessary** when all of the following Criteria are met:

A. Signs and symptoms of a primary mitochondrial disorder are present (see Policy Guidelines); and

B. One of the following is met:

1. A clinical diagnosis cannot be made without additional testing, and a muscle or liver biopsy has not been performed; or

2. A genetic diagnosis may be informative for reproductive planning purposes.

II. Genetic testing for diagnosis of primary mitochondrial disorders is considered **investigational** when Criterion I. 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 PRIMARY MITOCHONDRIAL DISORDERS

(Not all-inclusive)

- Alpers (aka Alpers-Huttenlocher) syndrome
- Barth syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Coenzyme Q_{10} deficiency
- Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) syndrome
- Infantile-onset spinocerebellar ataxia (IOSCA)
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome
- Maternally inherited deafness and diabetes (MIDD)
- Mitochondrial DNA depletion syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Mitochondrial recessive ataxia syndrome (MIRAS)
- Myoclonus epilepsy with ragged red fibers (MERFF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome
- Sensory ataxia neuropathy, dysarthria, ophthalmoplegia (SANDO)

SIGNS AND SYMPTOMS

Primary mitochondrial disorders can have a variety of presentations, depending on the molecular cause. They are often multisystem disorders, and may include (not all-inclusive):

- skeletal muscle myopathy
- cardiomyopathy
- encephalopathy
- ophthalmoplegia
- neuropathy

- hypotonia/muscle weakness
- seizures
- developmental delay
- ataxia
- deafness
- short stature

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any specific signs and symptoms and/or relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

MITOCHONDRIAL DNA

Mitochondria are organelles within each cell that contain their own set of DNA, distinct from the nuclear DNA that makes up most of the human genome. Human mitochondrial DNA (mtDNA) consists of 37 genes. Thirteen genes code for protein subunits of the mitochondrial oxidative phosphorylation complex and the remaining 24 genes are responsible for proteins involved in the translation and/or assembly of the mitochondrial complex.[1] Additionally, there are over 1000 nuclear genes coding for proteins that support mitochondrial function.[2] The protein products from these genes are produced in the nucleus and later migrate to the mitochondria.

Mitochondrial DNA differs from nuclear DNA (nDNA) in several important ways. Inheritance of mtDNA does not follow traditional Mendelian patterns. Rather, mtDNA is inherited only from maternal DNA so disorders that result from variants in mtDNA can only be passed on by the mother. Also, there are thousands of copies of each mtDNA gene in each cell, as opposed to nDNA, which contains only one copy per cell. Because there are many copies of each gene, variants may be present in some copies of the gene but not others. This phenomenon is called heteroplasmy. Heteroplasmy can be expressed as a percentage of genes that have the variant ranging from 0% to 100%. Clinical expression of the variant will generally depend on a

threshold effect (i.e., clinical symptoms will begin to appear when the percentage of mutated genes exceeds a threshold amount).[3]

PRIMARY MITOCHONDRIAL DISORDERS

Primary mitochondrial disorders arise from dysfunction of the mitochondrial electron transport chain (ETC). The ETC is responsible for aerobic metabolism, and dysfunction, therefore, affects a wide variety of physiologic pathways dependent on aerobic metabolism. Organs with a high-energy requirement, such as the central nervous system, cardiovascular system, and skeletal muscle, are preferentially affected by mitochondrial dysfunction.

Table 1 (below) lists some of the more common primary mitochondrial disorders. Most of these disorders are characterized by multisystem dysfunction, which generally includes myopathies and neurologic dysfunction, and may involve multiple other organs. Each defined mitochondrial disease has a characteristic set of signs or symptoms. The severity of illness is heterogeneous and can vary markedly. Some patients will have only mild symptoms for which they never require medical care, while other patients have severe symptoms, a large burden of morbidity, and a shortened life expectancy.

The prevalence of these disorders has risen over the last two decades as the pathophysiology and clinical manifestations have been better characterized. It is currently estimated that the minimum prevalence of primary mitochondrial diseases is at least 1 in 5000.[1 4]

Diagnosis

The diagnosis of primary mitochondrial diseases can be difficult. The individual symptoms are nonspecific, and symptom patterns can overlap considerably. As a result, a patient often cannot be easily classified into any particular syndrome.[5] Biochemical testing is indicated for patients who do not have a clear clinical diagnosis of a specific disorder. Measurement of serum lactic acid is often used as a screening test but the test is neither sensitive nor specific for mitochondrial diseases.[2]

A muscle biopsy can be performed if the diagnosis is uncertain after biochemical workup. However, this invasive test is not definitive in all cases. The presence of "ragged red fibers" on histologic analysis is consistent with a mitochondrial disease. Ragged red fibers represent a proliferation of defective mitochondria.[1] This characteristic finding may not be present in all types of mitochondrial diseases and also may be absent early in the course of disease.[2]

Treatment

Treatment of primary mitochondrial disease is largely supportive because there are no specific therapies that impact the natural history of the disorder.[5] Identification of complications such as diabetes and cardiac dysfunction is important for early treatment of these conditions. A number of vitamins and cofactors (e.g., coenzyme Q, riboflavin) have been used but empirical evidence of benefit is lacking.[6] Exercise therapy for myopathy is often prescribed but the effect on clinical outcomes is uncertain.[5] The possibility of gene transfer therapy is under consideration but is at an early stage of development and untested in clinical trials.

Genetic Testing

Primary mitochondrial diseases can be caused by pathogenic variants in the maternally inherited mtDNA or one of many nDNA genes. Genetic testing for mitochondrial diseases may

involve testing for single nucleotide variants, deletion and duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. The type of testing done depends on the specific disorder being considered. For some primary mitochondrial diseases such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibers (MERFF), most variants are single nucleotide variants, and there is a finite number of variants associated with the disorder. When testing for one of these disorders, known pathogenic variants can be tested for with polymerase chain reaction, or sequence analysis can be performed on the particular gene. For other mitochondrial diseases, such as chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome, the most common variants are deletions, and therefore duplication and deletion analysis would be the first test when these disorders are suspected. Table 1 provides examples of clinical symptoms and particular genetic variants in mtDNA or nDNA associated with particular mitochondrial syndromes.[5 7] A repository of published and unpublished data on variants in human mtDNA is available in the MITOMAP database.[8] Lists of mtDNA and nDNA genes that may lead to mitochondrial diseases and testing laboratories in the U.S. are provided at Genetic Testing Registry of the National Center for Biotechnology Information website.[9]

Table 1. Examples of Mitochondrial Diseases, Clinical Manifestations, and Associated Pathogenic Genes (not all inclusive)

Syndrome	Main Clinical Manifestations	Major Genes Involved
MELAS	• Stroke-like episodes at age <40 y • Seizures and/or dementia • Pigmentary retinopathy • Lactic acidosis	• *MT-TL1*, *MT-ND5* (>95%) • *MT-TF, MT-TH, MT-TK, MT-TQ, MT-TS1, MT-TS2, MT-ND1, MT-ND6* (rare)
MERFF	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• *MT-TK* (>80%) • *MT-TF, MT-TP* (rare)
CPEO	• External ophthalmoplegia • Bilateral ptosis	• Various deletions of mitochondrial DNA
Kearns-Sayre syndrome	• External ophthalmoplegia at age <20 y • Pigmentary retinopathy • Cerebellar ataxia • Heart block	• Various deletions of mitochondrial DNA
Leigh syndrome	• Subacute relapsing encephalopathy • Infantile-onset • Cerebellar/brainstem dysfunction	• *MT-ATP6, MT-TL1, MT-TK, MT-TW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3* • *Mitochondrial DNA deletions (rare)* • *SUCLA2, NDUSFx, NDFVx, SDHA, BCS1L, SURF1, SCO2, COX15*
LHON	• Painless bilateral visual failure • Male predominance • Dystonia • Cardiac pre-excitation syndromes	• *MT-ND1, MT-ND4, MT-ND6*

Syndrome	Main Clinical Manifestations	Major Genes Involved
NARP	• Peripheral neuropathy • Ataxia • Pigmentary retinopathy	• *MT-ATP6*
MNGIE	• Intestinal malabsorption • Cachexia • External ophthalmoplegia • Neuropathy	• *TP*
IOSCA	• Ataxia • Hypotonia • Athetosis • Ophthalmoplegia • Seizures	• *TWINKLE*
SANDO	• Ataxic neuropathy • Dysarthria • Ophthalmoparesis	• *POLG*
Alpers syndrome	• Intractable epilepsy • Psychomotor regression • Liver disease	• *POLG, DGUOK, MPV17*
GRACILE	• Growth retardation • Aminoaciduria • Cholestasis • Iron overload • Lactic acidosis	• *NDUSFx*
Coenzyme Q_{10} deficiency	• Encephalopathy • Steroid-resistant nephrotic syndrome • Hypertrophic cardiomyopathy • Retinopathy • Hearing loss	• *COQ2* • *COQ9* • *CABC1* • *ETFDH*

Adapted from Chinnery (2014)5, and Angelini (2009).[7]
CPEO: chronic progressive external ophthalmoplegia; GRACILE: growth retardation, aminoaciduria, cholestasis, iron overload, early death; IOSCA: infantile onset spinal cerebellar atrophy; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERFF: myoclonic epilepsy with ragged-red fibers; MNGIE: mitochondrial neurogastrointestinal encephalopathy; NARP: neuropathy, ataxia, and retinitis pigmentosa; SANDO: sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

EVIDENCE SUMMARY

The purpose of genetic testing in patients who have signs and symptoms of mitochondrial diseases is to confirm the diagnosis. Diagnosis of a specific mitochondrial disease is complex due to the phenotypic heterogeneity and general lack of genotype-phenotype associations, particularly in infants and children. Identifying a disease-causing variant can end the diagnostic odyssey for families and help to avoid muscle (or in some cases, liver) biopsy for patients. While the current treatment for most patients with mitochondrial disease is primarily supportive, potential treatments exist for patients with coenzyme Q_{10} deficiency and mitochondrial neurogastrointestinal encephalopathy, although evidence for their effectiveness is not conclusive.

CLINICAL VALIDITY

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The evidence on the clinical sensitivity and specificity of genetic testing for mitochondrial diseases is limited. There are some small case series of patients with a well-defined syndrome such as MELAS syndrome, and some studies include larger numbers of patients with less specific clinical diagnoses. There are wide variations in reported testing yields, probably reflecting the selection process used to evaluate patients for testing.

Several series of patients with mixed diagnoses or suspected mitochondrial diseases have been published. In these studies, the variant detection rate (or yield) may or may not be an accurate estimate of clinical sensitivity, because the proportion of patients with a mitochondrial disease is uncertain (see Table 2).

Table 2. Studies Reporting Diagnostic Yield for Suspected Mitochondrial Diseases

Study	Population	N	Genetic Test	Design	Yield, n (5)
Riley (2020)[10]	Australian cohort of children with suspected mitochondrial disease	40	Trio GS	• Prospective enrollment • Selection method not reported	• 22 (67.5%) with "causal" variants • 22 (50%) with a "definitive molecular diagnosis" per modified Nijmegen mitochondrial disease severity scale
Nogueira (2019)[11]	Children and adults suspected of having mitochondrial disease	146	Panel of 209 genes	• Prospective /retrospective not reported • Selection method not reported	• 16 (11%) with "causative" variants • 20 (14%) with VUS • 54/107 (50%) with defects identified on muscle biopsy
Fang (2017)[12]	Children and young adults suspected of having mitochondrial disease	141	Targeted panel	• Prospective enrollment • Selection method not reported	• 40 (28%) with "causative" variants
Legati (2016)[13]	Patients clinically diagnosed with mitochondrial disease	NGS: 125 WES: 10	Custom panel of 132 genes, WES for those negative	• Prospective/ retrospective not reported • Selection method not reported	*NGS:* • 19 (15%) with "causative" variants • 27 (22%) with possible pathogenic variants *WES:* • 6 (60%) with "causative" variants
Pronicka (2016)[14]	Patients referred for possible or probable	113	WES followed by SS	• Prospective /retrospective samples included;	• 67 (59%) with likely pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (5)
	mitochondrial disease			consecutive patients included in prospective sample • Selection method for retrospective samples not reported	• 30 (64%) of neonates with likely pathogenic variants
Kohda (2016)[15]	Children with early-onset respiratory chain disease	142	mtWGS plus WES of the nDNA	• Prospective enrollment • Selection method not reported	• 29 (20%) with known pathogenic variants • 53 (37%) inconclusive but possibly pathogenic variants
Wortmann (2015)[16]	Children and young adults with a suspected mitochondrial disease	109	Panel of 238 genes followed by WES	• Prospective enrollment • Selection method not reported	• 42 (39%) with pathogenic variants
Ohtake (2014)[17]	Patients with mitochondrial respiratory chain diseases	104	WES of the nDNA	• Prospective/ retrospective not reported • Selection method not reported	• 18 (17%) with known pathogenic variants • 27 (26%) with likely pathogenic variants
Taylor (2014)[18]	Patients with suspected mitochondrial disease and multiple respiratory chain complex defects	53	WES validated with SS	• Prospective/ retrospective not reported; selection method not reported but only included patients with multiple respiratory chain complex defects	• 28 (53%) with known pathogenic variants • 4 (8%) with likely pathogenic variants
Lieber (2013)[19]	Patients with suspected mitochondrial diseases and heterogeneous clinical symptoms	102	mtWGS and 1,598 nuclear genes	• Prospective/ retrospective not reported • Patients in a repository having highest clinical suspicion of disease selected	• 22 (22%) with likely pathogenic variants • 26 (25%) VUS
DaRe (2013)[20]	Patients with diagnosed or	148	Panel of 447 genes	• Prospective /retrospective	• 13 (9%) possible pathogenic variants

Study	Population	N	Genetic Test	Design	Yield, n (5)
	suspected mitochondrial diseases			not reported; consecutive patients	• 67 (45%) with VUS
McCormick (2013)[21]	Patients with suspected mitochondrial disease	152	mtWGS, array, SS	• Retrospective chart review; consecutive patients included	• 25 (16%) with "definite" mitochondrial disease • 46 (30%) with "probable" or "possible" mitochondrial disease
Calvo (2012)[22]	Infants with clinical and biochemical evidence of oxidative phosphorylation disease	42	mtWGS and 1034 nuclear genes	• Prospective/ retrospective not reported • Selection method not reported	• 10 (24%) with known pathogenic variants • 13 (31%) possible pathogenic variants
Qi (2007)[23]	Patients with mitochondrial encephalopathies (MELAS, MERRF, Leigh syndrome, LHON, or an overlap syndrome)	552	PCR-RFLP analysis, PCR	• Prospective/ retrospective not reported • Selection method not reported	• 64 (12%) with pathogenic variants

GS: genome sequencing; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF: myoclonic epilepsy with ragged red fibers; mtDNA: mitochondrial DNA; nDNA: nuclear DNA: NGS: next-generation sequencing; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; VUS: variant of uncertain significance; WES: whole-exome sequencing; mtWGS: whole mitochondrial genome sequencing; SS: Sanger sequencing.

The clinical specificity of genetic testing for mitochondrial diseases is largely unknown, but false-positive results have been reported.[24] Some epidemiologic evidence is available on the population prevalence of pathogenic variants, which provides some indirect evidence on the potential for false-positive results.

Elliott (2008) published a study of population-based testing reported that the prevalence of pathogenic variants is higher than the prevalence of clinical disease.[25] In this study, 3,168 consecutive newborns were tested for the presence of one or more of the 10 most common mtDNA variants thought to be associated with clinical disease. At least one pathogenic variant was identified in 15 (0.54%) of 3,168 people (95% confidence interval 0.30% to 0.89%). This finding implies that there are many more people with a variant who are asymptomatic than there are people with clinical disease, and this raises the possibility of false-positive results on genetic testing.

An earlier population-based study by Majamaa (1998) evaluated the prevalence of the nucleotide 3,243 variant associated with MELAS syndrome.[26] This study included 245,201 subjects from Finland. Participants were screened for common symptoms associated with MELAS, and screen-positive patients were tested for the variant. The population prevalence was estimated at 16.3 (0.16%) in 100,000. This study might have underestimated the prevalence because patients who screened negative were not tested for the variant.

In addition to false-positive results, there are variants of uncertain significance detected in substantial numbers of patients. The number of variants increases when NGS methods are used to examine a larger portion of the genome. In a study by DaRe (2013), which used targeted exome sequencing, variants of uncertain significance (VUS) were far more common than definite pathogenic variants.[20] In that study, 148 patients with suspected or confirmed mitochondrial diseases were tested using a genetic panel that included 447 genes. Thirteen patients were found to have pathogenic variants. In contrast, VUS were very common, occurring at a rate of 6.5 per patient.

A further consideration is the clinical heterogeneity of variants known to be pathogenic. Some variants associated with mitochondrial diseases can result in heterogeneous clinical phenotypes, and this may cause uncertainty about the pathogenicity of the variant detected. For example, the nucleotide 3,243 variant in the *MT-TL1* gene is found in most patients with clinically defined MELAS syndrome.[27] This same variant has also been associated with chronic progressive external ophthalmoplegia and Leigh syndrome.[28] Therefore, the more closely the clinical syndrome matches MELAS, the more likely a positive genetic test will represent a pathogenic variant.

CLINICAL UTILITY

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence on clinical utility was identified.

There are two ways that clinical utility might be demonstrated from a chain of evidence. First, confirmation of the diagnosis may have benefits in ending the need for further clinical workup and eliminating the need for a muscle biopsy. Second, knowledge of pathogenic variant status may have benefits for individuals in determining their risk of passing on the disorder to offspring.

Confirmation of Diagnosis in Individuals with Signs and/or Symptoms of a Mitochondrial Disease

For patients with signs and symptoms consistent with a defined mitochondrial syndrome, testing can be targeted to those pathogenic variants associated with that particular syndrome. In the presence of a clinical picture consistent with the syndrome, the presence of a known pathogenic variant will confirm the diagnosis with a high degree of certainty. Confirmation of the diagnosis by genetic testing can result in a reduced need for further testing, especially a muscle biopsy. However, a negative genetic test in the blood does not rule out a mitochondrial disease and should be reflexed to testing in the affected tissue to avoid the possibility of missing tissue-specific variants or low levels of heteroplasmy in blood.

There is no specific therapy for mitochondrial diseases. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing would lead to management changes, such as increased surveillance for

complications of the disease and/or the prescription of exercise therapy or antioxidants. However, the impact of these management changes on health outcomes is not known. A Cochrane review updated by Pfeffer (2012) did not find any clear evidence supporting the use of any intervention for the treatment of mitochondrial disorders.[29]

Reproductive Testing

When there is a disease of moderate severity or higher, it is reasonable to assume that many patients will consider the results of testing in reproductive decision-making. For purposes of informing family planning, when a pathogenic variant is detected in the nDNA of a prospective parent or in the mtDNA of a prospective mother, the prospective parent can choose to refrain from having children. If the variant is in the nDNA, the prospective parent could also choose medically-assisted reproduction during which pre-implantation testing would permit a choice to avoid an affected offspring. The use of pre-implantation testing when a pathogenic variant is identified in the mtDNA of an affected mother is complicated by issues of heteroplasmy of the mtDNA variant, threshold levels, and phenotypic expression leading.

PRACTICE GUIDELINE SUMMARY

MITOCHONDRIAL MEDICINE SOCIETY

The Mitochondrial Medicine Society (2015) published a consensus statement on the diagnosis and management of mitochondrial disease.[30] Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without an explicit critical appraisal) using the Oxford Centre for Evidence-Based Medicine criteria. Consensus recommendations were reported using the Delphi method. A subset of the consensus recommendations for DNA testing are as follows:

1. "Massively parallel sequencing/NGS [next-generation sequencing] of the mtDNA [mitochondrial DNA] genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations.
2. mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
    a. If a single small deletion is identified using polymerase chain reaction-based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
    b. When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.
3. When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered."

SUMMARY

There is enough research to show that diagnostic genetic testing for primary mitochondrial

diseases can improve health outcomes for certain patients. Primary mitochondrial diseases are multisystem diseases that arise from dysfunction in the mitochondrial protein complexes involved in oxidative metabolism. Although there are no specific treatments for these disorders, they can be difficult to diagnose, and genetic testing may allow patients to avoid more invasive muscle or liver biopsies. Genetic testing also has the potential to inform reproductive testing and decision-making. Therefore, diagnostic genetic testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing to diagnose primary mitochondrial disorders can improve health outcomes for patients that do not meet the policy criteria. There is no specific therapy for mitochondrial diseases. Treatment is largely supportive management for complications of the disease. It is possible that confirmation of the diagnosis by genetic testing would lead to management changes, such as increased surveillance for complications of the disease and/or the prescription of exercise therapy or antioxidants. However, the impact of these management changes on health outcomes is not known. Therefore, this testing is considered investigational when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder–associated genetic variants
	81401	Molecular Path Level 2: includes the following genes: MT-TS1, MT-RNR1, MT-ATP6, MT-ND4, MT-ND6, MT-ND5, MT-TL1, MT-TS1, MT-RNR1
	81403	Molecular Path Level 4: includes the following genes: MT-RNR1, MT-TS1
	81404	Molecular Path Level 5: includes the following genes: C10orf2, MPV17, NDUFA1, NDUFAF2, NDUFS4, SCO2, SLC25A4 , TACO1
	81405	Molecular Path Level 6: includes the following genes: BCS1L, COX10, COX15, DGUOK, MPV17, NDUFV1, RRM2B, SCO1, SURF1, TK2 , TYMP
	81406	Molecular Path Level 7: includes the following genes: FASTKD2, NDUFS1, SDHA
	81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
	81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
HCPCS	None	

Date of Origin: *January 2022*

Regence

Medical Policy Manual Genetic Testing, Policy No. 56

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

Effective: March 1, 2025

Next Review: November 2025
Last Review: January 2025

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

Targeted testing for specific gene variants, including *EGFR* and *BRAF* analysis, can be used to predict treatment response to targeted therapy in patients with advanced NSCLC.

MEDICAL POLICY CRITERIA

I. Testing for *NTRK, NRG1,* and *RET* gene fusions and *BRAF*, *EGFR*, *ALK*, *ERBB2* (HER2), *KRAS*, *MET, PD-L1*, and *ROS1* variants may be considered **medically necessary** for patients with non-small cell lung cancer (NSCLC) for selection of therapy.

II. The Oncomine™ Dx Target test may be considered **medically necessary** for patients with NSCLC for selection of therapy.

III. Testing for purposes other than treatment selection in NSCLC is considered **investigational**.

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

POLICY GUIDELINES

The Oncomine™ Dx Target test was approved by the FDA as a companion diagnostic to aid is selecting NSCLC patients for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®). The test identifies tumors that have *EGFR* variants, *ROS1* fusions, and/or the *BRAF* V600E variant.

The FDA approved cobas® EGFR Mutation Test v2 is only intended to be used to aid in identifying patients with NSCLC whose tumors have defined *EGFR* mutations and for whom safety and efficacy of a drug have been established. This test may be run on either tumor or plasma samples.

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. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided, if any

CROSS REFERENCES

1. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. BRAF Gene Mutation Testing To Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
4. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
6. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46
7. Molecular Testing in the Management of Pulmonary Nodules, Laboratory, Policy No. 73
8. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. In up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease.[1] Treatment of

advanced NSCLC has generally been with platinum-based chemotherapy, with a median survival of 8 to 11 months and a one-year survival of 30% to 45%.[2, 3] More recently, the identification of specific, targetable oncogenic “driver” variants in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

EPIDERMAL GROWTH FACTOR RECEPTOR (*EGFR*)

EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Laboratory and animal experiments have shown that therapeutic interdiction of the EGFR pathway could be used to halt tumor growth in solid tumors that express EGFR.[4] These observations led to the development of two main classes of anti-EGFR agents for use in various types of cancer: small molecule TKIs and monoclonal antibodies (MAbs) that block EGFR-ligand interaction.[5] The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in non-smoking, Asian women, with adenocarcinoma, in whom *EGFR* variants have been reported to be up to 30-50%. The reported prevalence in the Caucasian population is approximately 10%.[6]

Variants in two regions of the *EGFR* gene (exons 18-24)—small deletions in exon 19 and a point mutation in exon 21 (L858R)—appear to predict tumor response to first and second generation tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib.[7, 8] In addition, a single point mutation in exon 20 (T790M) appears to predict tumor response to third generation TKIs such as osimertinib. These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

Testing is intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the EGFR gene are considered good candidates for treatment with first and second generation TKIs. Patients with the point mutation in exon 20 (T790M), which is indicative of acquired resistance to first and second generation TKIs, are considered good candidates for third generation TKIs. Patients found to be wild-type are unlikely to respond to TKIs, so other treatment options should be considered.

ALK

ALK is a TK that is aberrantly activated in NSCLC due to a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2. The *EML4-ALK* rearrangement (“*ALK*-positive”) is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

BRAF

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently altered in NSCLC, in approximately 1-3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants.[9] Most *BRAF* variants occur more frequently in smokers.

ERBB2

ERBB2 is the gene that codes for the human epidermal growth factor receptor 2 (HER2) protein. HER2 is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. HER2 is expressed in approximately 25% of NSCLC. *ERBB2* variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.[9]

KRAS

KRAS is a G-protein involved in the EGFR-related signal transmission. The *KRAS* gene, which encodes RAS proteins, can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EFG receptor. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20-30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

MET

MET amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.

NRG1

NRG1 gene fusions are relatively rare but can act as oncogenic drivers for NSCLC and other cancer types. They are mainly seen in lung invasive mucinous adenocarcinomas.

NTRK

NTRK gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK gene fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers.

PD-L1

Programmed cell ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

RET

RET (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported. RET fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.

ROS1

ROS1 codes for a receptor TK of the insulin receptor family, and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%. Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

REGULATORY STATUS

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and

Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, which was released on July 14, 2011,[8] to address the "emergence of new technologies that can distinguish subsets of populations that respond differently to treatment." As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices "when an appropriate scientific rationale supports such an approach." In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

The Oncomine™ Dx Target test is an FDA approved companion diagnostic test for *EGFR* variants, *ROS1* gene fusions, *RET* variants, *ERBB2* variants, and the *BRAF* V600E variant, to aid in selection of the following targeted therapies for NSCLC:

- gefitinib (Iressa®)
- crizotinib (Xalcori®)
- dabrafenib (Tafinlar®) plus trametinib (Mekinist®)
- pralsetinib (Gavreto®)
- amivantamab (Rybrevant®)
- fam-trastuzumab deruxtecan-nxki (Enhertu®)
- selpercatinib (Retevmo®)

There are two other U.S. Food and Drug Administration (FDA)-approved companion diagnostic tests that specifically test for *EGFR* variants in NSCLC, intended to be used with select FDA approved *EGFR* tyrosine kinase inhibitors (TKIs):

- The cobas® *EGFR* Mutation Test v2 is a companion diagnostic test for the detection of exon 19 deletions and exon 20 and 21 (T790M and L858R, respectively) substitution variants in the *EGFR* gene in NSCLC tumor tissue. The FDA states:

  > "The test is intended to be used as an aid in selecting patients with NSCLC for whose tumors have defined *EGFR* variants and for whom safety and efficacy of a drug have been established as follows:
  >
  > - Tarceva® (erlotinib) - Exon 19 deletions and L858R
  > - Tagrisso® (osimertinib) - T790M"

  This test (v2) was approved 11/13/2015 as a result of an expansion of the original cobas® *EGFR* Mutation Test to cover testing for the T790M point mutation for use of osimertinib.

- The therascreen® *EGFR* Rotor Gene Q polymerase chain reaction (PCR) Kit is an automated molecular assay designed to detect the presence of *EGFR* exon 19 deletions and the exon 21 (L858R) substitution variant in NSCLC tumor tissue. The test is intended to be used to select patients with NSCLC for whom GILOTRIF® (afatinib) or IRESSA® (gefitinib) is indicated.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing

medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The focus of the following review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

The clinical utility of testing for variants in the *EGFR* gene and others to guide TKI treatment in patients with advanced NSCLC has been unequivocally demonstrated. Testing for variants in the other genes is also well-supported by published evidence. Therefore, this review will focus on literature that has been published on the investigational indications described in this policy.

No studies were identified that evaluated targeted genetic testing for patients with NSCLC for purposes other than treatment selection.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)[11]

NCCN guidelines for the treatment of metastatic NSCLC (v.1.2025) recommend testing for genetic variants in *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, *ERBB2*, and *NRG1*, and testing for HER2 and PD-L1 expression for patients with non-squamous NSCLC (i.e., adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified). For patients with squamous cell carcinoma, the guidelines recommend PD-L1 testing, and considering *EGFR*, *ALK*, *KRAS*, *NTRK*, *MET*, *RET*, *ROS1, NRG1,* and *BRAF* molecular testing and HER2 expression testing.

According to these recommendations, molecular testing for all advanced or metastatic NSCLC should be conducted as a part of broad molecular profiling.

COLLEGE OF AMERICAN PATHOLOGISTS, INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER, AND ASSOCIATION FOR MOLECULAR PATHOLOGY (CAP/IASLC/AMP)

The 2018 updated guidelines issued jointly by the CAP/IASLC/AMP recommend:[12]

- *ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics. (Strong Recommendation)
- ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method. (Expert Consensus Opinion)
- *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels

performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *ERBB2* (HER2) molecular testing is not indicated as a routine stand-alone assay. outside the context of a clinical trial. It is appropriate to include *ERBB2* (HER2) mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)

Regarding cell-free DNA (cfDNA) testing, the guidelines state:

- There is currently insufficient evidence to support the use of circulating cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma. (No Recommendation)
- In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations. (Recommendation)
- Physicians may use cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKI; testing of the tumor sample is recommended if the plasma result is negative. (Expert Consensus Opinion)
- There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of EGFR T790M mutations at the time of EGFR TKI resistance. (No Recommendation)

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2021, the American Society of Clinical Oncology (ASCO) and Ontario Health published updated guidelines on therapy for stage IV NSCLC with driver alterations.[13] The updated recommendations were based on a systematic review of RCTs from December 2015 to January 2020 and meeting abstracts from ASCO 2020. The recommendations include the following:

- All patients with nonsquamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status, when possible.
- Targeted therapies against *ROS-1* fusions, *BRAF* V600e mutations, *RET* fusions, *MET* exon 14 skipping mutations, and *NTRK* fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting.
- Chemotherapy is still an option at most stages.

The above guidelines were updated in 2023 to add amivantamab monotherapy and mobocertinib monotherapy for second-line treatment in advanced NSCLC with an *EGFR* exon

20 insertion, and sotorasib monotherapy for second-line treatment in advanced NSCLC with a *KRAS*-G12C mutation.[14]

In 2022, ASCO published a guideline on the management of stage III NSCLC.[15] The recommendations were based on a literature search of systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Relevant recommendations include the following:

- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy.

SUMMARY

NTRK, NRG1, AND *RET* GENE FUSIONS AND *BRAF*, *EGFR*, *ALK*, *KRAS*, *MET, PD-L1*, *ERBB2,* AND *ROS1*

There is enough research to show that testing for *NTRK, NRG1,* and *RET* gene fusions and *BRAF*, *EGFR*, *ALK*, *KRAS*, *MET, PD-L1*, *ERBB2* (HER2), and *ROS1* variants can help to guide treatment for patients with non-small cell lung cancer (NSCLC). In addition, many clinical guidelines based on research recommend testing for patients with this disease. Therefore, this testing may be considered medically necessary for selection of therapy.

There is not enough research to show that for *NTRK, NRG1,* and *RET* gene fusions and *BRAF*, *EGFR*, *ALK*, *KRAS*, *MET, PD-L1*, *ERBB2* (HER2), and *ROS1* variants can improve health outcomes for NSCLC patients when not used for treatment selection. Therefore, this testing is considered investigational when policy criteria are not met.

ONCOMINE™ DX TARGET TEST

The Oncomine™ Dx Target Test is an FDA-approved companion diagnostic test to help identify non-small cell lung cancer (NSCLC) patients that may benefit from certain medications. The test identifies tumors that have variants in the *EGFR*, *ROS1*, and *BRAF* genes, which may respond to targeted treatments. This 23-gene test also includes testing for a number of genes that do not have clear evidence of clinical utility. While genetic test panels are generally considered to be investigational when there is not clinical utility for all genes in the panel, this test is the only FDA-approved companion diagnostic available to NSCLC patients to help with selection of certain targeted medications. Therefore, use of the Oncomine™ Dx Target test may be considered medically necessary to select patients with advanced or metastatic NSCLC for targeted treatment.

There is not enough research to show that the Oncomine™ Dx Target Test can improve health outcomes for NSCLC patients when not used for treatment selection. Therefore, the use of this test is considered investigational for patients that do not meet policy criteria.

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CODES

Codes	Number	Description
CPT	0022U	Targeted genomic sequence analysis panel, nonsmall cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/or absence of variants and associated therapy(ies) to consider
	0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
	81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
	81210	*BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)*
	81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) – which includes *RET* (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) – which includes *KRAS* (Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence; and *RET* (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) – which includes *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence
	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
HCPCS	None	

Date of Origin: *August 2010*

Regence

Medical Policy Manual Genetic Testing, Policy No. 59

Genetic Testing for Myeloid Neoplasms and Leukemia

Effective: June 1, 2024

Next Review: February 2025
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

Genetic testing, including testing for BCR/ABL1 (t(9;22)) translocations and for *ABL1, ASXL1, CALR, CEBPA, FLT3, IDH1, IDH2, JAK2*, *KIT, MPL, NPM1*, *RUNX1*, and/or *TP53* variants may inform the diagnostic, prognostic, and treatment selection processes for myelodysplastic-myeloproliferative neoplasms and select myeloid neoplasms.

MEDICAL POLICY CRITERIA

Note: Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to single-gene testing.

I. Genetic testing, including panel testing, for *BCR/ABL1* translocation (Philadelphia chromosome) and/or variants in any of the following genes may be considered **medically necessary** for evaluation, diagnosis, and/or treatment monitoring in myeloid neoplasms and leukemia: *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1* and/or *RUNX1*.

II. Targeted genetic panel testing for myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), and myelodysplastic myeloproliferative neoplasms (MPN/MDS), including acute myeloid leukemia (AML), may be considered **medically**

necessary for patients being evaluated for these disorders (see Policy Guidelines and Table 1).

III. Genetic testing for *ABL1* may be considered **medically necessary** to evaluate patients when either of the following are met:

A. In patients with chronic myelogenous (myeloid) leukemia (CML), to monitor response to tyrosine kinase inhibitor therapy; or

B. In patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), to evaluate for tyrosine kinase inhibitor resistance.

IV. Genetic testing for *ABL1* is considered **investigational** when Criterion III. is not met.

V. Non-targeted profiling panels for hematologic disorders are considered **investigational** (see Policy Guidelines).

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

POLICY GUIDELINES

PANEL TESTING

Targeted Panels for Myeloid Neoplasms

Targeted panel testing for myeloid neoplasms, (i.e., MPN, MDS, MPN/MDS, and AML, see Table 1 below) includes panels that are specifically designed to assess variants in patients suspected of having a myeloproliferative neoplasm, a myelodysplastic syndrome, or a disorder with overlapping features. They are generally less than 50 genes and may include the following genes: *ASXL1*, *CALR, CBL, EZH2*, *KIT*, *FLT3, JAK2, MPL*, *NMP1*, *CEBPA*, *IDH1*, *IDH2*, and *TP53*.

Examples of targeted panels for MPN/MDS/AML include, but are not limited to:

- NeoTYPE™ Myeloid Disorders Profile (Neogenomics)
- NGS Myeloid 37 Gene panel (Cellnetix)
- MyeloSeq™ (Washington University School of Medicine)
- NGS_AML Panel (Cellnetix)
- AML Mutation Analysis Panel (Molecular Pathology Laboratory Network)
- Onkosight™ Myeloid Malignancies Panel, MPN Panel, MDS Panel, or AML Panel
- Myeloid MPN/MDS/CMML Comprehensive Panel (Providence)
- Myeloid Gene Panel by NGS (University of Washington)
- TruSight® Myeloid Sequencing Panel

Non-targeted Panels

Some commercially available panels are not targeted toward genes that have clinical significance for a specific type of hematolymphoid disorder. They often include testing for a large number of genes that do not have demonstrated clinical utility, as well as testing for many disorders that could be distinguished based on clinical presentation.

Non-targeted panels for hematologic disorders include, but are not limited to:

- FoundationOne Heme (Foundation Medicine)
- FusionPlex Pan-Heme Panel (Laboratory for Precision Diagnostics, University of Washington)
- GeneTrails® Hematologic Malignancies 220 Gene Panel (Knight Diagnostic Laboratories)
- MyAML® 194 Targeted NGS Gene Panel (Invivoscribe)
- HopeSeq HemeComplete (City of Hope)
- NGS Hematology Molecular Profile (Sonora Quest Laboratories)
- Rapid Heme Panel (Dana-Farber Cancer Institute)
- Hematologic Malignancy Sequencing Panel (Penn Medicine)
- Neo Comprehensive™ - Myeloid Disorders (Neogenomics)

Table 1. Selected Diagnoses from the World Health Organization Classification of Hematolymphoid Disorders[1, 2]

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Juvenile myelomonocytic leukemia (JMML)
Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis
Mast cell sarcoma
Myelodysplastic neoplasms (MDS)
MDS with low blasts and 5q deletion
MDS with low blasts and *SF3B1* mutation
Myelodysplastic neoplasm with increased blasts
Refractory cytopenia of childhood
Chronic myelomonocytic leukemia (CMML)
Acute myeloid leukemia (AML) and related neoplasms
AML with defining genetic abnormalities
AML, defined by differentiation
Acute basophilic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Myeloid sarcoma

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:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested

4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - History and physical exam including any relevant diagnoses related to the genetic testing
    - Sample collection (e.g., blood draw) date
    - Conventional testing and results

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome, Genetic Testing, Policy No. 02
2. Genetic Testing for α-Thalassemia, Genetic Testing, Policy No. 19
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. ClonoSEQ® Testing for the Assessment of Measurable Residual Disease (MRD), Genetic Testing, Policy No. 88
5. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
6. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31
7. Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, Transplant, Policy No. 45.36
8. Medication Policy Manual, Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

DIAGNOSING MYELOID NEOPLASMS AND ACUTE LEUKEMIA

Myeloid neoplasms may be acute or chronic, are a type of hematologic malignancy, and usually derive from bone marrow progenitor cells that normally develop into erythrocytes, granulocytes (neutrophils, basophils, and eosinophils), monocytes, or megakaryocytes. Classification of myeloid neoplasms and acute leukemias has evolved over the past decade, based in part on the advancement of available technologies and results from repeat validation studies.

In recent history, diagnosis of the various forms of myeloid neoplasms has been based on a complex set of clinical, pathological, and biological criteria first introduced by the Polycythemia Vera Study Group (PVSG) in 1996[3, 4] and the World Health Organization (WHO) in 2001.[5] Both of these classifications use a combination of clinical, pathological, and/or biological criteria to arrive at a definitive diagnosis, predominantly reliant on status of Philadelphia chromosome presence. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease. Some diagnostic methods (e.g., bone marrow microscopy) are not well standardized and others (e.g., endogenous erythroid colony formation) are neither standardized nor widely available.[6-8] Diagnosis and monitoring of patients with Philadelphia chromosome negative myeloid neoplasms poses a challenge because many of the laboratory and clinical features of these diseases can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis or myeloid fibrosis. In addition, these entities can be difficult to distinguish on morphological bone marrow exam and diagnosis can be complicated by changing disease patterns.

The most up-to-date classification and benchmark for diagnosis of hematopoietic and lymphoid tissues is a result of collaboration between the Society for Hematopathology and the European

Association for Haematopathology and is published by the WHO, most recently in 2022.[2] This edition varies from the previous versions with a refinement of diagnostic criteria and emphasis on actionable biomarkers. The current classification of myeloid neoplasm and acute leukemia subgroups are delineated in Table 2.

Table 2. WHO Myeloid Proliferations and Neoplasms Classification, adapted[2]

MYELOID NEOPLASMS, CHRONIC

Myeloproliferative Neoplasms (MPN)

- Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia
- Juvenile myelomonocytic leukemia (JMML)
- MPN, not otherwise specified (NOS)

Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

Myelodysplastic Neoplasms (MDS)

- MDS with low blasts and isolated 5q deletion
- MDS with low blasts and SF3B1 mutation
- MDS with low blasts, NOS
- MDS with increased blasts
- MDS with fibrosis
- MDS, NOS
- MDS with biallelic TP53 alteration (provisional)
- MDS with other defined driver gene alterations

MDS / acute myeloid leukemia (MDS/AML)

- MDS/AML with *NMP1* mutation
- MDS/AML with *MECOM* rearragement
- MDS/AML, NOS

MDS of childhood

- Refractory cytopenia of childhood
- Childhood MDS

MDS with proliferative evolution

- Chronic myelomonocytic leukemia
- MDS with proliferative evolution and neutrophilia
- MDS with proliferative evolution, SF3B1 mutation and thrombocytosis
- MDX with proliferative evolution, NOS

MYELOID NEOPLASMS, ACUTE

AML with defining genetic abnormalities

- Acute promyelocytic leukemia
- AML with *RUNX1::RUNX1T1* fusion
- AML with *CBFB::MYH11* fusion
- AML with *DEK::NUP214* fusion
- AML with *RBM15::MRTFA* fusion
- AML with *BCR::ABL1* fusion
- AML with *NUP98* rearrangement
- AML with *NPM1* mutation
- AML with *NUP98* rearrangement
- AML with other defined driver gene alterations
- AML with myelodysplasia-related cytogenetics

AML, defined by differentiation

- AML with minimal differentiation
- AML with without maturation
- AML with maturation
- Acute basophilic leukemia
- AML with myelomonocytic differentiation
- AML with monocytic differentiation
- AML with plasmacytoid dendritic cell differentiation (provisional)
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia

Myeloid sarcoma

MYELOID NEOPLASMS, SECONDARY

Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions

- Myeloid neoplasm post cytotoxic therapy
- Myeloid neoplasm associated with germline predisposition
- AML following other hematolymphoid malignancy
- Myeloid proliferations associated with Down syndrome
- Myeloid neoplasm associated with malignant germ cell tumor

MYELOID/LYMPHOID NEOPLASMS AND OTHER LEUKAEMIAS OF AMBIGUOUS LINEAGE

Myeloid/Lymphoid neoplasms with eosinophilia and defining gene rearrangement

- Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
- Myeloid/lymphoid neoplasms with *PMC1-JAK2* fustion

Acute leukemias of ambiguous lineage

Mixed-phenotype acute leukaemia with *BCR-ABL1* fusion

Mixed-phenotype acute leukaemia with *KMT2A* rearrangement

Mixed-phenotype acute leukaemia, B/myeloid

Acute leukaemia of ambiguous lineage, NOS

It is important to note that the presence of any one or more of the gene variants included in this policy may not be sufficient to confirm a diagnosis, rather, testing may help support other

clinical, laboratory, or pathological findings.

TREATMENT MONITORING

CML represents one of the earliest examples of the use of molecular information to revolutionize patient management. A unique chromosomal change (the Philadelphia chromosome) and an accompanying unique gene rearrangement (*BCR-ABL*) resulting in a continuously activated tyrosine kinase enzyme were identified. These led to the development of a targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions.

REGULATORY STATUS

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for gene variant testing related to myeloid neoplasms and acute lymphoblastic leukemia. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of Clinical Laboratory Improvement Act (CLIA) and laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA does not require regulatory review of LDTs.

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, which was released on July 14, 2011,[9] to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

The LeukoStrat® CDx *FLT3* Mutation Assay offered by Invivoscribe. According to Invivoscribe, the test is indicated at initial diagnosis of AML to determine eligibility for Rydapt® (midostaurin), Xospata® (gilteritinib), and Vanflyta® (quizartinib), and may also be used for risk stratification.[10] The assay includes internal tandem duplication variant testing for *FLT3* as well as variants in the tyrosine kinase domain. The assay is an FDA-approved companion diagnostic test for use with these medications and therefore may be standard of care in screening patients for use with this specific kinase inhibitor.

Abbott Real*Time* IDH2 is an *in vitro* polymerase chain reaction (PCR) assay for the qualitative detection of single nucleotide variants (SNVs) in the human isocitrate dehydrogenase-2 (IDH2) gene. The test aids in identifying acute myeloid leukemia patients for treatment with Idhifa® (enasidenib). Enasidenib is an oral medication used to treat patients with AML when the disease recurs after or does not respond to front-line therapies. The Abbott Real*Time* IDH2 assay received FDA premarket approval in August 2017.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in

DNA and serves as an international standard.[11] It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

BCR-ABL1 (*ABL1*) KINASE DOMAIN ANALYSIS

Screening for *BCR-ABL1* kinase domain variants in chronic phase CML is recommended for patients with inadequate initial response to TKI treatment, those with evidence of loss of response, and for patients who have progressed to accelerated or blast phase CML.[3] The focus of the following discussion is on kinase domain point variants and treatment outcomes in systematic reviews.

In 2010, the Agency for Healthcare Research and Quality published a systematic review on *BCR-ABL1* pharmacogenetic testing for tyrosine kinase inhibitors in CML.[12] Thirty-one publications of *BCR-ABL1* testing met the eligibility criteria and were included in the review (20 of dasatinib, seven of imatinib, three of nilotinib, and one with various TKIs). The report concluded that the presence of any *BCR-ABL1* variant does not predict differential response to TKI therapy, although the presence of the T315I variant uniformly predicts TKI failure. However, during the public comment period the review was strongly criticized by respected pathology organizations for lack of attention to several issues that were subsequently insufficiently addressed in the final report. Importantly, the review grouped together studies that used kinase domain variant screening methods with those that used targeted methods and combined studies that used variant detection technologies with very different sensitivities. The authors dismissed the issues as related to analytic validity and beyond the scope of the report. However, in this clinical scenario assays with different intent (screening vs. targeted) and assays of very different sensitivities may lead to different clinical conclusions, so an understanding of these points is critical.

Branford (2009) summarized much of the available evidence regarding kinase domain variants detected at imatinib failure, and subsequent treatment success or failure with dasatinib or nilotinib.[13] The T315I variant was most common; although about 100 variants have been

reported, the seven most common (at residues T315, Y253, E255, M351, G250, F359, and H396) accounted for 60-66% of all variants. However, preexisting or emerging variants T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Detection of the T315I variant at imatinib failure is associated with lack of subsequent response to high-dose imatinib, or to dasatinib or nilotinib. For these patients, allogeneic stem-cell transplantation remained the only available treatment until the advent of new agents such as ponatinib.[14] However these variants do not correspond to clinical significance, and based on clinical studies, the majority of imatinib-resistant variants remain sensitive to dasatinib and nilotinib.

Preexisting or emerging variants T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging variantsY253H, E255K/V, and F359V/C have been reported for decreased clinical efficacy with nilotinib treatment following imatinib failure. In the survey reported by Branford, a total of 42% of patients tested had T315I or one of these dasatinib- or nilotinib-resistant variants. In the absence of any of these actionable variants, various treatment options are available. Note that these data have been obtained from studies in which patients were all initially treated with imatinib; no data are available regarding variants developing during first-line therapy with dasatinib or nilotinib.[15]

Unlike in CML, resistance in ALL to TKIs is less well studied. Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or by competition of other coexisting subclones.[16] In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic complete response or clinical relapse warrants variant analysis.

***ASXL1*, *CALR*, *IDH1, IDH2* AND *TP53* IN MYELOID NEOPLASMS AND LEUKEMIA**

Testing for the *ASXL1*, *CALR*, *IDH1, IDH2* and *TP53* is required to meet WHO diagnostic criteria for patients with all of the most common Philadelphia-chromosome-negative MPNs.. The most recent revisions to the WHO criteria (2022) are heavily based on repeat validation studies.[2] The following evidence highlights the diagnostic and prognostic significance of *ASXL1*, *CALR*, *IDH1, IDH2* and *TP53* as specified by WHO diagnostic criteria and National Comprehensive Cancer Network (NCCN) guidelines.

ASXL1

For chronic myelomonocytic leukemia (CMML), *ASXL1* is amongst the most frequently mutated genes, observed in 40-50% of CMML patients.[17, 18] *ASXL1* is also reported to be associated with chromatin modification in MPNs, including polycythemia vera, as well as pre- and overt primary myelofibrosis.[19, 20]

CALR

Evidence for *CALR* demonstrates that a significant proportion of patients with myeloproliferative neoplasms and normal *JAK2* V617F status have a *CALR* variant.[21-23] Variants in exon 9 of *CALR* are found in 20-35% of all patients with ET and myelofibrosis. Fifty-two base pair deletions (*Type 1*) and five base pair insertions (*Type 2*) are the most common.

It is suggested that ET patients with *CALR* variants have lower polycythemic transformation rates, but not lower myelofibrotic transformation rate, compared with ET patients harboring a *JAK2* variant. Chen (2014) reported a higher platelet count, younger age of diagnosis, lower

leukocyte count, and decreased risk for thrombosis, compared with a *JAK2* positive ET population.[24] Tefferi (2014) reported survival and blast transformation in primary myelofibrosis (PMF) were significantly affected by variant status, though not in ET.[25] The outcome was best in *CALR*-variant patients and worst in *JAK2/CALR/MPL*-negative PMF patients. *CALR*-variant ET has also been associated with better thrombosis-free survival and lower leukocyte counts. However, overall survival has been reported as not different among *CALR*-variant and non-variant ET.[26, 27]

IDH1/2

For PMF and ET, WHO criteria specify *IDH1/2* (as well as others, including *ASXL1*) as having diagnostic significance for those without *JAK2, CALR,* and *MPL* variants. In myeloproliferative neoplasms, *IDH1* and *IDH2* variants are among a growing number of higher-risk molecular markers. Both are associated with shorter overall survival and leukemia-free survival in patients with PMF and polycythemia vera.[20, 28] In a study of the prognostic significance of *ASXL1, EZH2, SRSF2, IDH1* and *IDH2,* Vannucchi (2013) analyzed samples from 897 PMF patients (483 European patients and 396 from the Mayo clinical validation cohort). Median survival was significantly shorter (81 vs. 148 months, $p<0.0001$) in PMF patients with at least one of the genes.

TP53

Like *IDH1/2* described above, for PMF, *TP53* is associated with leukemic transformation, which is a common risk amongst patients with myeloproliferative neoplasms.[29] Furthermore, *TP53* is associated with inferior leukemia-free survival in those with ET. This progression is associated with poor clinical outcomes and resistance to standard AML therapies. Thus, *TP53* variants have also been analyzed to subdivide AML into prognostic subsets (see below). Additionally, *TP53* variants have been identified as one of the most common molecular abnormalities associated with myelodysplastic syndromes and may aid in diagnosis.[30-32]

ACUTE MYELOID LEUKEMIA

AML is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood, and/or other tissues. It is the most common type of leukemia in adults and is generally associated with a poor prognosis. It was estimated that in 2014, 18,860 people would be diagnosed with AML and 10,460 would die of the disease. Median age at diagnosis is 66 years, with approximately one in three patients diagnosed at 75 years of age or older.[33]

Conventional cytogenetic analysis (karyotyping) is a key component of the diagnostic evaluation of patients with suspected acute leukemia. The cytogenetic profile of the tumor is currently the most powerful predictor of prognosis in AML and is used to guide risk-adapted treatment strategies. Molecular variants, including those in *CEBPA*, *FLT3*, *KIT*, *NPM1*, *RUNX1*, and *TP53* genes, can be used to subdivide AML into prognostic subsets. (See Table 3.) Patients with better-prognosis disease based on cytogenetics (e.g., core-binding factor AML) who have a *c-KIT* variant in leukemic blast cells do just as poorly with post-remission standard chemotherapy as patients with cytogenetically poor-risk AML.[34] Similarly, individuals with cytogenetically normal AML (intermediate-prognosis disease) can be subcategorized into groups with better or worse prognosis based on the variant status of the *NPM1* and *FLT3* genes. Patients with variants in *NPM1* but without a *FLT3-ITD* fusion have post-remission outcomes with standard chemotherapy that are similar to those with better-prognosis

cytogenetics; in contrast, patients with any other combination of variants in those genes have outcomes similar to those with poor-prognosis cytogenetics.[35] A provisional category of AML with a *RUNX1* variant classifies de novo cases which are not associated with MDS-related cytogenetic abnormalities. This distinct group of AML patients also appears to have a worse prognosis than other AML types.[36-39]

The World Health Organization (WHO) classification of AML was adapted by the NCCN to estimate individual patient prognosis to guide management, as shown in Table 3:[40]

Table 3. Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1)/ *RUNX1*::*RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD Wild-type *NPM1* with FLT3-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/ *MLLT3::KMT2A* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1)/ *DEK*::*NUP214* t(v;11q23.3)/ *KMT2A*-rearranged t(9;22)(q34.1;q11.2)/ *BCR::ABL1* t(8;16)(p11.2;p13.3)/ *KAT6A::CREBBP* inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM*(*EVI1*) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* Mutated *TP53*

Genetic Testing for Molecular Subtypes of AML

A number of systematic reviews with meta-analyses have highlighted the evolving classification of AML into distinct molecular subtypes based on *CEBPA*, *FLT3-ITD*, *KIT*, *NPM1*, and *TP53*, particularly in patients with normal karyotype.[41-46] These studies support the WHO and NCCN risk status classifications, and additionally highlight the importance of *KIT* testing in the initial evaluation and for prognosis.

PANEL TESTING FOR MYELOID NEOPLASMS

As indicated in NCCN guidelines and the WHO classification system, testing for variants in multiple genes may be indicated for diagnosis or treatment decisions in patients diagnosed with, or suspected of having, a myeloid neoplasm (see Practice Guideline Summary below). A number of studies have been published that describe the use of genetic panel tests that include these genes for diagnosis and prognosis of AML[47-51] and MDS[52-54].

PRACTICE GUIDELINE SUMMARY

WORLD HEALTH ORGANIZATION

In 2016 the WHO published diagnostic criteria for myeloid neoplasms and acute leukemia, which include testing for a number of genetic variants, as shown in Table 2.[1] The 2022 major criteria for myeloproliferative neoplasms are unchanged.[2]

NATIONAL COMPREHENSIVE CANCER NETWORK

The NCCN has published guidelines for Chronic Myeloid Leukemia (v.2.2024)[55], Acute Lymphoblastic Leukemia (v.4.2023)[56], which include recommendations regarding *BCR-ABL1* testing.

NCCN guidelines for Acute Myeloid Leukemia (v.2.2024)[40], Myelodysplastic Syndromes (v.1.2024)[57], and Myeloproliferative Neoplasms (v.1.2024)[58] include recommendations for testing a number of genes that have clinical significance for these disorders, including *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1,* and *RUNX1*.

SUMMARY

BCR/ABL1 (t(9;22)) TRANSLOCATION ANALYSIS, *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1* AND/OR *RUNX1*

There is enough research to show that *BCR/ABL1* (t(9;22)) translocation analysis (Philadelphia chromosome) and genetic testing for *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA, FLT3, KIT, NPM1 and/or RUNX1* variants is important to guide diagnosis and treatment of myeloid neoplasms and leukemia. Additionally, these tests are recommended by clinical practice guidelines for various myeloid disorders. Therefore, testing for *BCR/ABL1* (t(9;22)) translocation analysis (Philadelphia chromosome) and genetic testing for *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA, FLT3, KIT, NPM1 and/or RUNX1* variants is considered medically necessary for evaluation, diagnosis, and/or treatment monitoring for myeloid neoplasms and leukemia.

BCR-ABL KINASE DOMAIN (*ABL1*)

In chronic myeloid leukemia, there is enough research to show clinical utility for evaluation of *ABL1* variants for tyrosine kinase inhibitor (TKI) resistance. TKI resistance in acute lymphoblastic leukemia (ALL) has not been studied as well as in CML. However, there is enough research to show *ABL1* genetic testing for evaluation of TKI resistance may lead to an improvement in health outcomes for patients with ALL who are receiving a TKI. Practice guidelines based on research recommend *ABL1* testing for ALL and CML in specific clinical scenarios. Therefore, *ABL1* genetic testing for evaluation of TKI resistance may be considered medically necessary when policy criteria are met. Due to insufficient evidence, evaluation of *ABL1* variants is considered investigational when policy criteria are not met.

TARGETED PANEL TESTING

There is enough research to show that targeted panel testing may be important for diagnosis and guide treatment decisions for patients suspected of having or diagnosed with myeloproliferative neoplasms (MPN), myelodysplastic neoplasms (MDS), and myelodysplastic myeloproliferative neoplasms (MPN/MDS), including acute myeloid leukemia (AML). Clinical practice guidelines recommend panel testing for these disorders.

Therefore, targeted panel testing for MPN, MDS, MPN/MDS or AML may be considered medically necessary.

NON-TARGETED PANEL TESTING

Non-targeted panels include testing for a large number of genes and are not targeted toward genes that have clinical significance for a specific type of hematolymphoid disorder. They often include testing for many genes that are not necessary to guide treatment, as well as testing for disorders that could be distinguished based on clinical presentation. There are no clinical practice guidelines based on research that recommend testing for all of the genes in these panels. Therefore, the use of non-targeted hematologic panel testing is considered investigational.

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CODES

NOTE: BCR/ABL1 (t(9;22)) translocation analysis has specific CPT codes: 81206-8, 0016U, and 0040U. This differs from than BCR-ABL kinase domain (*ABL1*) variant analysis.

Codes	Number	Description
CPT	0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
	0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
	0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
	0027U	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
	0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
	0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
	81170	*ABL1* (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81175	*ASXL1* (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
	81176	*ASXL1* (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, EXON 12)
	81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
	81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
	81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
	81218	*CEBPA* (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
	81219	*CALR* (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
	81245	*FLT3* (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
	81246	*FLT3* (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)

Codes	Number	Description
	81270	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81272	*KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
	81273	*KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
	81279	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
	81310	*NPM1* (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
	81334	*RUNX1* (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, EXONS 3-8)
	81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
	81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
	81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
	81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
	81401	Molecular pathology procedure, Level 2 - which includes *ABL1 (ABL proto oncogene 1, non-receptor tyrosine kinase)* (eg, acquired imatinib resistance), T315I variant
	81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon)
	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed DNA analysis or combined DNA and RNA analysis
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and

Codes	Number	Description
		copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
HCPCS	None	

Date of Origin: *August 2010*

Regence

Medical Policy Manual Genetic Testing, Policy No. 63

Genetic Testing for PTEN Hamartoma Tumor Syndrome

Effective: September 1, 2024

Next Review: May 2025
Last Review: July 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 *PTEN* hamartoma tumor syndrome (PHTS) includes several syndromes with heterogeneous clinical symptoms, which may place individuals at an increased risk of developing certain types of cancer. PHTS can be diagnosed with the identification of a *PTEN* variant.

MEDICAL POLICY CRITERIA

I. Genetic testing for *PTEN*, including in the evaluation of *PTEN* hamartoma tumor syndrome, may be considered **medically necessary** when one or more of the following criteria are met:

   A. In a first-degree relative of a proband with a known *PTEN* disease-associated variant

   B. In a patient with any of the following:

      1. Two or more biopsy-proven trichilemmomas
      2. Autism spectrum disorder and macrocephaly
      3. Adult Lhermitte-Duclos syndrome

   C. In a patient with two or more of the following:

1. Autism spectrum disorder
2. Breast Cancer
3. Colon cancer
4. Endometrial cancer (epithelial)
5. Esophageal glycogenic acanthoses, three or more
6. Gastrointestinal hamartomas (including ganglioneuromas, adenomas, hyperplastic polyps; three or more)
7. Intellectual disability defined as IQ less than or equal to 75
8. Lipomas, three or more
9. Macrocephaly (megalocephaly; defined as greater than or equal to 97th percentile, 58 cm in adult woman, 60 cm in adult men)
10. Macular pigmentation of glans penis
11. Mucocutaneous lesions, three or more with clinical documentation
12. Renal cell carcinoma
13. Testicular lipomatosis
14. Thyroid cancer or thyroid structural lesions (e.g. adenoma, multinodular goiter)
15. Vascular anomalies (including multiple intracranial developmental venous anomalies)

II. Genetic testing for *PTEN* is considered **investigational** when Criterion I. is not met.

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

POLICY GUIDELINES

TESTING IN A FIRST-DEGREE RELATIVE

When a *PTEN* pathogenic variant has been identified in the proband, testing of asymptomatic at-risk relatives can identify those family members who have the family-specific variant, for whom an initial evaluation and ongoing surveillance should be performed.

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
- Current Symptomology
- Documentation of first-degree relative when there is known variant

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome, Genetic Testing, Policy No. 02
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
4. Biomarkers for Cardiovascular Disease, Laboratory, Policy No. 78

BACKGROUND

The *PTEN* (phosphatase and tensin homologue) hamartoma tumor syndrome is characterized by hamartomatous tumors and *PTEN* germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (PLS).

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules and present by the late 20s. The lifetime risk of developing breast cancer is 25-50%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer, which is usually follicular carcinoma, is approximately 10%. The risk for endometrial cancer is not well defined but may approach 5-10%.

BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. Additional features include high birth weight, developmental delay and mental deficiency (50% of affected individuals), a myopathic process in proximal muscles (60%), joint hyperextensibility, pectus excavatum, and scoliosis (50%).

PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

CS is the only PHTS disorder associated with a documented predisposition to cancer; however, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* pathogenic variants should be assumed to have cancer risks similar to those with CS.

CLINICAL DIAGNOSIS

A presumptive diagnosis of PHTS is based on clinical findings; however, because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* disease-associated variant is identified.

MANAGEMENT

Treatment

Treatment of the benign and malignant manifestations of PHTS is the same as for their sporadic counterparts.

Surveillance

The most serious consequences of PHTS relate to the increased risk of cancers, including breast, thyroid and endometrial, and to a lesser extent, renal. Therefore, the most important aspect of management of an individual with a *PTEN* disease-associated variant is increased cancer surveillance to detect tumors at the earliest, most treatable stages.

MOLECULAR DIAGNOSIS

PTEN is a tumor suppressor gene on chromosome 10q23 and is dual specificity phosphatase with multiple but incompletely understood roles in cellular regulation.[1] *PTEN* pathogenic variants are inherited in an autosomal dominant manner.

Because CS is likely underdiagnosed, the actual proportion of simplex cases (defined as individuals with no obvious family history) and familial cases (defined as ≥2 related affected individuals) cannot be determined. The majority of CS cases are simplex. It is estimated that 50-90% of cases of CS are de novo and approximately 10-50% of individuals with CS have an affected parent.

Because of the phenotypic heterogeneity associated with the hamartoma syndromes, the diagnosis of PHTS is made only when a *PTEN* disease-associated variant is identified. Up to 85% of patients who meet the clinical criteria for a diagnosis of CS and 65% of patients with a clinical diagnosis of BRRS have a detectable *PTEN* variant. Some data suggest the up to 20% of patients with Proteus syndrome and up to 50% of patients with a Proteus-like syndrome have *PTEN* variants.

Most of these pathogenic variants can be identified by sequence analysis of the coding and flanking intronic regions of genomic DNA. A smaller number of variants are detected by deletion/duplication or promoter region analysis.

Penetrance: More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, primarily trichilemmomas and papillomatous papules, as well as acral and plantar keratoses.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratory testing for PTEN variants is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a pathogenic variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (i.e., sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, which refers to how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence from well designed, studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and
- Improve health outcomes as a result of those decisions.

ANALYTIC VALIDITY

According to a large reference laboratory, analytical sensitivity and specificity for bidirectional sequencing of the *PTEN*-related promoter, coding region and intron-exon boundaries is 99%.[3]

CLINICAL VALIDITY

Many reports on the prevalence of the features of Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) have been based upon data compiled from case reports and studies of small cohorts. Most of these reports were published before adoption of the International Cowden Consortium diagnostic criteria for CS in 1996, and the true frequencies of the clinical features in CS and BRRS are not known.[1]

According to a large reference laboratory, the clinical sensitivity of *PTEN*-related disorders sequencing is 85% for CS, 65% for BRRS, 20% for *PTEN*-related Proteus syndrome (PS) and 50% for Proteus-like syndrome (PSL). For *PTEN*-related deletion/duplication, it is up to 10% for BRRS and/or CS-like syndrome.[3]

Germline *PTEN* variants have been identified in ~80% of patients meeting diagnostic criteria for CS and in 50 to 60% of patients with a diagnosis of BRRS, using PCR-based sequence analysis of the coding and flanking intronic regions of the gene.[4, 5] Marsh (1998) screened DNA from 37 CS families and *PTEN* variants were identified in 30 of 37 CS families (81%), including single nucleotide variants, insertions, and deletions.[4] The *PTEN* variant detection rate is much lower in breast cancer patients without other symptoms.[6, 7]

Whether the remaining patients have undetected *PTEN* variants or variants in other, unidentified genes, is not known.[8]

A study by Pilarski (2011) determined the clinical features that were most predictive of a disease-associated variant in a cohort of patients tested for *PTEN* variants.[1] Molecular and clinical data were reviewed for 802 patients referred for *PTEN* analysis by a single laboratory. All of the patients were classified as to whether they met revised International Cowden Consortium Diagnostic criteria. Two hundred and thirty of the 802 patients met diagnostic criteria for a diagnosis of CS. Of these, 79 had a *PTEN* pathogenic variant, for a detection rate of 34%. The authors commented that this variant frequency was significantly lower than

previously reported, possibly suggesting that the clinical diagnostic criteria for CS are not as robust at identifying patients with germline *PTEN* variants as previously thought. In contrast, in their study, of the patients meeting diagnostic criteria for BRRS, 23 of 42 (55%) had a pathogenic variant, and seven of nine patients (78%) with diagnostic criteria for both CS and BRRS had a variant, consistent with the literature.

Section Summary

Evidence from several small studies indicated that the clinical sensitivity of genetic testing for *PTEN* variants may be highly variable. This may reflect the phenotypic heterogeneity of the syndromes and an inherent referral bias as patients with more clinical features of CS/BRRS are more likely to get tested. The true clinical specificity is uncertain because the syndrome is defined by the variant.

CLINICAL UTILITY

The clinical utility of genetic testing can be considered in the following clinical situations:

1. Individuals with suspected *PTEN* hamartoma tumor syndrome (PHTS)
2. Family members of individuals with PHTS, and
3. Prenatal testing.

Individuals with Suspected PHTS

The clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. There is no direct evidence for the clinical utility of genetic testing in these patients as no studies were identified that described how a molecular diagnosis of PHTS changed patient management.

However, for patients who are diagnosed with PHTS by identifying a *PTEN* pathogenic variant, the medical management focuses on increased cancer surveillance to detect tumors at the earliest, most treatable stages.

- Family members.

  When a *PTEN* pathogenic variant has been identified in a proband, testing of at-risk relatives can identify those who also have the pathogenic variant and have *PTEN* hamartoma tumor syndrome (PHTS). These individuals need initial evaluation and ongoing surveillance.

- Prenatal screening.

  Prenatal diagnosis is possible for pregnancies at increased risk, by amniocentesis or chorionic villus sampling; the disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Recent studies reporting on the clinical features of individuals with a *PTEN* pathogenic variant have indicated there is insufficient evidence to support the inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. However, there was sufficient evidence identified to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis and vascular anomalies. These identified clinical features are included in CS testing minor criteria

in National Comprehensive Cancer Network guidelines (see Policy Guidelines section above) and described in a recent systematic review.[9, 10]

Section Summary

Direct evidence for the clinical utility of *PTEN* testing is lacking. However, the clinical utility of genetic testing for *PTEN* variants is that genetic testing can confirm the diagnosis in patients with clinical signs and symptoms of PHTS. Management changes include increased surveillance for the cancers associated with these syndromes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic recommend the following for CS/PHTS management (3.2024):[10]

For Women:

- Breast awareness starting at age 18 years.
- Clinical breast exam every 6 to 12 months, starting at age 25 years or 5 to 10 years before the earliest known breast cancer in the family (whichever comes first).
- Breast screening:
    - Annual mammography and breast MRI screening with or without contrast starting at age 30 years or 10 years before the earliest known breast cancer in family (whichever comes first).
    - Age > 75, management should be considered on an individual basis.
    - For individuals with pathogenic/likely pathogenic *PTEN* variant who are treated for breast cancer, and have not had bilateral mastectomy, screening of remaining breast tissue with annual mammography and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants identified. For those with clinical CS/PTHS syndrome, consideration of risk-reducing surgery should be based on family history.
- Endometrial cancer screening, consider starting by age 35 years:
    - Encourage patient education and prompt response to symptoms (eg abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle.
    - Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.
    - Endometrial cancer screening does not have proven benefit in women with CS/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.
    - Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in

premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.

- Discuss option of hysterectomy upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

For Men and Women:

- Annual comprehensive physical exam starting at age 18 years or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Annual thyroid ultrasound, starting at age 7 years. This may also be considered for children at 50% risk of inheriting a known mutation whose parents wish to delay genetic testing until age 18 y.
- Colonoscopy, starting at age 35 years, unless symptomatic or a close relative with colon cancer before age 40 years, then start 5-10 years before earliest known colon cancer in the family. Colonoscopy should be done every 5 years or more frequently if patient is symptomatic or polyps found.
- Consider renal ultrasound starting at age 40 years, then every 1 to 2 years.
- There may be an increased risk of melanoma, and the prevalence of other skin characteristics with CS/PTHS may independently make routine dermatology evaluations of value. Annual dermatology recommendations are recommended.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

For Relatives:

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Reproductive options:

- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies.

U.S MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER

In 2022, the US Multi-Society Task Force on Colorectal Cancer (USMSTF), a group of colorectal cancer (CRC) content experts appointed by the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy, published recommendations on the diagnosis and management of cancer risk in the gastrointestinal hamartomatous polyposis syndromes, including the following regarding genetic testing:[11]

> We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first- or second-degree

relatives. Genetic testing (if indicated) should be performed using a multigene panel test. (Strong recommendation, low quality of evidence).

We recommend genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. (Strong recommendation, low quality of evidence).

We recommend genetic evaluation for any individual with 1) 5 or more juvenile polyps of the colon or rectum; or 2) 2 or more juvenile polyps in other parts of the gastrointestinal tract; or (3) any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome. (Strong recommendation, low quality of evidence).

We recommend individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions. (Strong recommendation, low quality of evidence).

SUMMARY

There is enough research to show that *PTEN* genetic testing can help to determine appropriate cancer surveillance, leading to improved health outcomes for patients at high risk for *PTEN* hamartoma tumor syndrome. Clinical guidelines based on research recommend this testing for certain individuals. Therefore, *PTEN* genetic testing may be considered medically necessary when a presumptive diagnosis of a *PTEN* hamartoma tumor syndrome has been made based on clinical signs, and for first-degree relatives of an individual with a known disease-associated *PTEN* variant.

There is not enough research to show that *PTEN* genetic testing improves health outcomes for individuals who do not meet the policy criteria. Therefore, genetic testing for a *PTEN* variant is considered investigational for all other indications.

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CODES

Codes	Number	Description
CPT	0235U	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81321	*PTEN (phosphatase and tensin homolog)* (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	;known familial variant
	81323	;duplication/deletion variant
HCPCS	None	

Date of Origin: *May 2013*

Regence

Medical Policy Manual Genetic Testing, Policy No. 64

Evaluating the Utility of Genetic Panels

Effective: April 1, 2024

Next Review: July 2025
Last Review: March 2025

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

Genetic panel tests evaluate many genes simultaneously, and have been developed for numerous indications, including hereditary cancer risk assessment, pharmacogenetics, and diagnosis of congenital disorders. Many panel tests include genes that do not have demonstrated clinical utility for their testing.

MEDICAL POLICY CRITERIA

Note: Where applicable, specific policies that have criteria and evidence used to review genetic panel tests are noted (see *Policy Cross-References* in the table below).

When there is not enough research to show that a gene and/or gene variant in a genetic panel test may be used to manage treatment decisions and improve net health outcomes, then the entire genetic panel test is considered **investigational**, including but not limited to the following (with or without any optional add-on genes or components):

Test Name	Laboratory	Policy Cross-Reference
Abnormal Genitalia/ Disorders of Sex Development Panel	Blueprint Genetics	None
Aeon Pain Management PGX Profile	Aeon Clinical Laboratories	GT10

Ambiguous Genitalia Panel	Prevention Genetics	None
Amyotrophic Lateral Sclerosis Advanced Evaluation Gene Panel	Athena Diagnostics	None
Amyotrophic Lateral Sclerosis Panel	Laboratory for Precision Diagnostics, University of Washington	None
Amyotrophic Lateral Sclerosis / Frontotemporal Lobar Degeneration Panel	GeneDx	None
Arthrogryposes Panel	Blueprint Genetics	None
ASD/ID Genetic Test Panel	Quadrant Laboratories	None
Ataxia Panel	Blueprint Genetics	None
Ataxia Complete Recessive Evaluation	Athena Diagnostics	None
Ataxia, Comprehensive Evaluation	Athena Diagnostics	None
Ataxia/Episodic Ataxia Disorders (including any add-on components, e.g., mtDNA, SCA, HTT, FRDA Repeat Expansion Analysis)	Labcorp/MNG Laboratories	None
Ataxia Xpanded Panel	GeneDx	None
Autism Spectrum Disorders Panel	Prevention Genetics	None
AutismNext	Ambry Genetics™	None
Autism/ID and Autism/ID Xpanded Panel	GeneDx	None
Autoinflammatory Syndrome Panel	Blueprint Genetics	None
Autosomal Dominant Thrombocytopenia Panel	Versiti	None
Bacterial Typing by Whole Genome Sequencing	Mayo Clinic	None
Beacon Expanded Carrier Panels (with or without X-linked disorders)	Fulgent	GT81
Bleeding Disorders Panel	Prevention Genetics	None
Bone Marrow Failure Panel	Oregon Health & Science University, Knight Diagnostic Lab	None
Bone Marrow Failure Syndrome Panel	Blueprint Genetics	None
BRCAPlus and BRCAPlus Expanded Panel	Ambry Genetics™	GT02
BROCA Cancer Risk Panel	University of Washington	GT02
CancerNext™ and CancerNext™ Expanded	Ambry Genetics™	None

CancerNext™ +RNAinsight™	Ambry Genetics™	None
CancerTYPE ID®	bioTheranostics	GT15
Cardiac Arrhythmia Panel	Laboratory for Precision Diagnostics, University of Washington	None
CardioNext	Ambry Genetics™	None
Cataract Panel Test	Blueprint Genetics	None
CentoNeuro Panel	Centogene	None
Cholestasis Panel	Oregon Health & Science University	None
Ciliopathies Panels	Oregon Health & Science University	None
Cleft Lip/Cleft Palate Panel	Prevention Genetics	None
Cleft Lip/Palate and Associated Syndromes Panel	Blueprint Genetics	None
CMNext Panel	Ambry Genetics™	None
Coagulation Disorder Panel	Versiti	None
Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel	ARUP	None
ColoNext™ and ColoNext™ +RNAinsight™	Ambry Genetics™	GT06
Colorectal Cancer Panel	GeneDx	GT06
ColoSeq™ Lynch and Polyposis	University of Washington	GT06
Combined Cardiac Panel	GeneDx	None
Combined Hereditary Dementia and Amyotrophic Lateral Sclerosis Panel	Invitae	None
Common Cancer Management Panel	GeneDx	None
Comprehensive Arrhythmia/Cardiomyopathy Panel	Laboratory for Precision Diagnostics, University of Washington	None
Comprehensive Bleeding Disorder Panel	Versiti	None
Comprehensive Brain Malformation Panel	Prevention Genetics	None
Comprehensive Brain Malformations Panel	GeneDx	None
Comprehensive Common Cancer Panel	GeneDx	None
Comprehensive Congenital Heart Disease Panel	Prevention Genetics	None

Comprehensive Dystonia Panel	Labcorp/MNG Laboratories	None
Comprehensive Hematology and Hereditary Cancer Panel	Blueprint Genetics	None
Comprehensive Hereditary Cancer Panel	Blueprint Genetics	None
Comprehensive Hereditary Cancer Panel	Quest Diagnostics	None
Comprehensive Immune and Cytopenia Panel	Blueprint Genetics	None
Comprehensive Inherited Kidney Disease Panel	Prevention Genetics	None
Comprehensive Inherited Retinal Dystrophies Panel	Prevention Genetics	None
Comprehensive Ocular Disorders (includes RPGR ORF15) Panel	Prevention Genetics	None
Comprehensive Neuromuscular Panel	Prevention Genetics	None
Comprehensive Pharmacogenetic Panel	Advanced Genomics	GT10
Comprehensive Platelet Disorder Panel	Versiti	None
Comprehensive Short Stature Syndrome Panel	Blueprint Genetics	None
Comprehensive Skeletal Dysplasias and Disorders Panel	Blueprint Genetics	None
Congenital Abnormalities of the Kidney Tract (CAKUT) Panel	Prevention Genetics	None
Congenital Adrenal Hyperplasia Panel	Blueprint Genetics	None
Congenital Anomalies of the Gastrointestinal Tract Panel	Prevention Genetics	None
Congenital Diaphragmatic Hernia Panel	Prevention Genetics	None
Congenital Hypothyroidism and Thyroid Hormone Resistance Panel	Prevention Genetics	None
Congenital Limb Malformation Panel	Prevention Genetics	None
Congenital Stationary Night Blindness Panel	Prevention Genetics	None
Cornelia de Lange and Related Disorders Panel	Prevention Genetics	None
Craniosynostosis NGS Panel	Fulgent	None
Cystic Kidney and Liver Diseases Panel	GeneDx	None
Cystic Kidney Disease Panel	Blueprint Genetics	None
DetoxiGenomic® Profile Test	Genova® Diagnostics	GT10

Differences in Sex Development Sequencing	Seattle Children's Hospital	None
Differences of Sex Development (DSD) Panel	Prevention Genetics	None
Dystonia and Choreatic Movement Disorder Panel	University of Washington	None
Dystonia Panel	GeneDx	None
Dystonia & Parkinsonism Panel	GeneDx	
Early Advantage Panel	NxGEN MDx	GT82
Empower Multi-Cancer and Multi-Cancer Expanded and Comprehensive Panels	Natera, Inc.	None
Female Infertility NGS Panel	Fulgent	None
Fibrinolytic Disorder Panel	Versiti	None
Foresight™ Carrier Screen Universal Panel and Universal Panel Plus	Myriad	GT81
FusionPlex Pan-Heme Panel	Laboratory for Precision Diagnostics, University of Washington	GT59
GenArray™	GenPath Diagnostics	None
GeneAware Complete Panel	Miraca, Baylor Genetics	GT81
GeneSeq®: Cardio-Early-onset Coronary Artery Disease/Familial Hypercholesterolemia Profile	Labcorp	GT11
GeneSight® Psychotropic Genetic Testing	Assurex Health/Myriad	GT53
Genetic Platelet Disorders Panel	Labcorp	None
GeneticsNow® Comprehensive Germline Panel	GoPath	None
GeneTrails® Comprehensive Heme Panel (previously GeneTrails® Hematologic Malignancies 220 Gene Panel)	Oregon Health & Science Univ	GT59
Genomic Unity® Ataxia Repeat Expansion and Sequence Analysis	Variantyx	None
Genomic Unity® Comprehensive Ataxia Repeat Expansion and Sequence Analysis	Variantyx	None
Genomic Unity Movement Disorders Analysis	Variantyx	None

Genomind® Professional PGx Express™	Genomind LLC	GT53
Guideline-based Hereditary Cancer Panel	Quest Diagnostics	None
Hereditary Breast Cancer Panel	Quest Diagnostics	GT02
Hereditary Leukemia Panel	Blueprint Genetics	None
Hereditary Ovarian Cancer Panel	Prevention Genetics	GT02
Horizon™ 27	Natera, Inc.	GT81
Horizon™ 106	Natera, Inc.	GT81
Horizon™ 274	Natera, Inc.	GT81
Horizon™ 421	Natera, Inc.	GT81
HSP, Comprehensive Evaluation	Athena Diagnostics	None
Hydrocephalus Panel	Prevention Genetics	None
Hyperparathyroidism Panel	Blueprint Genetics	None
Hypoglycemia Panel - Expanded	Prevention Genetics	None
Hypogonadotropic Hypogonadism/ Kallmann Syndrome Panel	Prevention Genetics	None
Hypogonadotropic Hypogonadism Panel	GeneDx	None
IDgenetix	Castle Biosciences	GT53
InheriGen Panel and InheriGen Plus	GenPath Diagnostics	GT81
Inherited Bone Marrow Failure Panel	Prevention Genetics	None
Inherited Pancreatic Cancer Panel	Oregon Health & Science University, Knight Diagnostic Lab	None
Inherited Thrombocytopenia Panel	Versiti	None
Inheritest Ashkenazi Jewish Carrier Screening Panel	LabCorp/Integrated Genetics	GT81
Inheritest 100 PLUS Panel, 300 PLUS Panel and 500 PLUS Panel	LabCorp/Integrated Genetics	GT81
Intellectual Disability, Epilepsy, and Autism (IDEA) Panel	Prevention Genetics	None
Invitae Amyotrophic Lateral Sclerosis Panel (with or without C9orf72)	Invitae	None
Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel	Invitae	None
Invitae Arrhythmia Comprehensive Panel	Invitae	None
Invitae Autoinflammatory and Autoimmunity Syndromes Panel	Invitae	None

Invitae Bone Marrow Failure Syndromes Panel	Invitae	None
Invitae Brain Malformations Panel	Invitae	None
Invitae Breast and Gyn Cancers Guidelines-Based Panel	Invitae	None
Invitae Breast Cancer Guidelines-Based Panel	Invitae	GT02
Invitae Broad Carrier Screen	Invitae	GT81
Invitae Cancer Genetic Risk Panel	Invitae	None
Invitae Cataracts Panel	Invitae	None
Invitae Cerebral Palsy Spectrum Disorders Panel	Invitae	None
Invitae Cholestasis Panel	Invitae	None
Invitae Ciliopathies Panel	Invitae	None
Invitae Colorectal Cancer Panel	Invitae	None
Invitae Common Hereditary Cancer Panel	Invitae	GT02
Invitae Comprehensive Lipidemia Panel	Invitae	None
Invitae Comprehensive Muscular Dystrophy Panel	Invitae	None
Invitae Comprehensive Myopathy Panel	Invitae	None
Invitae Comprehensive Neurometabolic Disorders Panels	Invitae	None
Invitae Comprehensive Neuromuscular Disorders Panel	Invitae	None
Invitae Comprehensive Neuropathies Panel	Invitae	None
Invitae Congenital Anomalies of Kidney and Urinary Tract (CAKUT) Panel	Invitae	None
Invitae Congenital Heart Defects and Heterotaxy Panel	Invitae	None
Invitae Congenital Heart Disease Panel	Invitae	None
Invitae Congenital Muscular Dystrophy Panel	Invitae	None
Invitae Congenital Myasthenic Syndrome Panel	Invitae	None
Invitae Cornelia de Lange and Related Disorders Panel	Invitae	None
Invitae Cystic Kidney Disease Panel	Invitae	None

Invitae Disorders of Sex Development Panel	Invitae	None
Invitae Dystonia Comprehensive Panel	Invitae	None
Invitae Ectodermal Dysplasias and Related Disorders Panel	Invitae	None
Invitae Epidermolysis Bullosa and Palmoplantar Keratoderma Panel	Invitae	None
Invitae Expanded Renal Disease Panel	Invitae	None
Invitae Frontotemporal Dementia Panel	Invitae	GT01
Invitae Glaucoma Panel	Invitae	None
Invitae Hereditary Amyotrophic Lateral Sclerosis, Frontotemporal Dementia and Alzheimer Disease Panel	Invitae	None
Invitae Hereditary Breast Cancer Panel	Invitae	GT02
Invitae Hereditary Breast and Gyn Cancers Panel	Invitae	GT02
Invitae Hereditary Gastric Cancer Panel	Invitae	None
Invitae Hereditary Lymphoma Panel	Invitae	None
Invitae Hereditary Nervous System/Brain Cancer Panel	Invitae	None
Invitae Hereditary Parkinson’s Disease and Parkinsonism Panel	Invitae	None
Invitae Hereditary Prostate Cancer Panel	Invitae	None
Invitae Hereditary Renal/Urinary Tract Cancers Panel	Invitae	None
Invitae Hereditary Sarcoma Panel	Invitae	None
Invitae Hereditary Spastic Paraplegia Comprehensive Panel	Invitae	None
Invitae Hereditary Thrombophilia Panel	Invitae	None
Invitae Hyperammonemia Panel	Invitae	None
Invitae Hypoglycemia Panel	Invitae	None
Invitae Hypogonadotrophic Hypogonadism Panel	Invitae	None
Invitae Hypoparathyroidism Panel	Invitae	None
Invitae Inborn Errors of Immunity and Cytopenias Panel	Invitae	None
Invitae Inherited Platelet Disorders Including Thrombocytopenia Panel	Invitae	None

Invitae Inherited Retinal Disorders Panel	Invitae	None
Invitae Leukodystrophy and Genetic Leukoencephalopathy Panel	Invitae	None
Invitae Limb and Digital Malformations Panel	Invitae	None
Invitae Metabolic Newborn Screening Confirmation Panel	Invitae	None
Invitae Microphthalmia, Anophthalmia, Coloboma (MAC) and Anterior Segment Dysgenesis Panel	Invitae	None
Invitae Monogenic Diabetes Panel	Invitae	None
Invitae Multi-Cancer Panel and Multi-Cancer+RNA Panel	Invitae	None
Invitae Myelodysplastic Syndrome/Leukemia Panel	Invitae	None
Invitae Nephrolithiasis Panel	Invitae	None
Invitae Nephrotic Syndrome and Focal Segmental Glomerulosclerosis (FSGS) Panel	Invitae	None
Invitae Neurodevelopmental Disorders (NDD) Panel	Invitae	None
Invitae Overgrowth and Macrocephaly Syndromes Panel	Invitae	None
Invitae Overgrowth Syndromes Panel	Invitae	None
Invitae Pancreatic Cancer Panel	Invitae	None
Invitae Pediatric Solid Tumors Panel	Invitae	None
Invitae Phagocytic Disorders Including Neutropenia Panel	Invitae	None
Invitae Primary Immunodeficiency Panel	Invitae	None
Invitae Progressive Renal Disease Panel	Invitae	None
Invitae Pulmonary Arterial Hypertension Panel	Invitae	None
Invitae RASopathies and Noonan Spectrum Disorders Panel	Invitae	None
Invitae Renal Tubular Disorders Panel	Invitae	None
Invitae Rett and Angelman Syndromes and Related Disorders Panel	Invitae	None
Invitae Rhabdomyolysis and Metabolic Myopathy Panel	Invitae	None

Invitae Skeletal Disorders Panel	Invitae	None
Leukodystrophy and Leukoencephalopathy Panel	Blueprint Genetics	None
Leukodystrophy and Leukoencephalopathy Panel	Prevention Genetics	None
Leukoencephalopathy NGS Panel	Fulgent	None
Limb Abnormalities and Reduction Defects Panel	GeneDx	None
Lymphoid Gene Panel by NGS	University of Washington	None
Metabolic Myopathies Panel	University of Washington	None
Metabolic Myopathies, Rhabdomyolysis, and Exercise Intolerance Panel	Prevention Genetics	None
Metabolic Myopathy and Rhabdomyolysis Panel	Blueprint Genetics	None
Metabolic Myopathy Panel	GeneDx	None
Migraine and Stroke Panel	Oregon Health & Science University, Knight Diagnostic Lab	None
Migraine Panel	Blueprint Genetics	None
MODY Panel	Blueprint Genetics	None
Movement Disorder Ataxia Panel	Laboratory for Precision Diagnostics, University of Washington	None
MVL Vision Panel	Molecular Vision Laboratory	None
MyAML® 194 Targeted NGS Gene Panel	Invivoscribe	GT59
MyGenVar Pharmacogenomics Test	Geisinger Medical Laboratory	GT10
myMRD NGS Panel	Lab for Personalized Molecular Medicine	None
Myopathies and Myotonia, Muscular Dystrophies and Limb Girdle Panel	Laboratory for Precision Diagnostics, University of Washington	None
myRisk™ Hereditary Cancer Panel (Update myRisk™)	Myriad	None
Nephrolithiasis Panel	Blueprint Genetics	None
Nephrotic Syndrome (NS)/Focal Segmental Glomerulosclerosis (FSGS) Panel	Prevention Genetics	None
Nephrotic Syndrome Panel	Blueprint Genetics	None
Neuro-ophthalmology Panel	Blueprint Genetics	None

Neurotransmitter Metabolism Deficiency NGS Panel	Fulgent	None
Non-Immune Hydrops Fetalis Panel	Prevention Genetics	None
NxGen MDx Hereditary Cancer Panel	NxGen MDx	None
NxGen Super Panel	NxGen MDx	GT81
OI and Genetic Bone Disorders Panel	Laboratory for Precision Diagnostics, University of Washington	None
OmniSeq® Immune Report Card	OmniSeq®	None
Optic Atrophy Panel	Blueprint Genetics	None
Osteogenesis Imperfecta and Low Bone Density Panel	ARUP	None
Overgrowth and Macrocephaly Syndromes Panel	Prevention Genetics	None
Pan Cardiomyopathy Panel	Prevention Genetics	
Pancreatic Cancer Panel	GeneDx	None
Parkinson Disease Panel	GeneDx	None
Pediatric Cancer Panel	Prevention Genetics	None
Personalized Medication Panel	UpFront Laboratories	GT10
Platelet Disorders, Comprehensive Gene Panel	Mayo Clinic	None
Platelet Disorders Panel	Oregon Health & Science University	None
Platelet Function Disorder Panel	Versiti	None
Premature Ovarian Failure Panel	Blueprint Genetics	None
Premature Ovarian Failure Panel	Prevention Genetics	None
Primary Antibody Deficiency Panel	ARUP	None
Primary Immunodeficiency (PID) and Primary Ciliary Dyskinesia (PCD) Panel	Blueprint Genetics	None
Primary Immunodeficiency Panel	Blueprint Genetics	None
Professional PGx and Professional PGx Express (CORE and FULL)	Genomind	GT53
ProstateNow®	Genetics Now/GoPath	None
Psych HealthPGx Panel	RPRD Diagnostics	GT53
ProstateNext +RNAinsight™	Ambry Genetics™	GT17
PyloriAR™/AmHPR® H. pylori Antibiotic Resistance NGS Panel	American Molecular Labs	None
Qherit 381 Diseases, Male	Quest Diagnostics	GT81

Qherit 421 Diseases, Female	Quest Diagnostics	GT81
Qherit Extended (both Female and Male versions)	Quest Diagnostics	GT81
Qherit Plus, Female	Quest Diagnostics	GT81
Renasight Kidney Gene Panel	Natera, Inc.	None
Retinal Dystrophy Panel	Blueprint Genetics	None
Retinal Dystrophy Panel	Laboratory for Precision Diagnostics, University of Washington	None
Rett/Angelman Syndrome Sequencing Panel	Seattle Children's Hospital	None
Rett/Angelman Syndrome Panel	GeneDx	None
RightMed® Panels and Gene Report/Medication Report (including the Mental Health, PGx16, and Comprehensive Tests with or without F2 and F5)	OneOme	GT10/GT53
Riskguard™	Exact Sciences	None
Sarcoma Comprehensive NGS Fusion Panel	Neogenomics	None
Sarcoma Targeted Gene Fusion Panel	Mayo Clinic	None
Skeletal Disorders and Joint Problems Panel	Prevention Genetics	None
Spastic Paraplegia (NGS Panel and Copy Number Analysis + mtDNA)	Labcorp/MNG Laboratories	None
Stroke, Cerebral Hemorrhage, Hemiplegia, and Migraines Panel	Prevention Genetics	None
Syndactyly Panel	Prevention Genetics	None
Tempus nP	Tempus	GT53
Tempus xG and xG+	Tempus	None
Thrombocytopenia Panel	Blueprint Genetics	None
Thrombosis Panel	Versiti	None
UCSF Pharmacogenomics Panel	UCSF Genomic Medicine Lab	GT10
UroSeq	Know Error	None
VACTERL Association and Related Disorders Panel	Prevention Genetics	None
VanSeq Expanded Sequencing Panel	Seattle Children's Hospital	None
Vascular Malformations Panel	ARUP	None
VistaSeq Breast Cancer Panel	LabCorp	GT02

VistaSeq Hereditary Cancer Panel	LabCorp	None
VistaSeq Pancreatic Cancer Panel	LabCorp	None
VistaSeq Renal Cell Cancer Panel	LabCorp	None
Vitreoretinopathy Panel	Molecular Vision Laboratory	None
Vitreoretinopathy Panel and Vitreoretinopathy Panel Plus	Blueprint Genetics	None
Xpanded Adult Movement Disorders Panel	GeneDx	None
Xpanded Congenital Heart Defects Panel	GeneDx	None
YouScript® Personalized Prescribing System	YouScript	GT10

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

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test, if available:
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided

CROSS REFERENCES

1. Medical Policy Manual: Genetic Testing Section Table of Contents

BACKGROUND

New genetic technology, such as next generation sequencing and chromosomal microarray, has led to the ability to examine many genes simultaneously.[1] This in turn has resulted in a proliferation of genetic panels. The intended use for these panels is variable. For example, for the diagnosis of hereditary disorders, a clinical diagnosis may already be established, and genetic testing is performed to determine whether there is a hereditary condition, and/or to determine the specific variant that is present. In other cases, there is a clinical syndrome (phenotype) with a broad number of potential diagnoses and genetic testing is used to make a specific diagnosis. For cancer panels, there are also different intended uses. Some panels may be intended to determine whether a known cancer is part of a hereditary cancer

syndrome. Other panels may include somatic variants in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select best treatment.

Panels using next generation technology are currently available in the areas of cancer, cardiovascular disease, neurologic disease, psychiatric conditions, and for reproductive testing.[2-4] These panels are intuitively attractive to use in clinical care because they can screen for numerous variants within a single or multiple genes quickly, and may lead to greater efficiency in the work-up of genetic disorders. It is also possible that these "bundled" gene tests can be performed more cost effectively than direct sequencing, although this may not be true in all cases. However, panel testing also provides information on genetic variants that are of unclear clinical significance or which would not lead to changes in patient management.

One potential challenge of genetic panel testing is the availability of a large amount of ancillary genetic information, much of which has uncertain clinical consequences and management strategies. Identification of variants for which the clinical management is uncertain may lead to unnecessary follow-up testing and procedures, all of which have their own inherent risks.

Additionally, the design and composition of genetic panel tests have not been standardized. Composition of the panels is variable, and different commercial products for the same condition may test different sets of genes. The make-up of the panel is determined by the specific lab that has developed the test. In addition, the composition of any individual panel is likely to change over time, as new variants are discovered and added to the existing panels.

GENETIC COUNSELING

Due to the complexity of interpreting genetic test results, patients should receive pre- and post-test genetic counseling from a qualified professional when testing is performed to diagnose or predict susceptibility for inherited diseases. The benefits and risks of genetic testing should be fully disclosed to individuals prior to testing, and counseling concerning the test results should be provided.

REGULATORY STATUS

The majority of genetic panel tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Note: Separate Medical Policies may apply to some specific genetic tests and panels not addressed in the criteria below. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[5] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Genetic cancer susceptibility panels utilizing next generation sequencing are best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. The clinical utility of genetic panel testing refers to the likelihood that the panel will result in improved health outcomes.
For positive test results, the health benefits are related to interventions that reduce the risk of developing the disease, earlier or more intensive screening to detect and treat early disease symptoms, or interventions to improve quality of life.

- Alternatively, negative test results may prevent unnecessary intensive monitoring, invasive tests or procedures, or ineffective therapies.

For genetic panels that test for a broad number of variants, some components of the panel may be indicated based on the patient's clinical presentation and/or family history, while other components may not be indicated. The impact of test results related to non-indicated variants must be well-defined and take into account the possibility that the information may cause harm by leading to additional unnecessary interventions that would not otherwise be considered based on the patient's clinical presentation and/or family history.

Therefore, the focus of the following review is on evidence from well-designed controlled trials or large cohort studies that demonstrate the clinical utility of each panel test, i.e., the ability of results from the comprehensive genetic panels to:

1. Guide decisions in the clinical setting related to either treatment, management, or prevention; and

2. Improve health outcomes as a result of those decisions.

A limited body of literature exists on the potential clinical utility of available next generation sequencing (NGS) panels.

NONRANDOMIZED STUDIES

Desmond (2015) reported on an observational study assessing whether testing of hereditary cancer gene variants other than BRCA1/2 altered clinical management in a prospectively collected cohort of 1046 patients from three institutions who were negative for BRCA1/2.[6] Patients were tested with the 29-gene Hereditary Cancer Syndromes test (Invitae) or the 25-gene MyRisk test (Myriad Genetics). The investigators evaluated the likelihood of a post-test change in management considering gene-specific consensus management guidelines, gene-associated cancer risks, and personal and family history. Of this cohort, 40 patients (3.8%, 95% CI 2.8% to 5.2%) harbored deleterious variants, most commonly in moderate-risk breast and ovarian cancer genes and Lynch syndrome genes. Among 63 variant-positive patients, 20 were found to harbor variants in high-risk genes associated with detailed NCCN management guidelines which would change the pretest recommendations for screening and/or preventive surgery. However, the most common variants found were those in genes associated with low or moderately increased breast cancer risk (40 of 63 patients), where a change in management would be recommended for these patients in a minority of cases (10 of 40), involving either increased screening or preventive surgery. Since this study only reported anticipated changes in management, these variant-positive patients were not provided with these post-test recommendations. The investigators conceded that the potential clinical effect reported in this cohort is likely to apply only to an appropriately ascertained cohort, thereby limiting the generalizability of the results.

Kurian (2014) evaluated the information from a NGS panel of 42 cancer associated genes in women who had been previously referred for clinical BRCA1/2 testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012.[7] The authors aimed to assess concordance of the results of the panel with prior clinical sequencing, the prevalence of potentially clinically actionable results, and the downstream effects on cancer screening and risk reduction. Potentially actionable results were defined as pathogenic variants that cause recognized hereditary caner syndromes or have a published association with a two-fold or greater relative risk of breast cancer compared to average risk women. In total, 198 women participated in the study. Of these, 174 had breast cancer and 57 carried 59 germline BRCA variants. Testing with the panel confirmed 57 of 59 of the pathogenic BRCA variants; of the two others, one was detected but reclassified as a VUS and the other was a large insertion that would not be picked up by NGS panel testing. Of the women who tested negative for *BRCA* variants (n=141), 16 had pathogenic variants in other genes (11.4%). The affected genes were *ATM* (n=2), *BLM* (n=1), *CDH1* (n=1), *CDKN2A* (n=1), *MLH1* (n=1), *MUTYH* (n=5), *NBN* (n=2), *PRSS1* (n=1), and *SLX4* (n=2). Eleven of these variants had been previously reported in the literature and five were novel. 80% of the women with pathogenic variants in the non BRCA1/2 genes had a personal history of breast cancer. Overall, a total of 428 VUS were identified in 39 genes, among 175 patients.

Six women with variants in *ATM*, *BLM*, *CDH1*, *NBN* and *SLX4* were advised to consider annual breast MRIs because of an estimated doubling of breast cancer risk, and six with variants in CDH1, MLH1 and MUTYH were advised to consider frequent colonoscopy and/or endoscopic gastroduodenoscopy (once every 1 to 2 years) due to estimated increases in gastrointestinal cancer risk. One patient with a MLH1 variant consistent with Lynch syndrome underwent risk-reducing salpingo-oophorectomy and early colonoscopy which identified a tubular adenoma that was excised (she had previously undergone hysterectomy for endometrial carcinoma).

Mauer (2014) reported a single academic center's genetics program's experience with NGS panels for cancer susceptibility.[8] The authors conducted a retrospective review of the outcomes and clinical indications for the ordering of Ambry's next generation sequencing panels (BreastNext, OvaNext, ColoNext, and CancerNext) for patients seen for cancer genetics counseling from April 2012 to January 2013. Of 1,521 new patients seen for cancer genetics counseling, 1,233 (81.1%) had genetic testing. Sixty of these patients (4.9% of the total) had a next generation sequencing panel ordered, 54 of which were ordered as a second-tier test after single-gene testing was performed. Ten tests were cancelled due to out-of-pocket costs or previously identified variants. Of the 50 tests obtained, five were found to have a deleterious result (10%, compared with 131 [10.6%] of the 1,233 single-gene tests ordered at the same center during the study time frame). The authors report that of the 50 completed tests, 30 (60%) did not affect management decisions, 15 (30%) introduced uncertainty regarding the patients' cancer risks, and five (10%) directly influenced management decisions.

A number of other studies have evaluated the impact of panel testing on clinical management of a variety of conditions, including prostate cancer,[9] breast and/or ovarian cancer,[10-13] and non-specific hereditary cancers,[14] as well as genetic profiling of tumor tissue to guide cancer treatment.[15, 16] While some of these studies noted specific changes in medical management resulting from the testing, none of them evaluated whether these changes led to improvements in patient outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

A 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addresses the application of next-generation sequencing.[17] According to this statement:

> ASCO recognizes that concurrent multigene testing (i.e., panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUS) in a substantial proportion of patient cases. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history.
>
> This type of testing may be particularly useful in situations where there are multiple high-penetrance genes associated with a specific cancer, the prevalence of actionable mutations in one of several genes is high, and it is difficult to predict which gene may be mutated on the basis of phenotype or family history.
>
> So far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing- this heterogeneity presents a number of challenges. All panels include high-penetrance genes that are known to cause autosomal-dominant predisposition syndromes, but often include genes that are not necessarily linked to the disease for which the testing is being offered. There is uncertainty regarding the appropriate risk estimates and management strategies for families with unexpected mutations in high-penetrance genes when there is no evidence of the associated syndrome. Clinical utility remains the fundamental issue with respect to testing for mutations in moderate penetrance genes. It is not yet clear whether clinical management should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers. Early experience with panel-based testing indicates that a substantial proportion of tests identify a VUS in 1 or more genes, and VUSs are more common in broad-panel testing both because of the number of genes tested and because of the limited understanding of the range of normal variation in some of these genes.

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer (v.1.2023)[18] state the following regarding multi-gene testing:

- An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history

through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a P/LP [pathogenic/likely pathogenic] variant in a gene that will impact medical management for the individual or their at-risk family members.

- There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- Some individuals may carry P/LP germline variants in more than one cancer susceptibility gene; thus, consideration of a multi-gene panel for individuals already known to carry a single P/LP germline variant from phenotype-directed testing may be considered on a case-by-case basis, based on the degree of suspicion for there being additional variants.
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of P/LP variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history.
- It may be possible to refine risks associated with both moderate and high-penetrance genes, taking into account the influence of gene/gene or gene/environment interactions. In addition, certain P/LP variants in a gene may pose higher or lower risk than other P/LP variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their at-risk relatives.
- P/LP variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring if the partner is also a carrier.
- As more genes are tested, there is an increased likelihood of finding VUS, mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).
- There are significant limitations in interpretation of polygenic risk scores (PRSs). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including more diverse populations.

SUMMARY

Genetic test panels are available for many clinical conditions. Genetic test panels may be focused to a few genes or include a large number of genes. The advantage of genetic test panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of the genetic workup. A disadvantage of genetic test panels is that the results may provide information on genetic variants that are of unclear clinical significance, or which would not lead to changes in patient management. These results may potentially cause harm by leading to additional unnecessary interventions and anxiety that would not otherwise be considered based on the patient’s clinical presentation and/or family history. There is not enough research to show that the genetic panels listed in the policy criteria can lead to better health outcomes for patients. When there is not enough research to show that all genes and/or gene variants in a genetic test panel may be useful for guiding patient management to improve health outcomes, the entire genetic test panel is considered investigational.

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CODES

NOTE: There are few specific codes for molecular pathology testing by panels. If the specific analyte is listed with a CPT code, the specific CPT code should be reported. If the specific analyte is not listed with a specific CPT code, unlisted code 81479 should be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

Codes	Number	Description
CPT	0008U	Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, pbp1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue or fecal sample, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin
	0010U	Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate
	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
	0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
	0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)]
	0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)]
	0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence

Codes	Number	Description
		analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) (Use 0130U in conjunction with 81435, 0101U)
	0131U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)
	0132U	Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)
	0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) (Use 0133U in conjunction with 81162)
	0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure) (Use 0134U in conjunction with 81162, 81432, 81435)
	0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure) (Use 0135U in conjunction with 81162)
	0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
	0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
	0175U	
	0216U	Neurology (inherited ataxias), genomic DNA sequence analysis of 12 common genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variant
	0217U	Neurology (inherited ataxias), genomic DNA sequence analysis of 51 genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
	0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 22 genes, blood, buccal swab, or amniotic fluid
	0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid
	0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 60 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid, comprehensive
	0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), analysis of 9 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, by next

Codes	Number	Description
		generation sequencing and PLAU by array comparative genomic hybridization), blood, buccal swab, or amniotic fluid
	0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 62 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid
		Hematology (inherited thrombocytopenia), genomic sequence analysis of 42 genes, blood, buccal swab, or amniotic fluid
	0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 40 genes and duplication/deletion of PLAU, blood, buccal swab, or amniotic fluid
	0278U	Hematology (genetic thrombosis), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid
	0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
	0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
	0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
	0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
	0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
	0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes
	0474U	Hereditary pan-cancer (eg, hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene
	0475U	Hereditary prostate cancer related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer
	0476U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes
	0477U	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes

Codes	Number	Description
	0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status
	0533U	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function
	81105	Human platelet antigen 1 genotyping (HPA-1), ITGB3 (integrin, BETA 3 [platelet glycoprotein iiia], antigen CD61 [gpiiia]) (eg, neonatal alloimmune thrombocytopenia [nait], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)
	81106	Human platelet antigen 2 genotyping (hpa-2), GP1BA (glycoprotein ib [platelet], alpha polypeptide [GPIBA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, hpa-2a/b (T145M)
	81107	Human platelet antigen 3 genotyping (HPA-3), ITGA2B (integrin, ALPHA 2b [platelet glycoprotein iib of iib/iiia complex], antigen CD41 [GPIIB]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S)
	81108	Human platelet antigen 4 genotyping (HPA-4), ITGB3 (integrin, BETA 3 [platelet glycoprotein IIIA], antigen CD61 [GPIIIA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)
	81109	Human platelet antigen 5 genotyping (HPA-5), ITGA2 (integrin, ALPHA 2 [CD49B, ALPHA 2 subunit of VLA-2 receptor] [GPIA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E))
	81110	Human platelet antigen 6 genotyping (HPA-6W), ITGB3 (integrin, BETA 3 [platelet glycoprotein IIIA, antigen CD61] [GPIIIA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)
	81111	Human platelet antigen 9 genotyping (HPA-9W), ITGA2B (integrin, ALPHA 2B [platelet glycoprotein IIB of IIB/IIIA complex, antigen CD41] [GPIIB]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M)
	81112	Human platelet antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [Nait], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
	81176	;targeted sequence analysis (eg, EXON 12)
	81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants
	81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	;known familial variants
	81203	;duplication/deletion variants
	81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)

Codes	Number	Description
	81206	*BCR/ABL1 (t(9;22))* (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
	81207	;minor breakpoint, qualitative or quantitative
	81208	;other breakpoint, qualitative or quantitative
	81209	*BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
	81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
	81220	*CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81221	;known familial variant
	81222	;duplication/deletion variants
	81223	;full gene sequence
	81224	;intron 8 poly-T analysis (eg, male infertility)
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81240	*F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	*F5 (coagulation factor V)* (eg, hereditary hypercoagulability) gene analysis, Leiden variant
	81242	*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
	81243	*FMR1 (Fragile X messenger ribonucleoprotein 1)* (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
	81245	*FLT3 (fms-related tyrosine kinase 3)* (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
	81246	;tyrosine kinase domain (TKD) variants (eg, D835, I836)
	81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, a, a-)

Codes	Number	Description
	81248	;known familial variant(s)
	81249	;full gene sequence
	81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
	81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
	81252	*GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)* (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	;known familial variant
	81254	*GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)* (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
	81256	*HFE (hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
	81257	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
	81261	*IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
	81262	;direct probe methodology (eg, Southern blot)
	81263	*IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
	81264	*IGK@ (Immunoglobulin kappa light chain locus)* (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
	81270	*JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81272	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)*
	81273	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)*
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81287	*MGMT (O-6-methylguanine-DNA methyltransferase)* (eg, glioblastoma multiforme), promoter methylation analysis
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

Codes	Number	Description
	81291	*MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	;known familial variants
	81294	;duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	;known familial variants
	81297	;duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	;known familial variants
	81300	;duplication/deletion variants
	81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
	81303	;known familial variants
	81304	;duplication/deletion variants
	81310	*NPM1 (nucleophosmin)* (eg, acute myeloid leukemia) gene analysis, exon 12 variants
	81311	*NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)*
	81314	*PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)*
	81315	*PML/RARalpha, (t(15;17))*, *(promyelocytic leukemia/retinoic acid receptor alpha)* (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
	81316	;single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	;known familial variants
	81319	;duplication/deletion variants
	81321	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, *PTEN* hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	;known familial variants
	81323	;duplication/deletion variants
	81324	*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	;full sequence analysis
	81326	;known familial variants
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)

Codes	Number	Description
	81331	*SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome),
	81332	*SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1)* (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
		TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using
	81342	*TRG@ (T cell antigen receptor, gamma)* (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
		Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities
	81350	*UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1)* (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (eg, *28, *36, *37)
	81355	*VKORC1 (vitamin K epoxide reductase complex, subunit 1)* (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
	81400	Molecular pathology procedure, Level 1
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81408	Molecular pathology procedure, Level 9
	81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	~~81433~~	~~Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11~~ (Deleted 01/01/2025)
	81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A

Codes	Number	Description
	81437	Hereditary neuroendocrine tumor-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants; genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
	~~81438~~	~~Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL~~ (Deleted 01/01/2025)
	81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
	81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
	81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection

Codes	Number	Description
	81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81471	;duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *October 2013*

Regence

Medical Policy Manual Genetic Testing, Policy No. 65

Genetic Testing for Methionine Metabolism Enzymes, including MTHFR

Effective: March 1, 2025

Next Review: November 2025
Last Review: January 2025

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

Genes involved in methionine metabolism, particularly *MTHFR*, have been associated with a variety of conditions, including depression, epilepsy, thrombophilia, and gastrointestinal conditions.

MEDICAL POLICY CRITERIA

Genetic testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, or *MMADHC* genes is considered **investigational** for all indications.

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

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Medical Policy Manual, Genetic Testing, Policy No. 20
2. Genetic Testing for Diagnosis and Management of Behavioral Health Conditions, Medical Policy Manual, Genetic Testing, Policy No. 53
3. Evaluating the Utility of Genetic Panels, Medical Policy Manual, Genetic Testing, Policy No. 64
4. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80

BACKGROUND

Methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*), methionine synthase reductase (*MTRR*), cobalamin reductase (*MMADHC),* and cystathione β-synthase (*CBS)* are genes that provide instructions to make the respective enzymes MTHFR, MTR, MTRR, MMADHC, and CBS, which play a role in converting the amino acid homocysteine (Hcy) to methionine. When abnormal copies of the genes are present, they may result in reduced function of the enzyme, leading to elevated homocysteine levels. Abnormally high levels of Hcy in the blood have been associated with several chronic illnesses, such as attention-deficit/hyperactivity disorder (ADHD), cardiovascular disease, epilepsy, headache, gastrointestinal symptoms and conditions, psychiatric disorders, osteoporosis, and Parkinson's disease.

Genetic testing for abnormalities in the *MTHFR*, *MTR*, *MTRR*, *MMADHC* and *CBS* genes has been proposed for several purposes:

- Diagnose or assess disease risk in symptomatic individuals;
- Screen for disease risk in asymptomatic individuals (i.e., general health screening);
- Direct treatment decisions (e.g., nutritional supplementation).

REGULATORY STATUS

Four genotyping tests for variations in the *MTHFR* gene cleared by the U.S. Food and Drug Administration (FDA) were identified as the Verigene MTHFR Nucleic Acid Test (Nanosphere, Inc.), eSensor MTHFR Genotyping Test (Osmetech Molecular Diagnostics), Invader MTHFR 677 (Hologic, Inc.), and Invader MTHFR 1298 (Hologic, Inc.).[1] Genotyping for other components may be offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant or variation that is present or in excluding a variant or variation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and

3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

For some indications, the published literature regarding genetic testing for homocysteine-related variants in the *CBS*, *MTHFR*, *MTR*, *MTRR*, or *MMADHC* genes is limited to association studies. Studies of genetic associations aim to test whether single-locus alleles or genotype frequencies differ between two groups of individuals (usually diseased subjects and healthy controls). For many indications, evidence has accumulated which supports an association between a homocysteine-related variant and the condition or symptom. However, there is limited evidence to establish a causal relationship or to demonstrate how treatment based on gene testing leads to improved health outcomes related to any condition.

Current guidelines for establishing causality require direct evidence which demonstrates that testing-based treatment is greater than the combined influence of all confounding factors for the given condition.[3] This direct evidence could come from well-designed, randomized controlled trials. Evidence from non-randomized trials may also be considered when testing-based treatment results in an improvement of symptoms which is so sizable that it rules out the combined effect of all other possible causes of the condition. Currently, no published studies have been identified that demonstrate the clinical utility of homocysteine-related variant testing for any associated disease or condition. In order to isolate the independent contribution of homocysteine-related variant testing on health outcomes, studies which control for confounding factors are essential. Large, well-designed, randomized controlled trials (RCTs) with adequate follow-up are needed.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Examples of studies that investigated the association between the *MTHFR* gene variants and attention-deficit hyperactivity disorder (ADHD) are described below.

Association Studies

Table 1. Evidence for Genes Associated with ADHD

Gene(s)	Condition(s)	Evidence	Conclusions
MTHFR	ADHD	Ergul (2012), case-control[4] Gokcen (2011), case-control [5]	No association between the *MTHFR* 677T allele, *MTHFR* 1298C allele, and ADHD was found. There were no statistically significant differences in genotype distributions of the C677T alleles between the ADHD and the control groups.
MTHFR	ADHD after acute lymphoblastic leukemia	Krull (2008), cohort[6]	The A1298C genotype lead to a 7.4-fold increase in diagnosis, compared with a 1.3-fold increase for the C677T genotype.
MTHFR	ADHD Myelomeningocele	Spellicy (2012), cohort[7]	A positive association was identified between the SNV rs4846049 in the 3'-untranslated region of the *MTHFR* gene and the attention-deficit hyperactivity disorder phenotype in myelomeningocele participants

SNV: Single nucleotide variant

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with ADHD.

CARDIOVASCULAR DISEASE

Randomized Controlled Trials

An RCT by Qin (2020) evaluated the interaction between *MTHFR* genotypes and serum folate and vitamin B_{12} on risk of first ischemic stroke in patients randomized to receive enalapril with or without folic acid in the China Stroke Primary Prevention Trial (CSPPT).[8] CSPPT was a double-blind, RCT conducted from May 19, 2008, to August 24, 2013 in multiple communities in China. The study and included men and women (n=20,499) between 45 and 75 years of age with hypertension, defined as resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Participants were randomized to receive tablets containing either 10 mg enalapril alone (n=10,256) or 10 mg enalapril plus 0.8 mg folic acid (n=10,243) to be taken daily, for a median duration of 4.5 years. There was no overall association found between baseline serum folate and B_{12} levels and risk of stroke in the enalapril-only group. Folic acid supplementation was associated with a reduction in total Hcy (tHcy) levels and stroke risk in patients with baseline low folate and B_{12} levels. Overall, there was no difference in stroke reduction between the MTHFR 677 CC and TT genotypes. However, subgroup analysis showed that the reduction in risk was greater for those with low baseline low folate and B_{12} levels for those with a CC genotype, while for those with a TT genotype, risk reduction was the greatest for those with the highest baseline folate and B_{12} levels.

Association Studies

Examples of studies that address the association of the *CBS* and *MTHFR* genes with cardiovascular disease are described below.

Table 2. Evidence for Genes Associated with Cardiovascular Disease

Gene(s)	Condition(s)	Evidence	Conclusions
MTHFR and *CBS*	Venous thrombosis	Amaral (2017), cohort study[9]	Patients with *MTHFR* 1298CC and *CBS* haplotype 844ins68/T833C homozygotes were at increased risk for venous thrombosis. Significant interactions were identified among the *MTHFR* C677T, *MTHFR* A1298C and *CBS* haplotype 844ins68/T833C variants and Hcy levels.
MTHFR	Congenital heart disease	Yuan (2017), meta-analysis[10] Horita (2017), case-control[11] Zhao (2012), case-control [12]	In the meta-analysis, five studies were considered low-quality and 16 were considered high-quality. The analysis showed a significant association between *MTHFR* C677T and congenital heart disease (CHD). No association was found between variants and coronary heart disease or coronary atherosclerosis. Individuals carrying the heterozygous CG and homozygous GG genotypes had a 15%

Gene(s)	Condition(s)	Evidence	Conclusions
			reduced risk to develop CHD than the CC genotype carriers. Additional stratified analyses demonstrated that *CBS* -4673C>G is significantly related to septation defects and conotruncal defects
MTHFR	Congenital heart defects	Noori (2017), case-control[13] Khatami (2017), case-control[14]	SNVs in the *MTHFD1, eNOS, CBS*, and *ACE* genes were significantly higher in the patients than in controls. The presence of the TT genotype of C677Twas associated with the highest risk of congenital heart defects and ventricular septal defect Significantly higher occurrences of the AG and GG A66G variant, but not the TT C677T variant, occurred in patients as compared to controls. Heterozygous (AG) and homozygous (GG) A66G variants were significantly associated with congenital heart defects and tetralogy of Fallot.
MTHFR	Stroke	Dong (2021), meta-analysis[15] Hou (2018), case-control[16] Zhao (2017), randomized controlled trial[17] Xu (2017), cohort[18] He (2017), case-control[19] Wald (2002), meta-analysis[20]	*MTHFR* A1298C alleles were significantly associated with stroke under the C allelic genetic model (OR 1.19, 95% CI 1.07 to1.32, p=0.001), as well as dominant and recessive models. Subgroup analysis showed this association only in Asian populations. The frequency of T allele of *MTHFR* C677T (rs1801133) was significantly higher in ischemic stroke patients than in controls and the presence of the MTHFR T allele was an independent risk factor for ischemic stroke even after adjusting for conventional risk factors. Folic acid intervention significantly reduced stroke risk in participants with CC/CT genotypes and high homocysteine levels. *MTHFR* genotype alone had did not significantly associate with mortality, but the tHcy-mortality association was significantly stronger in the CC/CT genotype than in the TT genotype. When compared to the homozygous TT genotype, *MTHFR* rs868014 TC and CC genotypes were significantly associated with increased risk of ischemic stroke. The seven *MTHFR* studies of stroke (1217 cases, mean age at event 63 years) yielded

Gene(s)	Condition(s)	Evidence	Conclusions
			relatively few data, so the confidence interval for the summary result was wide.
CBS	Stroke	Hendrix (2017), case-control [21] Ding (2012), meta-analysis [22]	Significant associations between *CBS* T833C genetic variant and risk of stroke were observed in most genetic models. In the subgroup analysis based on ethnicity, significant associations were observed in most genetic models in Chinese but not in Caucasian. The insertion allele of the 844ins68 insertion variant was significantly associated with aneurysmal subarachnoid hemorrhage. The GG genotype of the CBS G/A single nucleotide variant (rs234706) was independently associated with poor functional outcome at discharge and last follow-up. No association was found with clinical vasospasm or delayed cerebral ischemia (DCI).
BHMT1, BHMT2, *CBS*, *CTH*, *MTHFR*, *MTR*, *MTRR*, *TCN1*, and *TCN2*	Stroke	Hsu (2011), cohort [23]	Only *TCN2* SNV rs731991 was associated with recurrent stroke risk
MTRR	Acyanotic congenital heart disease in children	Hassan (2017), case-control[24]	Statistically significant differences in genotype frequencies were found for both variants, with more TT and GG genotypes of the C524T and A66G variants, respectively in the patient populations as compared to controls
MTHFR	Rheumatoid arthritis and atherosclerosis	Adb El-Aziz (2017), cohort[25]	The T variant had significantly greater chances of developing rheumatoid arthritis and atherosclerosis. The *MTHFR* TT genotype was an independent risk factor for thick carotid intima-media and was associated with higher Hcy levels.
MTHFR	Coronary artery disease	Conkbayir (2017), cohort[26] Bickel (2016) [27] van Meurs (2013), meta-analysis [28]	Statistically significant associations were found between the *MTHFR* C677 wild-type allele and a decreased rate of high LDL cholesterol ($p<0.05$) and between the *HPA-1* a/b variant and an increased rate of high total cholesterol levels ($p<0.05$) While Hcy levels were associated with cardiovascular events and *MTHFR* SNVs were associated with Hcy levels ($p<0.001$), the SNVs

Gene(s)	Condition(s)	Evidence	Conclusions
			had no impact on coronary artery disease prognosis Individuals within the highest 10% of the genotype risk score (GRS) had 3-µmol/L higher mean tHcy concentrations than did those within the lowest 10% of the GRS ($p=1\times10^{-36}$). The GRS was not associated with risk of CAD
MTHFR	Hypertension	Liu (2017), cohort[29] Tang (2016), case-control[30] Ghogomu (2016), case-control[31] Armani-Midoun (2016), case-control [32]	In patients with mild-to-moderate essential hypertension the TT *MTHFR* 677 genotype carriers had higher risk of hypercholesterolemia and abnormal low-density lipoprotein cholesterol than those with the CC and CT genotypes. No significant gene-disease association was found in an Algerian population A higher frequency of the *MTHFR* 677T allele was found in patients with H-type hypertension compared to those with common hypertension. A significant association between the *MTHFR* variant and hypertension was found in Camaroonian patients.
MTHFR	Cardiovascular disease	Grarup (2013), cohort[33] Raina (2016), case-control [34] Chen, case-control[35] Wald (2002)	Authors did not find consistent association of the variants with cardiovascular diseases C677T and *MTR* A2756G were linked to cardiovascular disease an association between *MTHFR* C677T and coronary heart disease
MTHFR	Heart failure	Strauss (2017), case-control [36]	Hyperhomocysteinemia and the *MTHFR* 677TT/1298AA, 677CC/1298CC genotypes were associated heart failure, regardless of etiology.
MTHFR	abdominal aortic aneurysm	Liu (2016), meta-analysis[37]	An analysis of 12 case-control studies with a total of 3,555 cases and 6,568 controls found no significant association between the *MTHFR* C677T variant and AAA risk in the overall population and within Caucasian or Asian subpopulations. Significant associations were found in other subgroups, including cases with a mean age < 70 years.
MTHFR	Cervico-cerebral artery dissection	Ruiz-Franco (2016), case-control[38]	A higher prevalence of the TT genotype was seen among cases verses controls.

Gene(s)	Condition(s)	Evidence	Conclusions
MTHFR	atherosclerosis	Lin (2016), case-control[39] Heidari (2016), case-control[40]	There was a higher prevalence of the TT genotype in cases LINE-1 methylation levels were lower in cases than controls, and that this methylation was also lower in carriers of the *MTHFR* 677T allele An association between *MTHFR* genotype and atherosclerosis was found in Iranian patients.
MTHFR	myocardial infarction	Hmimech (2016), case-control[41]	No significant gene-disease association was found for *MTHFR* C677T.
MTHFR	peripheral artery disease	Liu (2021), meta-analysis[42]	An association between *MTHFR* C677T homozygosity and peripheral arterial disease were found, but there was no significant association between the T allele carrier and peripheral arterial disease.

SNV: single nucleotide variant; tHcy: total homocysteine

Clinical Utility

Additional meta-analysis, systematic reviews and cohort studies were identified which evaluated the associated of *MTHFR* and *CBS* variants and cardiovascular disease[43-50]; however, no studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with cardiovascular disease.

DIABETES

Studies describing the association between *MTHFR* variants and diabetes and diabetes-associated conditions are described.

Association Studies

Table 3. Evidence for Genes Associated with Diabetes

Gene(s)	Condition(s)	Evidence	Conclusions
MTHFR	Diabetic nephropathy	Ramanathan (2017), case-control [51]	C677T and A1298C *MTHFR* variants were associated with diabetic C677T was significantly associated with advanced stage chronic kidney disease
MTHFR	Diabetic neuropathy	Kakavand Hamidi (2017), case-control [52] Jiménez-Ramírez (2017), case-control[53]	677C>T variant was significantly less frequent in patients with neuropathy in two studies Results regarding the association of the 1298A>C variant and neuropathy were mixed
ACE, *FABP2*, *MTHFR*, and *FTO*	Dyslipidemia	Raza (2017), case-control[54]	*ACE* and *MTHFR* variants were significantly associated with type 2 diabetes regardless of dyslipidemia status *FABP2* and *FTO* variants were significantly associated with type 2 diabetes without dyslipidemia

ENZYME DEFICIENCY

Studies that address the clinical utility of gene testing for enzyme deficiency (enzymes made by the *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* genes) and gene testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* were not identified.

EPILEPSY

Examples of studies describing the association between *MTHFR* variants and epilepsy are described below.

Association Studies

Ullah (2018) assessed the association between *MTHFR* variants and seizure control in epileptic patients treated with carbamazepine.[55] Patients included were from the Pakhtun population of Khyber Pakhtunkhwa. Poor seizure control was significantly more likely in patients with heterozygous variants (677CT and 1298AC) of *MTHFR* at both three and six months following the initiation of therapy. However, no statistically significant association was identified in dose and plasma level of carbamazepine between different *MTHFR* genotypes or between responder and non-responder patients.

Scher (2011) studied whether the *MTHFR* C677T or A1298C variants are associated with risk of epilepsy including post-traumatic epilepsy (PTE) in a representative military cohort.[56] Authors randomly selected 800 epilepsy patients and 800 matched controls based on ICD-9-CM diagnostic codes. The odds of epilepsy were increased in subjects with the TT versus CC genotype (crude odds ratio [OR] 1.52, 95% confidence interval [CI] 1.04 to 2.22, p=0.031; adjusted OR 1.57, 95% CI 1.07 to 2.32, p=0.023). In the sensitivity analysis, risk was most evident for patients with repeated rather than single medical encounters for epilepsy (crude OR 1.85, 95% CI 1.14 to 2.97, p=0.011, adjusted OR 1.95 95% CI 1.19 to 3.19, p=0.008), and particularly for PTE (crude OR 3.14, 95% CI 1.41 to 6.99, p=0.005; adjusted OR 2.55. 95% CI 1.12 to 5.80, p=0.026). Authors conclude a potential role for the common *MTHFR* C677T variant as predisposing factors for epilepsy including PTE.

Semmler (2013) aimed to determine whether there was a pharmacogenetic interaction between folate, vitamin B12 and genetic variants and Hcy plasma level in antiepileptic drug (AED)-treated patients.[57] In this single center study, authors measured Hcy, folate and vitamin B12 plasma levels in a population of 498 AED-treated adult patients with epilepsy. In addition, authors analyzed the genotypes of seven common genetic variants of Hcy metabolism: *MTHFR* C677CT and A1298C, *MTR* c.2756A>G, dihydrofolate reductase (*DHFR*) c.594+59del19bp, *CBS* c.844_855ins68, transcobalamin 2 (*TCN2*) C776G and *MTRR* G66A. Authors concluded, in AED-treated patients, folate and vitamin B12 play important roles in the development of hyperhomocysteinemia, whereas genetic variants of Hcy metabolism do not and thus do not contribute to the risk of developing hyperhomocysteinemia during AED treatment.

Coppola (2012) assessed the role of AEDs and *MTHFR* C677T on tHcy in pediatric patients with epilepsy treated for at least six months with various treatment regimens protocols including the newer AEDs.[58] The study group was composed of 78 patients (35 males, 43 females), aged between 3 and 15 years (mean 8.9 years). Thirty-five patients were taking AED monotherapy, 43 polytherapy. Sixty-three healthy sex- and age-matched children and adolescents served as controls. The mean tHcy value in the patient group was higher than the

mean value in the control group (12.11 ± 7.68 µmol/L vs. 7.4±4.01 µmol/L, p<0.01). DNA analysis for the *MTHFR* C677T variant showed the CT genotype in 46%, CC in 35% and TT in 17.8% of cases. Decreased folic acid serum levels significantly correlated with increased tHcy levels (p<0.003). The authors concluded that their study confirmed the association between hyperhomocysteinemia and epilepsy. The elevation of tHcy is essentially related to low folate levels. Correction of poor folate status, through supplementation, remains the most effective approach to normalize tHcy levels in patients on AED mono- or polytherapy.

Additional association studies[59-61] were identified which evaluated the association of *MTHFR* variants and epilepsy.

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with epilepsy.

HEADACHE

Association studies were limited to the *MTHFR*, *MTR*, and *MTRR* gene variants and headache.

Systematic Reviews

Schürks (2010) conducted a systematic review and meta-analysis on the association of *MTHFR* C677T and ACE D/I variants and migraine including aura status.[62] Thirteen studies investigated the association between the *MTHFR* C677T variant and migraine. The TT genotype was associated with an increased risk for any migraine, which only appeared for migraine with aura (pooled OR 1.48, 95% CI 1.02 to 2.13), but not for migraine without aura. Nine studies investigated the association of the ACE D/I variant with migraine. The II genotype was associated with a reduced risk for migraine with aura (pooled OR 0.71, 95% CI 0.55 to 0.93) and migraine without aura (pooled OR 0.84, 95% CI 0.70 to 0.99). Extractable data did not allow investigation of gene-gene interactions. Authors concluded that the *MTHFR* 677TT genotype is associated with an increased risk for migraine with aura among non-Caucasian populations.

Samaan (2011) investigated the effect of *MTHFR* C677T on propensity for migraine and to perform a systematic review and meta-analysis of studies of *MTHFR* and migraine to date.[63] Individuals with migraine (n=447) were selected from the Depression Case Control (DeCC) study to investigate the association between migraine and *MTHFR* C677T single nucleotide variant (SNV) rs1801133 using an additive model compared to non-migraineurs adjusting for depression status. A meta-analysis was performed and included 15 studies of *MTHFR* and migraine. *MTHFR* C677T variant was associated with migraine with aura (MA) (OR 1.31, 95% CI 1.01 to 1.70, p=0.039) that remained significant after adjusting for age, sex and depression status. A meta-analysis of 15 case-control studies showed that T allele homozygosity is significantly associated with MA (OR 1.42, 95% CI 1.10 to 1.82) and total migraine (OR 1.37, 95% CI 1.07 to 1.76), but not migraine without aura (OR 1.16, 95% CI 0.36 to 3.76). In studies of non-Caucasian population, the TT genotype was associated with total migraine (OR 3.46, 95% CI 1.22 to 9.82), whereas in studies of Caucasians this variant was associated with MA only (OR 1.28, 95% CI 1.002 to 1.63). Authors concluded that *MTHFR* C677T is associated with MA in individuals selected for depression study.

Association Studies

The following association studies were published following the search dates of the above systematic reviews.

Menon (2012) examined the genotypic effects of *MTHFR* and *MTRR* gene variants on the occurrence of migraine in response to vitamin supplementation.[64] Authors used a six-month randomized, double-blinded placebo-controlled trial of daily vitamin B supplementation (B6, B9 and B12) on reduction of Hcy and of the occurrence of migraine in 206 female patients diagnosed with migraine with aura. Vitamin supplementation significantly reduced Hcy levels ($p<0.001$), severity of headache in migraine ($p=0.017$) and high migraine disability ($p=0.022$) in migraineurs compared with the placebo effect ($p>0.1$). When the vitamin-treated group was stratified by genotype, the C allele carriers of the *MTHFR* C677T variant showed a higher reduction in Hcy levels ($p<0.001$), severity of pain in migraine ($p=0.01$) and percentage of high migraine disability ($p=0.009$) compared with those with the TT genotypes. Similarly, the A allele carriers of the *MTRR* A66G variants showed a higher level of reduction in Hcy levels ($p<0.001$), severity of pain in migraine ($p=0.002$) and percentage of high migraine disability ($p=0.006$) compared with those with the GG genotypes. Genotypic analysis for both genes combined indicated that the treatment effect modification of the *MTRR* variant was independent of the *MTHFR* variant. Authors concluded that vitamin supplementation is effective in reducing migraine.

Roecklein (2013) performed a haplotype analysis of migraine risk and *MTHFR*, *MTR*, and *MTRR*.[65] Study participants are from a random sub-sample participating in the population-based AGES-Reykjavik Study, including subjects with non-migraine headache (n=367), migraine without aura (n=85), migraine with aura (n=167), and no headache (n=1,347). Authors concluded that haplotype analysis suggested an association between *MTRR* haplotypes and reduced risk of migraine with aura.

Essmeister (2016) performed a study to confirm reports that *MTHFR* C677T and an ACE variant increased susceptibility to migraines.[66] There were 420 migraine patients and 258 controls included in the study, which ultimately found no significant associations between the variants and any type of migraine.

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with headache.

COLORECTAL CANCER

Association studies on gastrointestinal symptoms and conditions were limited to the *MTHFR*, *MTR*, *MTRR*, and the *CBS* genes.

Systematic Reviews

Wu (2015) performed a meta-analysis to determine the association between *MTRR* A66G variant and colorectal cancer (CRC) susceptibility, including a total of 6,020 cases and 8,317 controls in 15 studies.[67] Increased risk of CRC was observed, when using the allele model (G vs A: $p=0.01$, OR 1.07, 95% CI 1.02 to 1.12), the genotype model (GG vs AA: $p=0.006$, OR 1.15, 95% CI 1.04 to 1.28). When using the genotype model, increased risk of CRC was observed when using the dominant model (GG+GA vs AA: OR 1.11, 95% CI 1.01 to 1.22, $p=0.04$) and the recessive model (GG vs GA+AA: OR 1.08, 95% CI 1.00 to 1.17, $p=0.04$).

Ethnicity-specific analysis determined that these associations are significant among Caucasians, but not East Asians.

Figueiredo (2013) note that over 60 observational studies primarily in non-Hispanic White populations have been conducted on selected genetic variants in specific genes, *MTHFR*, *MTR*, *MTRR*, *CBS*, *TCNII, RFC, GCPII, SHMT, TYMS*, and *MTHFD1*. These include five meta-analyses on *MTHFR* C677T (rs1801133) and *MTHFR* C1298T (rs1801131); two meta-analyses on *MTR* A2756C (rs1805087); and one for *MTRR* A66G (rs1801394).[68] In this meta-analysis authors observed some evidence for *SHMT* C1420T (rs1979277) (OR 0.85, 95% CI 0.73 to 1.00 for TT v. CC) and *TYMS* 5' 28 bp repeat (rs34743033) and CRC risk (OR 0.84, 95% CI 0.75 to 0.94 for 2R/3R v. 3R/3R and OR 0.82, 95% CI 0.69 to 0.98 for 2R/2R v. 3R/3R). Authors conclude in order to gain further insight into the role of folate variants in colorectal neoplasia, incorporating measures of the metabolites, including B-vitamin cofactors, Hcy and S-adenosylmethionine, and innovative statistical methods to better approximate the folate one-carbon metabolism pathway are necessary.

Teng (2013) investigated the association between the *MTHFR* C677T variant and the risk of colorectal cancer in a meta-analysis[69]. Overall, 71 publications including 31,572 cases and 44,066 controls were identified. The *MTHFR* C677T variant genotypes are significantly associated with increased risk of colorectal cancer. In the stratified analysis by ethnicity, significantly increased risks were also found among Caucasians for CC vs TT (OR 1.076, 95% CI 1.008 to 1.150, I^2=52.3%), CT vs TT (OR 1.102, 95%CI 1.032 to 1.177, I^2=51.4%) and dominant model (OR 1.086, 95%CI 1.021 to 1.156, I^2=53.6%). Asians for CC vs TT (OR1.226, 95% CI1.116 to 1.346, I^2=55.3%), CT vs TT (OR 1.180, 95% CI 1.079 to 1.291, I^2 =36.2%), recessive (OR 1.069, 95% CI 1.003 to 1.140, I^2=30.9%) and dominant model (OR 1.198, 95% CI 1.101 to 1.303, I^2=52.4%), and mixed populations for CT vs TT (OR 1.142, 95% CI 1.005 to 1.296, I^2=0.0%). However, no associations were found in Africans for all genetic models. Authors concluded that this meta-analysis suggests that the *MTHFR* C677T variant increases the risk for developing colorectal cancer, however no causality is noted.

Theodoratou (2012) reported on the first comprehensive field synopsis and creation of a parallel publicly available and regularly updated database (CRCgene) that cataloged all genetic association studies on colorectal cancer (http://www.chs.med.ed.ac.uk/CRCgene/).[70] Authors extracted data from 635 publications reporting on 445 variants in 110 different genes. Authors identified 16 independent variants at 13 loci (*MUTYH*, *MTHFR*, *SMAD7*, and common variants tagging the loci 8q24, 8q23.3, 11q23.1, 14q22.2, 1q41, 20p12.3, 20q13.33, 3q26.2, 16q22.1, and 19q13.1) to have the most highly credible associations with colorectal cancer, with all variants except those in *MUTYH* and 19q13.1 reaching genome-wide statistical significance in at least one meta-analysis model. Authors identified less-credible (higher heterogeneity, lower statistical power, BFDP>0.2) associations with 23 more variants at 22 loci. The meta-analyses of a further 20 variants for which associations have previously been reported found no evidence to support these as true associations.

Taioli (2009) performed both a meta-analysis (29 studies: 11,936 cases, 18,714 controls) and a pooled analysis (14 studies: 5,068 cases, 7,876 controls) of the C677T *MTHFR* variant and CRC, with stratification by racial/ethnic population and behavioral risk factors.[71] There were few studies on different racial/ethnic populations. The overall meta-analysis odds ratio for CRC for persons with the TT genotype was 0.83 (95% CI 0.77 to 0.90). An inverse association was observed in whites (OR 0.83, 95% CI 0.74 to 0.94) and Asians (OR 0.80, 95% CI 0.67 to 0.96) but not in Latinos or blacks. Similar results were observed for Asians, Latinos, and blacks in

the pooled analysis. The inverse association between the *MTHFR* 677TT genotype and CRC was not significantly modified by smoking status or body mass index; however, it was present in regular alcohol users only. Authors concluded that the *MTHFR* 677TT genotype seems to be associated with a reduced risk of CRC, but this may not hold true for all populations.

Association Studies

The following association studies were published following the search dates of the above systematic reviews.

Morishita (2018) assessed the association between variants in *MTR, MTRR, MTHFR,* and *SHMT* and risk of weight loss in patients with gastrointestinal cancers.[72] Clinical data from 59 patients with gastrointestinal cancers who visited the outpatient clinic for chemotherapy were analyzed. Weight loss of more than 5% or more than 10% over the first six months after the initiation of chemotherapy was assessed and no significantly association with the examined variants was identified.

Ding (2013), addressing the issue that studies on the association between *MTR* A2756G variant and CRC and colorectal adenoma (CRA) remain conflicting, conducted a meta-analysis of 27 studies, including 13,465 cases and 20,430 controls for CRC, and 4,844 cases and 11,743 controls for CRA.[73] . Potential sources of heterogeneity and publication bias were also systematically explored. Overall, the summary odds ratio of G variant for CRC was 1.03 (95% CI 0.96 to 1.09) and 1.05 (95% CI 0.99 to 1.12) for CRA. No significant results were observed in heterozygous and homozygous when compared with wild genotype for these variants. In the stratified analyses according to ethnicity, source of controls, sample size, sex, and tumor site, no evidence of any gene-disease association was obtained. Results from the meta-analysis of four studies on *MTR* stratified according to smoking and alcohol drinking status showed an increased CRC risk in heavy smokers (OR 2.06, 95% CI 1.32 to 3.20) and heavy drinkers (OR 2.00, 95% CI 1.28 to 3.09) for G allele carriers. This meta-analysis suggested that the *MTR* A2756G variant is not associated with CRC/CRA susceptibility, and that gene-environment interaction may exist.

Cheng (2015) investigated the association between SNVs in thirty folate-mediated one-carbon metabolism genes and CRC in 821 CRC case-control matched pairs in the Women's Health Initiative Observational Study cohort.[74] A statistically significant association was observed between CRC risk and a functionally defined candidate SNV (rs16879334, p.P450R) in *MTRR* (OR 0.61, 95% CI 0.4 to 0.93, p=0.02).

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients diagnosed with or suspected of having colorectal cancer or adenoma.

GENERAL HEALTH SCREENING

Studies that address the clinical utility for general health screening for gene testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* were not identified.

MANAGEMENT OF HOMOCYSTEINE LEVELS

Studies that address the clinical utility of gene testing for the management of Hcy levels and gene testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* were not identified.

MANAGEMENT OF VITAMIN B DEFICIENCIES (FOLATE, B_6, AND B_{12})

Studies that address the clinical utility of gene testing for the management of vitamin deficiencies and gene testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* were not identified.

OSTEOPOROSIS

There was a single report on *CBS* gene association with osteoporosis.

Authors determined the molecular basis of *CBS* deficiency in 36 Australian patients from 28 unrelated families, using direct sequencing of the entire coding region of the *CBS* gene.[75] The G307S and I278T variants were the most common. They were present in 19% and 18% of independent alleles, respectively.

PARKINSON'S DISEASE

Studies that address the association between *MTHFR* gene variants and Parkinson's disease (PD) are described below.

Association Studies

The objective of a small trial was to compare B6, B12, folic acid and tHcy levels in plasma of 83 levodopa treated PD patients and 44 controls.[76] Authors reported PD patients with the CT or TT genotype had significant higher tHcy levels than controls or PD patients with the CC allele. The concentrations of B6 or B12 did not differ, but folic acid was significant higher in PD patients with the CT variant. Based on results, authors recommended *MTHFR* genotyping, tHcy monitoring and early vitamin supplementation in PD patients.

Yasui (2000) measured plasma Hcy and cysteine levels in 90 patients with PD with the *MTHFR* C677T (T/T) genotype.[77] The authors found that the levels of Hcy-a possible risk factor for vascular disease-were elevated by 60% in levodopa-treated patients with PD, with the most marked elevation occurring in patients with the T/T genotype. Cysteine levels in subjects with PD did not differ from levels in control subjects. In the T/T genotype patients, Hcy and folate levels were inversely correlated. Authors concluded that increased Hcy might be related to levodopa, *MTHFR* genotype, and folate in PD.

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with Parkinson's disease.

PSYCHIATRIC DISORDERS

Mixed Psychiatric Disorders

Studies regarding the association between *MTHFR* and *MTR* variants and multiple psychiatric disorders are described below.

Systematic Reviews

Hu (2015) evaluated the association between *MTHFR* variants and risk of bipolar disorder or schizophrenia.[78] In a meta-analysis of 38 studies, the authors found a significant association between the *MTHFR* C677T variant and schizophrenia (comparison, TT vs CT or CC; OR 1.34, 95% CI 1.18 to 1.53). For bipolar disorder, there was a marginal association between the C677T variant and disease risk (comparison, TT vs CT or CC, OR 1.26, 95% CI 1.00 to 1.59). The clinical utility of *MTHFR* genotyping was not addressed in this analysis.

Peerbooms (2011) conducted a meta-analysis of all published case-control studies investigating associations between two common *MTHFR* single nucleotide variants, *MTHFR* C677T (sample size 29,502) and A1298C (sample size 7,934), and the major psychiatric disorders (i) schizophrenia (SZ), (ii) bipolar disorder (BPD), and (iii) unipolar depressive disorder (UDD).[79] In order to examine possible shared genetic vulnerability, authors also tested for associations between *MTHFR* and all of these major psychiatric disorders (SZ, BPD and UDD) combined. *MTHFR* C677T was significantly associated with all of the combined psychiatric disorders (SZ, BPD, and UDD); random effects OR 1.26 for TT versus CC genotype carriers, 95% CI 1.09 to 1.46); meta-regression did not suggest moderating effects of psychiatric diagnosis, sex, ethnic group or year of publication. Although *MTHFR* A1298C was not significantly associated with the combination of major psychiatric disorders, nor with SZ, there was evidence for diagnostic moderation indicating a significant association with BPD (random effects OR 2.03 for AA versus CC genotype carriers, 95% CI 1.07 to 3.86). The meta-analysis on UDD was not possible due to the small number of studies available.

Gilbody (2007) performed a meta-analysis of studies examining the association between variants in the *MTHFR* gene, including *MTHFR* C677T and A1298C, and common psychiatric disorders, including unipolar depression, anxiety disorders, bipolar disorder, and schizophrenia.**[80]** The primary comparison was between homozygote variants and the wild type for *MTHFR* C677T and A1298C. Authors conclude this meta-analysis did not identify an association between the *MTHFR* C677T variant and anxiety. The clinical utility of *MTHFR* was not addressed in this study.

Association Studies

Additional studies were identified which evaluated the association of *MTHFR* variants and psychiatric disorders.[81]

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with anxiety or other psychiatric disorders.

Bipolar Disorder

Association studies addressing *MTHFR* and bipolar disorders are described below.

Systematic Reviews

In the study described above, Peerbooms conducted a meta-analysis of all published case-control studies investigating associations between two common *MTHFR* SNVs, *MTHFR* C677T (sample size 29,502) and A1298C (sample size 7,934), and the major psychiatric disorders (i) SZ, (ii) BPD, and (iii) UDD.[79] Authors concluded this study provides evidence for shared genetic vulnerability for mood disorders, BPD and UDD, mediated by *MTHFR* 677TT

genotype, which is in line with epigenetic involvement in the pathophysiology of these psychiatric disorders.

Association Studies

No studies published after the search date of the above systematic review were identified that addressed MTHFR and bipolar disorders.

Clinical Utility

No studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with bipolar disorders.

Depression

Studies regarding the association between *MTHFR* and *MTR* variants and depression are described below.

Systematic Reviews

Wu (2013) conducted a meta-analysis to investigate a more reliable estimate of the association between the *MTHFR* C677T variant and depression.[82] The meta-analysis included 26 studies, including 4,992 depression cases and 17,082 controls. The authors concluded the *MTHFR* C677T variant was associated with an increased risk of depression, especially in Asian populations. However, there was no evidence indicating a correlation in the elderly.

Association Studies

Additional association studies[83-91] were identified which evaluated the association of *MTHFR* variants and depression. These studies reported mixed results.

Clinical Utility

Only one study has been identified, to date, that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with depression.

Bousman (2010) conducted a prospective cohort study to evaluate the association between *MTHFR* genetic variants and prognosis of major depressive disorder.[92] The study included 147 primary care attendees with major depression who underwent genotyping for two functional *MTHFR* variants (C677T [rs1801133] and A1298C [rs1801131]) and seven haplotype-tagging SNVs and serial measures of depression. The C677T variant was significantly associated with symptom severity trajectory measured by the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire–9 (p=0.038). The A1298C variant and the haplotype-tagging SNVs were not associated with disease prognosis. This study had several limitations, including small sample size, which leads to inadequate statistical power to detect differences in prognosis. Additionally, none of reported results were statistically significant after correction for multiple comparisons.

Schizophrenia

Studies that address the association between the *CBS* and *MTHFR* gene variants and schizophrenia are described below.

Association Studies

In a study by Kim (2014), the association of the two functional variants of *MTHFR*, C677T and A1298C, with the risk for schizophrenia was investigated.[93] The authors additionally conducted an updated meta-analysis on these associations. The authors also investigated the relationship between the variants and minor physical anomaly, which may represent neurodevelopmental aberrations in 201 schizophrenia patients and 350 normal control subjects. There was no significant association between either of the two variants and the risk of schizophrenia (X^2=0.001, p=0.971 for C677T; X^2=1.319, p=0.251 for A1298C). However, in meta-analysis, the C677T variant showed a significant association in the combined and Asian populations (OR 1.13, p=0.005, OR 1.21, p=0.011, respectively) but not in the Korean and Caucasian populations alone. The authors concluded, the present findings suggest that in the Korean population, the MTHFR variants are unlikely to be associated with the risk for schizophrenia and neurodevelopmental abnormalities related to schizophrenia.

In the study described above, Peerbooms conducted a meta-analysis of all published case-control studies investigating associations between two common *MTHFR* SNVs, *MTHFR* C677T (sample size 29,502) and A1298C (sample size 7,934), and the major psychiatric disorders (i) SZ, (ii) BPD, and (iii) UDD.[79] Authors concluded this study provides evidence for shared genetic vulnerability for SZ, BPD and UDD mediated by *MTHFR* 677TT genotype, which is in line with epigenetic involvement in the pathophysiology of these psychiatric disorders.

In the study described above, Gilbody performed a meta-analysis of studies examining the association between variants in the *MTHFR* gene, including *MTHFR* C677T and A1298C, and common psychiatric disorders, including schizophrenia.[80] The primary comparison was between homozygote variants and the wild type for *MTHFR* C677T and A1298C. For schizophrenia and *MTHFR* C677T, the fixed-effects odds ratio for TT versus CC was 1.44 (95% CI 1.21 to 1.70), with low heterogeneity (I^2=42%) based on 2,762 cases and 3,363 controls. Authors concluded this meta-analysis demonstrated an association between the *MTHFR* C677T variant and schizophrenia, though clinical utility was not addressed.

Golimbet (2009) investigated the association between the 844ins68 variant of the *CBS* gene and schizophrenia in a large Russian sample using case-control and family-based designs.[94] The sample comprised 1,135 patients, 626 controls and 172 families. There was a trend for association between the 844ins68 variant and schizophrenia in the case-control study, with higher frequency of the insertion in the control group. The FBAT revealed a statistically significant difference in transmission of alleles from parents to the affected proband, with preferential transmission of the variant without insertion. When the sample of patients was stratified by sex and forms of schizophrenia, the significantly lower frequency of insertion was observed in the group of female patients with chronic schizophrenia (n=180) as compared to psychiatrically well women. Authors concluded their study revealed a possible relation of the *CBS* 844ins68 variant to schizophrenia.

Van Winkel (2010) studied naturalistic cohort of 518 patients with a schizophrenia spectrum disorder screened for metabolic disturbances.[95] *MTHFR* A1298C, but not C677T, was associated with the metabolic syndrome, C/C genotypes having a 2.4 times higher risk compared to A/A genotypes (95% CI 1.25 to 4.76, p=0.009). Haplotype analysis revealed similar findings, showing greater risk for metabolic syndrome associated with the 677C/1298C haplotype compared to the reference 677C/1298A haplotype (OR 1.72, 95% CI 1.24 to 2.39,

p=0.001). These associations were not explained by circulating folate levels. Differences between A1298C genotype groups were considerably greater in the subsample treated with clozapine or olanzapine (OR C/C versus A/A 3.87, 95% CI 1.51 to 9.96) than in subsample treated with any of the other antipsychotics (OR C/C versus A/A 1.30, 95% CI 0.47 to 3.74), although this did not formally reach statistical significance in the current cross-sectional study (gene-by-group interaction X^2=3.0, df=1, p=0.08). Authors suggest that prospective studies evaluating the course of metabolic outcomes after initiation of antipsychotic medication are needed to evaluate possible gene-by-treatment interaction more specifically.

Clinical Utility

Additional studies[96] were identified which evaluated the association of methionine metabolism gene variants and schizophrenia; however, no studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with schizophrenia.

METHOTREXATE EFFICIENCY AND TOXICITY

Studies that address the association between the *MTHFR* gene variants and methotrexate efficiency and toxicity are described below.

Song (2021) published a systematic review on gene variants and high-dose methotrexate response and toxicity, which included nine polymorphisms in seven genes: *MTHFR*, *RFC1*, *ABCB1*, *SLCO1B1*, *TYMS*, *FPGS*, and *ATIC*.[97] The *MTHFR* C677T variant was associated with hepatic and renal toxicity and mucositis, while the A1298C polymorphism was associated with a reduced risk of renal toxicity.

In a systematic review, Fan (2017) examined evidence regarding an association between the *MTHFR* A1298C variant and outcome of methotrexate treatment in rheumatoid arthritis patients. Relevant literature through May 2016 was assessed.[98] Ten studies of methotrexate efficacy and 18 studies of methotrexate toxicity met inclusion criteria. Studies were not assessed for quality. Meta-analysis results did not show a significant association between *MTHFR* A1298C variants and methotrexate toxicity or efficiency. Subgroup analyses identified significant associations between *MTHFR* A128C variants and decreased methotrexate efficacy in the South Asian population and in the partial folate supplementation group. However, there were few studies in these subgroup analyses.

Another systematic review by Qiu (2017) assessed the association of variants in 28 genes with methotrexate toxicity in rheumatoid arthritis patients.[99] A literature search in February 2016 identified 16 studies that met inclusion criteria addressing *MTHFR* variants. No significant association between *MTHFR* variants and methotrexate toxicity was identified.

Clinical Utility

Additional studies published after the search dates of the above systematic reviews were identified which evaluated the association of methionine metabolism gene variants and toxicity and efficacy of methotrexate treatment.[100-106] However, no studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients being treated with methotrexate.

VENOUS THROMBOEMBOLISM

Variants in the *MTHFR* gene, particularly C667T, are associated with hyper-homocysteinemia, which is in turn considered a weak risk factor for venous thromboembolism (VTE). However, the clinical utility of testing for homocysteine levels has not been established. There is a large literature base on the association of homocysteine levels with coronary artery disease (CAD), and clinical trials on the impact of lowering homocysteine levels. This body of evidence indicates that testing or treating for homocysteinemia is not associated with improved outcomes.

For the association of *MTHFR* with VTE, the evidence is not definitive. Some studies have shown an association, but others have not. In one of the larger studies, the MEGA study, there was no association of the *MTHFR* variant with recurrent VTE.[107] Similarly, a systematic review by Wu (2006) reported that *MTHFR* was not associated with increased risk of postoperative VTE following orthopedic surgery.[108] A randomized controlled trial published in abstract form reported that there was no reduction in VTE associated with treatment of hyperhomocysteinemia.[109]

OTHER CONDITIONS

Additional studies were identified which evaluated the association of methionine metabolism gene variants and other conditions such as glaucoma,[110] psoriasis,[111-113] inflammatory bowel disease,[114-116] retinoblastoma,[117] leukemia,[118] rheumatoid arthritis,[119] Graves' ophthalmopathy,[120] autism,[121-124] myelodysplastic syndromes,[125] breast cancer,[19, 126-130] cancer susceptibility and prognosis,[131-138] fluoropyrimidine toxicity,[139] sudden sensorineural hearing loss,[140] male infertility,[141] amyotrophic lateral sclerosis,[142] and in vitro fertilization pregnancy outcome and pregnancy loss[143-151]; however, no studies were identified that addressed the clinical utility of *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene testing in patients with these conditions.

PRACTICE GUIDELINE SUMMARY

Currently no published clinical practice guidelines recommend gene testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, or *MMADHC*.

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS (ACMG)

ACMG published a 2013 guidelines that states, "*MTHFR* variant is only one of many factors contributing to the overall clinical picture, the utility of this testing is currently ambiguous."[152]

ACMG recommends *MTHFR* variant genotyping should **not** be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss. Further, *MTHFR* variant genotyping should not be ordered for at risk family members. *MTHFR* status does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation to reduce the risk of neural tube defects as per the general population guidelines.

Genetic testing for *CBS*, *MTR*, *MTRR*, and *MMADHC* is not addressed in ACMG guidelines.

SOCIETY FOR MATERNAL-FETAL MEDICINE

Originally released in 2019, and updated in 2022, the Society for Maternal-Fetal Medicine published the following recommendation for the Choosing Wisely initiative:[153]

"Don't test women for MTHFR mutations.

MTHFR is responsible for the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Genetic variant C677T and A1286C have been associated with a mild decrease in enzymatic activity, which in the setting of reduced folate levels has been found to be a risk factor for hyperhomocysteinemia. Although hyperhomocysteinemia is a risk factor for cardiovascular disease and venous thrombosis, its cause is multifactorial and independent of the MTHFR genotype, even in homozygotic individuals. Despite earlier (mostly case control) studies that found an association between the MTHFR genotype and adverse outcomes, recent studies of more robust design have not replicated these findings. Due to the lack of evidence associating genotype independently with thrombosis, recurrent pregnancy loss, or other adverse pregnancy outcomes, MTHFR genotyping should not be ordered as part of a workup for thrombophilia."

SUMMARY

There is not enough research to show that testing for variants in the *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* genes can improve health outcomes for people with any conditions. While many studies have found associations between MTHFR variants and a number of conditions, there is a lack of evidence that treating patients based on genetic testing can improve these conditions. In addition, clinical practice guidelines specifically recommend against *MTHFR* genetic testing, and there are no clinical guidelines based on research that recommend testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* gene variants. Therefore, genetic testing for *CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC* is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	81291	*MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
	81401	Molecular pathology procedure, Level 2
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
HCPCS	None	

Date of Origin: *January 2014*

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Effective: March 1, 2024

Next Review: January 2025
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

The inherited peripheral neuropathies are the most common inherited neuromuscular disease. Genetic testing has been suggested as a way to diagnose specific inherited peripheral neuropathies.

MEDICAL POLICY CRITERIA

Note: Please see Cross References for individual gene and panel testing for genes not associated with peripheral neuropathies and for reproductive carrier testing.

I. Genetic testing to diagnose an inherited peripheral neuropathy, including targeted panel testing (see Policy Guidelines), may be considered **medically necessary** when both of the following are met:

   A. When an individual has signs and/or symptoms of an inherited peripheral motor or sensory neuropathy; and

   B. One of the following is met:

      i. A definitive clinical diagnosis cannot be made; or

      ii. A genetic diagnosis is needed to inform reproductive planning.

II. Genetic testing to diagnose an inherited peripheral neuropathy is considered **investigational** when Criterion I. is not met, including for non-targeted panels (see Policy Guidelines).

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

POLICY GUIDELINES

PANEL TESTING

Targeted Panels for Inherited Peripheral Neuropathies

Targeted panel testing for peripheral neuropathies includes panels that are specifically designed to diagnose patients suspected of having an inherited peripheral neuropathy, such as Charcot-Marie-Tooth disease. They may include the following genes: *PMP22*, *MFN2*, *MPZ*, *LITAF*, and *GJB1*.

Examples of targeted panels for peripheral neuropathies include, but are not limited to:

- Distal Hereditary Motor Neuropathy Panel (Prevention Genetics)
- Hereditary Neuropathy Panel (GeneDx)
- Invitae Hereditary Sensory and Autonomic Neuropathy Panel (Invitae)
- Invitae Small Fiber Neuropathy Test (Invitae)

Non-targeted Panels

Some commercially available panels are not targeted toward genes that are specifically associated with peripheral neuropathies. They often include testing for a large number of disorders that could be distinguished based on clinical presentation.

Non-targeted panels for neuropathies and related disorders, but are not limited to:

- Comprehensive Neuropathy Panel (Prevention Genetics)
- Comprehensive Neuropathies (NGS Panel and Copy Number Analysis + mtDNA) (MNG Laboratories)
- Invitae Comprehensive Neuropathies Panel (Invitae)

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
3. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

The inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence is roughly one in 2,500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.[1]

Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary myelinopathies, depending upon which portion of the nerve fiber is affected.

Further anatomic classification includes fiber type (e.g., motor versus sensory, large versus small), and gross distribution of the nerves affected (e.g., symmetry, length-dependency).

The inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies, and other miscellaneous, rare types (e.g., hereditary brachial plexopathy, hereditary sensory autonomic neuropathies). Other hereditary metabolic disorders, such as Friedreich's ataxia, Refsum's disease, and Krabbe's disease, may be associated with motor and/or sensory neuropathies but typically have other predominating symptoms. This policy will focus on the hereditary motor and sensory neuropathies and hereditary neuropathy with liability to pressure palsies.

A genetic etiology of a peripheral neuropathy is generally suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course.[2] A family history of at least three generations with details on health issues, cause of death, and age at death should be collected.

HEREDITARY MOTOR AND SENSORY NEUROPATHIES

The majority of inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurological findings to the classic picture with pes cavus and "stork legs" to a severe polyneuropathy with respiratory failure.[3] CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies.[4] In addition, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different inheritance patterns. A 2015 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the five most commonly represented subtypes.[5]

CMT subtypes are characterized by variants in one of several myelin genes, which lead to abnormalities in myelin structure, function, or upkeep. There are seven subtypes of CMT, with type 1 (demyelinating) and 2 (axonal or non-demyelinating) representing the most common hereditary peripheral neuropathies.

Most cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. Most cases are CMT type 1 (approximately 40% to 50% of all CMT cases, with 78% to 80% of those due to *PMP22* variants). CMT type 2 is associated with about 10% to 15% of CMT cases. CMT2A is the most common subtype of CMT2 and about 20% of CMT2A is due to *MFN2* variants.

A summary of the molecular genetics of CMT is outlined in Table 1.

Table 1: Molecular Genetics of CMT Variants (adapted from Bird, 2022[6])

Locus Name	Gene	Protein Product	Prevalence (if known)
CMT type 1			
CMT1A	*PMP22*	Peripheral myelin protein 22	50% of CMT1
CMT1B	*MPZ*	Myelin P0 protein	25% of CMT1
CMT1C	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-α factor	
CMT1D	*EGR2*	Early growth response protein 2	
CMT1E	*PMP22*	Peripheral myelin protein 22 (sequence changes)	

Locus Name	Gene	Protein Product	Prevalence (if known)
CMT1F/2E	*NEFL*	Neurofilament light peptide	
CMT1G	*PMP2*	Peripheral myelin protein 2	
CMT type 2			
CMT2A1	*KIF1B*	Kinesin-like protein KIF1B	
CMT2A2A/B	*MFN2*	Mitofusin-2	
CMT2B	*RAB7A*	Ras-related protein Rab-7	
CMT2B1	*LMNA*	Lamin A/C	
CMT2B2	*PNKP*		
CMT2C	*TRPV4*	Transient receptor potential cation channel subfamily V member 4	
CMT2D	*GARS1*	Glycyl-tRNA synthetase	
CMT2F	*HSPB1*	Heat-shock protein beta-1	
CMT2G	LRSAM1	E3 ubiquitin-protein-ligase LRSAM1	
CMT2H	*GDAP1*	Ganglioside-induced differentiation-associated protein-1	
CMT2I/J	*MPZ*	Myelin P0 protein	
CMT2L	*HSPB8*	Heat-shock protein beta-8	
CMT2N	*AARS1*	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	*DYNC1H1*	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	*LRSAM1*	E3 ubiquitin-protein ligase LRSAM1	
CMT2Q	*DHTKD1*	Dehydrogenase E1 And Transketolase Domain Containing 1	
CMT2R	*TRIM2*	Tripartite Motif Containing 2	
CMT2S	*IGHMBP2*	DNA-binding protein SMUBP-2	
CMT2T	*MME*	Membrane Metalloendopeptidase	
CMT2U	*MARS1*	Methionine--tRNA ligase, cytoplasmic	
CMT2V	*NAGLU*	N-Acetyl-Alpha-Glucosaminidase	
CMT2W	*HARS1*	Histidyl-TRNA Synthetase 1	
CMT2X	*SPG11*	Spastic paraplegia 11	
CMT2Y	*VCP*	Valosin Containing Protein	
CMT2Z	*MORC2*	Microrchidia Family CW-Type Zinc Finger 2	
CMT type 4			
CMT4A	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	*MTMR2*	Myotubularin-related protein 2	
CMT4B2	*SBF2*	Myotubularin-related protein 13	
CMT4B3	*SBF1*	Set Binding Factor 1	
CMT4C	*SH3TC2*	SH3 domain and tetratricopeptide repeats-containing protein 2	
CMT4D	*NDRG1*	Protein NDRG1	
CMT4E	*EGR2*	Early growth response protein 2	
CMT4F	*PRX*	Periaxin	
CMT4H	*FGD4*	FYVE, RhoGEF and PH domain-containing protein 4	
CMT4J	*FIG4*	Phosphatidylinositol 3, 5-biphosphate	
X-linked CMT			
CMTX1	*GJB1*	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX3	*Xq26*	Unknown	
CMTX4	*AIFM1*	Apoptosis-inducing factor 1	
CMTX5	*PRPS1*	Ribose-phosphate pyrophosphokinase 1	
CMTX6	*PDK3*	Pyruvate dehydrogenase kinase isoform 3	

CMT1

Charcot-Marie-Tooth type 1 (CMT1) is an autosomal dominant, demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity, bilateral foot drop and palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve. Affected individuals usually become symptomatic between age five and 25 years, and lifespan is not shortened. Less than 5% of individuals become wheelchair dependent. CMT1 is inherited in an autosomal dominant manner. The CMT1 subtypes (CMT 1A-E) are separated by molecular findings and are often clinically indistinguishable. CMT1A accounts for 70 to 80% of all CMT1, and about two thirds of probands with CMT1A have inherited the disease-causing variant and about one third have CMT1A as the result of a *de novo* variant.

The largest proportion of CMT1 cases are due to variants in *PMP22*. CMT1A involves duplication of the gene *PMP22*. *PMP22* encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal *PMP22* gene dosage effects.[7] Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype whereas three normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype.[8]

CMT2

Charcot-Marie-Tooth type 2 (CMT2) is a non-demyelinating (axonal) peripheral neuropathy characterized by distal muscle weakness and atrophy, mild sensory loss, and normal or near-normal nerve conduction velocities. Clinically, CMT2 is similar to CMT1, although typically less severe.[8] The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

CMT4

Charcot-Marie-Tooth type 4 (CMT4) is a form of hereditary motor and sensory neuropathy that is inherited in an autosomal recessive fashion and occurs secondary to myelinopathy or axonopathy. It occurs more rarely than the other forms of CMT neuropathy

CMTX1

Charcot-Marie-Tooth X type 1 (CMTX1) is characterized by a moderate to severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.[9] Sensorineural deafness and central nervous system symptoms also occur in some families. CMTX1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (*Cx32)* detects about 90% of cases of CMTX1, which is available on a clinical basis.[9]

HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

In hereditary neuropathy with liability to pressure palsies (HNPP), also called tomaculous neuropathy, inadequate production of *PMP22* causes nerves to be more susceptible to

trauma or minor compression/entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some authors report presentation as early as birth or as late as the seventh decade of life.[10] The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for under diagnosis of the disease.[10] An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination.[11] HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode.[11] Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases the remaining symptoms are typically mild.

PMP22 is the only gene in which variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients and the remaining 20% of patients have point variants and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point variants in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.[12] Studies have also reported that the point variant frequency may vary considerably by ethnicity.[13] About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.[14]

TREATMENT

Currently there is no effective treatment to prevent or slow the progression of peripheral neuropathy and therapy for the inherited peripheral neuropathies is based on symptoms. A systematic review of exercise therapies for CMT including nine studies described in 11 articles reported significant improvements in functional activities and physiological adaptations with exercise.[15] Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.[16] Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.[17]

Supportive treatment for HNPP can include transient bracing (e.g., a wrist splint or ankle-foot orthosis) which may become permanent in some cases of foot drop.[18] Prevention of HNPP manifestations can be accomplished by wearing protective padding (e.g., elbow or knee pads) to prevent trauma to nerves during activity. Some authors report that vincristine should also be avoided in HNPP patients.[8, 18] Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit.[19] Attarian (2014) reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of three already approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A.[20] The study demonstrated the safety and tolerability of the drug. Mandel (2015) included this randomized controlled trial and three other trials, one of ascorbic acid and two of PXT3003, in a meta-analysis.[21]

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[22] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent
2. Clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease
3. Clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This review focuses on the clinical validity and utility of genetic testing. Most of the published data available for the clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the *PMP22* gene in the diagnosis of Charcot-Marie-Tooth (CMT) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively.

CLINICAL VALIDITY

The clinical sensitivity of the diagnostic test for CMT and HNPP can be dependent on variable factors such as the age or family history of the patient. A general estimation of the clinical sensitivity was presented in a report by Aretz (2010) on hereditary motor and sensory neuropathy and HNPP with a variety of analytic methods (MLPA, multiplex amplicon quantification [MAQ], qPCR, Southern blot, FISH, PFGE, dHPLC, high-resolution melting, restriction analysis and direct sequencing).[23] The clinical sensitivity (i.e., proportion of positive tests if the disease is present) for the detection of deletions/duplications to *PMP22* was reported to be about 50% and 1% for point variants. The clinical specificity (i.e., proportion of negative tests if the disease is not present) was reported to be nearly 100%.

An evidence-based review by England (2009) on the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathies concluded that genetic testing was established as useful for the accurate diagnosis and classification of hereditary polyneuropathies in patients with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype.[3] Six studies included in the review showed that when the

test for CMT1A duplication was restricted to patients with clinically probable CMT1 (i.e., autosomal dominant, primary demyelinating polyneuropathy), the yield is 54% to 80% as compared to testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathy where the yield was only 25% to 59% (average of 43%).

Sequential Testing

Given the genetic complexity of CMT, many commercial and private laboratories evaluate CMT with a testing algorithm based on patients' presenting characteristics. For the evaluation of clinical validity of genetic testing for CMT, we included studies that evaluated patients with clinically suspected CMT who were evaluated with a genetic testing algorithm that was described in the study.

Uchôa Cavalcanti (2021) reported on results from genetic testing of 503 patients (94 families and 192 unrelated individuals) who underwent testing in a Brazilian neuromuscular outpatient clinic from 2015 to 2020.[24] The diagnosis of CMT was established based on the presence of slowly progressive, motor and sensory neuropathy, independent of any family history. Patients were assessed utilizing clinical and neurophysiological data along with targeted gene panel sequencing. Among the 503 patients, a genetic diagnosis was reported in 394 patients (77 families and 120 unrelated individuals). The following confirmed genetic diagnoses were identified: demyelinating CMT (n=317), intermediate CMT (n=34), and axonal CMT (n=43). The genetic diagnosis rate in probands was 68.9% (197/286). The most common causative genes were *PMP22* duplication *GJB1*, *MFN2*, *GDAP1*, *MPZ*, *PMP22* point mutation, *NEFL*, *SBF2*, and *SH3TC2*.

Volodarsky (2021) reported the results of genetic testing, including comprehensive sequencing and copy number analysis of 34 genes, in a cohort of 2,517 Canadian patients.[25] A molecular diagnosis was made in 440 (17.5%) patients, and the diagnostic yield was greater for females (21%) than males (15%). Six genes constituted 80% of the overall results.

Saporta (2011) reported results from genetic testing of 1,024 patients with clinically suspected CMT who were evaluated at a single institution's CMT clinic from 1997 to 2009.[4] Patients who were included were considered to have CMT if they had a sensorimotor peripheral neuropathy and a family history of a similar condition. Patients without a family history of neuropathy were considered to have CMT if their medical history, neurophysiological testing, and neurological examination were typical for CMT1, CMT2, CMTX, or CMT4. There were 787 patients with clinically diagnosed CMT; of those, 527 (67%) had a specific genetic diagnosis as a result of their visit. Genetic testing decisions were left up to the treating clinician, and the authors noted that decisions about which genes to test changed over the course of the study period. The majority (98.2%) of those with clinically-diagnosed CMT1 had a genetic diagnosis, and of all of the patients with a genetic diagnosis, the majority (80.8%) had clinically-diagnosed CMT1. The authors characterize several clinical phenotypes of CMT based on clinical presentation and physiologic testing.

Rudnik-Schoneborn (2016) reported results from genetic testing of 1,206 index patients and 124 affected relatives who underwent genetic testing at a single reference laboratory from 2001 to 2012.[26] Patients were referred by neurologic or genetic centers throughout Germany, and were grouped by age at onset (early infantile [<2 years], childhood [2 to 10 years], juvenile [10 to 20 years], adult [20 to 50 years], and late adult [>50 years]), and by electroneurographic findings. Molecular genetic methods changed over the time period of the study, and testing was tiered depending on patient features and family history. Of the 674

index patients with a demyelinating CMT phenotype on nerve conduction studies, 343 (51%) had a genetic diagnosis; of the 340 index patients with an axonal CMT phenotype, 45 (13%) had a genetic diagnosis; and of the 192 with HNPP, 67 (35%) had a genetic diagnosis. The most common genetic diagnoses differed by nerve conduction phenotype: of the 429 patients genetically identified with demyelinating CMT (index and secondary), 89.3% were detected with *PMP22* del/dup (74.8%), *GJB1/Cx32* (8.9%), or *MPZ/P0* (5.6%) variant analysis. In contrast, of the 57 patients genetically identified with axonal CMT (index and secondary), 84.3% were detected with *GJB1/Cx32* (42.1%), *MFN2* (33.3%), or *MPZ/P0* (8.8%) analysis.

Gess (2013) reported on sequential testing for CMT-related genes from 776 patients with genetic testing at a single center for suspected inherited peripheral neuropathies from 2004 to 2012.[27] Most patients (n=624) were treated in the same center. The test strategy varied based on electrophysiologic data and family history. The yield of genetic testing was 66% (233/355) in patients with CMT1, 35% (53/151) in patients with CMT2, and 64% (53/83) in patients with HNPP. Duplications on chromosome 17 were the most common variants in CMT1 (77%), followed by *GJB1* (13%) and *MPZ* (8%) variants among those with positive genetic tests. For CMT2 patients, *GJB2* (30%) and *MFN2* (23%) variants were most common among those with positive genetic tests.

Ostern (2013) reported on a retrospective analysis of cases of CMT diagnostic testing referred to a single reference laboratory in Norway from 2004 to 2010.[28] Genetic testing was stratified based on clinical information supplied on patient requisition forms based on age of onset of symptoms, prior testing, results from motor NCV, and patterns of inheritance. The study sample included 435 index cases, of a total of 549 CMT cases tested (other tests were for at risk family members or other reasons). Patients were grouped based on whether they had symptoms of polyneuropathy, classical CMT, with or without additional symptoms or changes on imaging, or if they had atypical features or the physician suspected an alternative diagnosis. Among the cases tested, 72 (16.6%) were found to be variant positive, all of whom had symptoms of CMT. Most (69/72, 95.8%) of the positive molecular genetic findings were *PMP22* region duplications or sequence variants in *MPZ*, *GJB1*, or *MFN2* genes.

Murphy (2012) reported on the yield of sequential testing for CMT-related gene variants from 1,607 patients with testing sent to a single center.[29] Of the 916 patients seen in the authors' clinic, 601 (65.6%) had a clinical diagnosis of CMT (425 CMT, 46 HNPP), CMT1 (56.5%) and 115 had CMT2 (27.1%. Of those with CMT, 266 (62.6%) received a genetic diagnosis. Of the patients with a positive genetic test, variants in four genes (*PMP22* duplication, and *GJB1*, *MPZ*, and *MFN2*) represented 92% of all variants.

Panel Testing

Several studies have evaluated broader panel tests for hereditary peripheral neuropathies. Hoyer (2014) reported the yield of testing with next-generation sequencing (NGS) with a custom panel including 32 CMT genes and 19 other genes associated with inherited neuropathies among 81 families with CMT.[30] Pathogenic or likely pathogenic gene variants were identified in 37 (46%) of families. Of the 38 families with CMT1, 55% (21/38) had certain or likely pathogenic genotypes identified (11 copy number variants, ten point variants). Of the 33 families with CMT2, 36% (12/33) had certain or likely pathogenic genotypes identified.

Frasquet (2020) reported on the results of genetic testing, including NGS and Sanger sequencing of the *SORD* gene, in 163 patients (from 108 families) with distal hereditary motor neuropathies in Spain.[31] The most commonly identified genetic variants were in the *HSPB1*

(10.4%), *GARS1* (9.8%), *BICD2* (8.0%), and *DNAJB2* (6.7%) genes, while *SORD* variants accounted for 3.1%. A genetic diagnosis was found for 37/108 (34.2%) of the families.

Drew (2015) reported results of whole exome sequencing for 110 patients with inherited peripheral neuropathies who had previously had negative genetic testing for variants in common genes associated with peripheral neuropathies.[32] The authors identified 41 missense sequence variants in genes known to be associated with inherited peripheral neuropathies, nine of which were considered pathogenic, 12 of which were considered novel variants potentially implicated in the disease, and 20 of which were considered polymorphisms.

DiVincenzo (2014) reported the variant detection rate for 14 hereditary peripheral neuropathy-associated genes in a cohort of 17,880 patients with CMT disease who were referred to a commercial genetic testing laboratory.[33] Test methods included Sanger sequencing assay (n=100,102 assays), NGS assays (n=2,338), and MLPA assays (n=21,990). The genes evaluated include *PMP22, GJB1, MPZ, MFN2, SH3TC2, GDAP1, NEFL, LITAF, GARS, HSPB1, FIG4, EGR2, PRX*, and *RAB7A*. Of the patient cohort, 18.5% (n=3,312) had a genetic abnormality detected. Among those with a genetic abnormality in a CMT-related gene, 94.9% were positive in one of four genes (*PMP22, GJB1, MPZ, MFN2*). Duplications (56.7%) or deletions (21.9%) in the *PMP22* gene were the most common finding, followed by *GJB1* variants (6.7%).

Genotype-Phenotype Correlations

There is significant clinical variability within and across subtypes of CMT. Therefore, some studies have evaluated genotype-phenotype correlations within CMT cases.

Chao (2023) evaluated the clinical manifestations and genetic findings of 21 people from 9 families with *NEFL*-associated CMT in Taiwan.[34] The families had six different *NEFL* variants which represented almost 2% of CMT in Taiwan. All variants were heterozygous, and autosomal dominant inheritance was confirmed in four families. About 70% of the patients were characterized as having intermediate CMT based on ulnar nerve conduction velocities (MNCV). The phenotypes exhibited wide variability including a wide range of forearm MNCV of between 25 and 45m/s. The age at onset ranged from age 1-year to 40 years, and severity of symptoms varied. Delayed walking (after age 15 months) was experienced by 19% of patients.

Morel (2022) compared the genetic and clinical features of 7 French patients with *HINT1*-associated CMT to previous reports of *HINT1*-positive patients.[35] Homozygous *HINT1* variants are a rare cause of recessive axonal CMT that has been reported in many Eastern and Western European countries, as well as Asia, Africa, and South America. The 7 French patients were similar in presentation in terms of age of onset (mean age 7 years vs. 9 years in published reports) dysmorphologies (e.g., foot abnormalities in 6/7 French patients vs. 85% of published reports) and neuromuscular/sensory findings (all French patients had nerve conduction studies that found sensory-motor or distal motor neuropathy) to previously reported *HINT1* cohorts. However, unlike previous reports, 6 of the 7 French patients exhibited neurodevelopmental or psychiatric disorders, including intellectual disability, dyslexia, depression, attention deficit hyperactivity disorder, anxiety, and obsessive-compulsive disorder. Further study is needed to know whether the *HINT1* neuropathy phenotype is associated with developmental and/or psychiatric disorders.

Sanmaneechai (2015) characterized genotype-phenotype correlations in patients with CMT1B in terms of variants in the *MPZ* gene in a cohort of 103 patients from 71 families.[36] Patients underwent standardized clinical assessments and clinical electrophysiology. There were 47 different *MPZ* variants and three characteristic ages of onset, infantile (age range 0 to 5 years), childhood (age range 6 to 20 years), and adult (age ≥ 21 years). Specific variants clustered by age group, with only two variants found in more than one age group.

Considerable variability of phenotype has been observed within families with CMT2A.[37] Choi (2007) reported on genotype-phenotype correlations between *MFN2* variants and CMT2A symptoms in 160 families with CMT2A, 36 of which had *MFN2* variants.[38] Among patients with *MFM2* variants, disease severity was correlated with age of onset, but specific associations between genotype and disease severity are not reported.

Karadima (2015) investigated the association of *PMP22* variants and clinical phenotypes in 100 Greek patients referred for genetic testing for HNPP.[39] In the 92 index cases the frequency of *PMP22* deletions was 47.8% and the frequency of *PMP22* "micromutations" was 2.2%. Variant-negative patients were more likely to have an atypical phenotype (41%), absent family history (96%), and nerve conduction study findings not fulfilling HNPP criteria (80.5%).

CLINICAL UTILITY

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing. The clinical utility of genetic testing for hereditary peripheral neuropathies depends on how the results can be used to improve patient management. Published data for the clinical utility of genetic testing for inherited peripheral neuropathies is lacking.

The diagnosis of an inherited peripheral neuropathy can generally be made clinically. However, when the diagnosis cannot be made clinically, a genetic diagnosis may add incremental value. A diagnosis of an inherited peripheral neuropathy is important to direct therapy, regarding early referrals to physical therapy and avoidance of potentially toxic medications. Some specific medications for CMT are under investigation, but their use is not well-established. There are significant differences in prognosis for different forms of CMT, although whether different prognosis leads to choices in therapy that lead to different outcomes is uncertain. In some cases, genetic diagnosis of an inherited peripheral neuropathy may have the potential to avoid other diagnostic tests. There is evidence from observational studies to support the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy when a diagnosis cannot be made by other methods and, in turn, to initiate supportive therapies.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY[3]

The American Academy of Neurology (AAN) published an evidence-based in 2009, tiered approach for the evaluation of distal symmetric polyneuropathy, and for suspected hereditary neuropathies, which concluded that:

- genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (level A classification of recommendations- established as effective, ineffective, or harmful for the given condition in the specified population)
- genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (level C- possibly effective, ineffective, or harmful for the given condition in the specified population)
- initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion in *PMP22*, *GJB1* and *MFN2* screening
- there is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (level U-data inadequate or conflicting; given current knowledge)

These recommendations were reaffirmed in 2022.

AMERICAN ACADEMY OF FAMILY PHYSICIANS[40]

The American Academy of Family Physicians (AAFP) recommends genetic testing in a patient with suspected peripheral neuropathy if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology, and diseases such as diabetes, toxic medications, thyroid disease, and vasculitis can be ruled out.[40]

SUMMARY

There is enough evidence to show that genetic testing may improve overall health outcomes for certain individuals who have signs and/or symptoms of an inherited peripheral neuropathy. This includes individuals for whom a clinical diagnosis cannot be made, and those who require a genetic diagnosis to inform reproductive decision-making. Therefore, genetic testing for inherited peripheral neuropathies may be considered medically necessary when criteria are met.

There is not enough research to show that genetic testing for inherited peripheral neuropathies can change treatment decisions or improve health outcomes for individuals who do not meet the policy criteria, including those who lack signs and symptoms of peripheral neuropathy and those who have already received a clinical diagnosis and do not require molecular testing for reproductive purposes. Therefore, genetic testing for inherited peripheral neuropathies, including genetic panel testing, is considered investigational for these individuals.

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CODES

Codes	Number	Description
CPT	81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	;full gene sequencing
	81326	;family variant
	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *January 2014*

Regence

Medical Policy Manual Genetic Testing, Policy No. 68

Genetic Testing for Rett Syndrome

Effective: November 1, 2024

Next Review: July 2025
Last Review: September 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

Rett syndrome (RTT), a neurodevelopmental disorder affecting almost exclusively females, is usually caused by variants in the *MECP2* gene. Genetic testing is available to determine whether a pathogenic variant exists in a patient with clinical features of Rett syndrome, or in a patient's family member.

MEDICAL POLICY CRITERIA

I. Genetic testing for one or any combination of the following: *MECP2*, *FOXG1*, and *CDKL5,* for Rett syndrome may be considered **medically necessary** when all of the following criteria are met:

   A. To confirm a diagnosis of Rett syndrome in a child with developmental delay and signs/symptoms of Rett syndrome; AND

   B. When a definitive diagnosis cannot be made without genetic testing.

II. Targeted genetic testing for a known familial Rett-syndrome associated variant may be considered **medically necessary** to determine carrier status for an at-risk relative of an individual with Rett syndrome (see Policy Guidelines).

III. All other indications for genetic testing for Rett syndrome, including but not limited to prenatal screening in patients without a family history of the disorder, testing of other asymptomatic family members, and panel testing including genes other than *MECP2*,

FOXG1 and/or *CDKL5* are considered **investigational**.

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

POLICY GUIDELINES

Relatives at risk for being asymptomatic carriers of Rett syndrome include first-degree relatives with two X-chromosomes (e.g., mothers and sisters of affected individuals).

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Genetic Testing for Epilepsy, Genetic Testing, Policy No. 80
3. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

RETT SYNDROME

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting girls with an incidence of 1:10,000 female births, making it one of the most common genetic causes of intellectual disability in girls.[1] RTT is characterized by apparent normal development for the first 6 to 18 months of life, followed by the loss of intellectual functioning, loss of acquired fine and gross motor skills, and the ability to engage in social interaction. Purposeful use of the hands is replaced by repetitive stereotyped hand movements, sometimes described as hand-wringing.[1] Other clinical manifestations include seizures, disturbed breathing patterns with hyperventilation and periodic apnea, scoliosis, growth retardation, and gait apraxia.[2]

There is wide variability in the rate of progression and severity of the disease. In addition to the classical form of RTT, there are a number of recognized atypical variants. Variants of RTT may appear with a severe or a milder form. The severe variant has no normal developmental period; individuals with a milder phenotype experience less dramatic regression and milder

expression of the characteristics of classical RTT.

The diagnosis of RTT remains a clinical one, using diagnostic clinical criteria that have been established for the diagnosis of classic and variant Rett syndrome.[1-3]

TREATMENT OF RETT SYNDROME

There are currently no specific treatments that halt or reverse the progression of the disease, and there are no known medical interventions that will change the outcome of patients with RTT. Management is mainly symptomatic and individualized, focusing on optimizing each patient's abilities.[1] A multidisciplinary approach is generally used, with specialist input from dietitians, physiotherapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis and possible heart abnormalities may be recommended. The development of scoliosis (seen in about 87% of patients by age 25 years) and the development of spasticity can have a major impact on mobility, and the development of effective communication strategies. Occupational therapy can help children develop skills needed for performing self-directed activities (such as dressing, feeding, and practicing arts and crafts), while physical therapy and hydrotherapy may prolong mobility.

Pharmacological approaches to managing problems associated with RTT include melatonin for sleep disturbances and several agents for the control of breathing disturbances, seizures, and stereotypic movements. RTT patients have an increased risk of life-threatening arrhythmias associated with a prolonged QT interval, and avoidance of a number of drugs is recommended, including prokinetic agents, antipsychotics, tricyclic antidepressants, antiarrhythmics, anesthetic agents and certain antibiotics. In a mouse model of RTT, genetic manipulation of mutated *MECP2* has demonstrated reversibility.[4 5]

GENETICS OF RETT SYNDROME

Classic RTT results from an X-linked dominant condition. Variants in *MECP2* (methyl-CpG-binding protein 2), which is thought to control expression of several genes including some involved in brain development, were first reported in 1999. Subsequent screening of RTT patients has shown that over 80% of classical RTT have pathogenic variants in the *MECP2* gene. More than 200 variants in *MECP2* have been described. However, eight of the most commonly occurring missense and nonsense variants account for almost 70% of all cases, small C-terminal deletions account for approximately 10%, and large deletions, 8% to 10%.[6] *MECP2* variant type is associated with disease severity.[7] Whole duplications of the *MECP2* gene have been associated with severe X-linked intellectual disability with progressive spasticity, no or poor speech acquisition, and acquired microcephaly. In addition, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.

As the spectrum of clinical phenotypes is broad, an *MECP2* variation database was established to facilitate genotype-phenotype correlation analyses.[8]

Approximately 99.5% of cases of RTT are sporadic, resulting from a de novo variant, which arise almost exclusively on the paternally derived X chromosome. The remaining 0.5% of cases are familial and usually explained by germline mosaicism or favorably skewed X-chromosome inactivation in the carrier mother that results in her being unaffected or only slightly affected (mild intellectual disability). In the case of a carrier mother, the recurrence risk of RTT is 50%. If a variant is not identified in leukocytes of the mother, the risk to a sibling of the proband is below 0.5% (since germline mosaicism in either parent cannot be excluded).

The identification of a variant in *MECP2* does not necessarily equate to a diagnosis of RTT. Rare cases of *MECP2* variants have also been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked intellectual disability, PPM-X syndrome (an X-linked genetic disorder characterized by psychotic disorders [most commonly bipolar disorder], parkinsonism, and intellectual disability), autism and neonatal encephalopathy.[1]

A proportion of patients with a clinical diagnosis of RTT do not appear to have variants in the *MECP2* gene. Two other genes, *CDKL5* and *FOXG1*, have been shown to be associated with atypical variants of RTT. Variants in *CDKL5* are associated with a variant of RTT observed in females with apparently classic Rett syndrome in whom the presentation is dominated by seizures and onset is before age six months.[9] Variants in *FOXG1* are associated with a type of RTT referred to as congenital or precocious RTT, in which regression is never clearly identified but the clinical picture is otherwise classic.[10]

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[11] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

CLINICAL VALIDITY

A study be Henriksen (2020) reported the results of exome sequencing for a group of 91 females diagnosed with RTT in Norway.[12] A likely genetic cause was found for 86 of the patients, including 77 with an *MECP2* variant. Variants in *SMC1A*, *SYNGAP1*, *SCN1A*, *CDKL5*, *FOXG1* and chromosome 13q were also identified. The authors noted that the presence of an *MECP2* variant was a major determinant of the clinical phenotype.

Zhang (2018) investigated familial cases with RTT or X-linked mental retardation (XLMR).[13] For this study, 429 children were recruited from 427 Chinese families. Each child either had RTT or XLMR. All patients provided genomic DNA samples. Of the 427 families, three girls and five boys (from six families) were identified as having the *MECP2* variant. The three girls met the diagnostic criteria for RTT; the five boys had XLMR. The *MECP2* gene was sequenced and reviewers observed a random X-chromosome inactivation (XCI) pattern in all the girls and two of the mothers. A skewed XCI was seen in the other four mothers. In all *MECP2* variant cases, the variant was confirmed to be an identical variant inherited from the mother. No variants were inherited from the father. This study adds to the relatively sparse literature on familial cases with *MECP2* variants; with evidence for maternal inheritance of *MECP2* variants.

Vidal (2017) investigated the utility of next-generation sequencing (NGS) and its ability to genetically identify an affected person.[14] To achieve the effect of NGS, several different techniques were employed, such as Sanger sequencing and whole-exome sequencing. This study included 1,577 patients who exhibited signs of having RTT but had not yet been formally diagnosed. Using Sanger sequencing, 1,341 patients were evaluated, and 26% had genes variants identified (RTT). Two hundred forty-two patients were assessed using the Haloplex Custom Panel, and 22% were diagnosed genetically. Fifty-one patients were evaluated using the TruSight One panel, and 15 (29%) patients were diagnosed genetically; 25 patients were studied by whole-exome sequencing, and it was discovered that five variants occurred in genes previously associated with neurodevelopmental disorders with features similar to those of RTT syndrome. Reviewers conclude that NGS allows for more genes associated with RTT-like symptoms to be studied and therefore allows for a wider pool of patients to be studied, thus reducing cost and improving efficiency.

Halbach (2016) analyzed a cohort of a group of 132 well-defined RTT females aged between 2 and 43 years with extended clinical, molecular, and neurophysiological assessment.[15] Genotype-phenotype analyses of clinical features and cardiorespiratory data were performed after grouping variants by the same type and localization or having the same putative biological effect on the MeCP2 protein, and subsequently on eight single recurrent pathogenic variants. A less severe phenotype was seen in females with CTS, p.R133C, and p.R294X variants. Autonomic disturbances were present in all females, and not restricted to nor influenced by one specific group or any single recurrent variant. The objective information from non-invasive neurophysiological evaluation of the disturbed central autonomic control is of great importance in helping to organize the lifelong care for females with RTT. The study concluded that further research is needed to provide insights into the pathogenesis of autonomic dysfunction, and to develop evidence-based management in RTT.

Pidcock (2016) identified 96 RTT patients with pathogenic variants in the *MECP2* gene.[16] Among 11 pathogenic variant groups, a statistically significant group effect of variant type was observed for self-care, upper extremity function, and mobility, on standardized measures administered by occupational and physical therapists. Patients with R133C and uncommon variants tended to perform best on upper extremity and self-care items, whereas patients with R133C, R306C and R294X had the highest scores on the mobility items. The worst performers

on upper extremity and selfcare items were patients with large deletions, R255X, R168X, and T158M variants. The lowest scores for mobility were found in patients with T158M, R255X, R168X, and R270X variants. On categorical variables as reported by parents at the time of initial evaluation, patients with R133C and R294X were most likely to have hand use, those with R133C, R294X, R306C and small deletions were most likely to be ambulatory, and those with R133C were most likely to be verbal.

Sajan (2017) analyzed 22 RTT patients without apparent *MECP2*, *CDKL5*, and *FOXG1* pathogenic variants were subjected to both whole-exome sequencing and single-nucleotide polymorphism array-based copy-number variant (CNV) analyses.[17] Three patients had *MECP2* variants initially missed by clinical testing. Of the remaining 19, 17 (89.5%) had 29 other likely pathogenic intragenic variants and/or CNVs (10 patients had two or more). Interestingly, 13 patients had variants in a gene/region previously reported in other neurodevelopmental disorders (NDDs), thereby providing a potential diagnostic yield of 68.4%. The genetic etiology of RTT without *MECP2*, *CDKL5*, and *FOXG1* variants is heterogeneous, overlaps with other NDDs, and complicated by a high variant burden. Dysregulation of chromatin structure and abnormal excitatory synaptic signaling may form two common pathological bases of RTT.

Maortua (2013) evaluated the presence of *MECP2* variants (sequencing of four exons and rearrangements) in 120 female patients with suspected Rett syndrome, 120 female patients with intellectual disability of unknown origin and 861 (519 females and 342 males) controls.[18] Eighteen different pathological variants were identified in both patients suspected of Rett syndrome and in those without a specific diagnosis. Authors concluded, "*MECP2* must be studied not only in patients with classical/atypical Rett syndrome but also in patients with other phenotypes related to Rett syndrome."

Two studies published in 2013 and 2012 respectively[19 20] used the InterRett database to examine genotype and RTT severity. Of 357 girls with epilepsy who had *MECP2* genotype recorded, those with large deletions were more likely than those with 10 other common variants to have active epilepsy (odds ratio [OR]: 3.71 (95% confidence interval [CI]: 1.13, 12.17); p=0.03) and had the earliest median age at epilepsy onset (3 years 5 months). Among all girls in the database, those with large deletions were more likely to have never walked (OR: 0.42 (95% CI: 0.22, 0.79), p=0.007). Among 260 girls with classic RTT enrolled in the multicenter RTT Natural History study, those with the R133C substitution variant had clinically less severe disease, assessed by the Clinical Severity, Motor Behavior Analysis, and Physician Summary scales.[6] Fabio et al reported similar genotype-phenotype correlations among 144 patients with RTT in Italy.[21]

Huppke (2009) analyzed the *MECP2* gene in 31 female patients diagnosed clinically with RTT.[22] Sequencing revealed variants in 24 of the 31 patients (77%). Of the seven patients in whom no variants were found, five fulfilled the criteria for classical RTT. In this study, 17 different variants were detected, 11 of which had not been previously described. Several females carrying the same variant displayed different phenotypes, suggesting that factors other than the type or position of variants influence the severity of RTT.

Lotan (2006) reviewed and summarized six articles that attempted to disclose a genotype-phenotype correlation, which included the two studies outlined above.[2] The authors found that these studies have yielded inconsistent results and that further controlled studies are needed before valid conclusions can be drawn about the effect of variant type on phenotypic

expression.

A study by Cheadle (2000) analyzed variants in 48 females with classical sporadic RTT, seven families with possible familial RTT, and five sporadic females with features suggestive, but not diagnostic, of RTT.[23] The entire *MECP2* gene was sequenced in all cases. Variants were identified in 44/55 (80%) of unrelated classical sporadic and familial RTT patients. Only one out of five (20%) sporadic cases with suggestive but non-diagnostic features of RTT had variants identified. Twenty-one different variants were identified (12 missense, four nonsense, and five frame-shift variants); 14 of the variants identified were novel. Significantly milder disease was noted in patients carrying missense variants as compared to those with truncating variants.

Section Summary

Although the AHRQ report reported finding no studies on clinical validity for RTT, there is evidence from several small studies indicates that the clinical sensitivity of genetic testing for classical RTT is reasonably high, in the range of 75 to 80%. However, the sensitivity may be lower when classic features of RTT are not present. The clinical specificity is unknown but is also likely to be high, as only rare cases of *MECP2* variants have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, nonsyndromic X-linked intellectual disability, PPM-X syndrome, autism and neonatal encephalopathy.

CLINICAL UTILITY

The AHRQ report found that the majority of the clinical studies identified for RTT were for indirect assessment of clinical utility as “most of the genetic tests relevant to this report are intended to establish an etiologic diagnosis and rarely used in isolation to confirm a clinical diagnosis”.[24] Finally, no studies were identified that directly assessed the impact of genetic testing on health outcomes.

However, the clinical utility of genetic testing can be considered in the following clinical situations: 1) individuals with suspected RTT, 2) family members of individuals with RTT, and 3) prenatal testing for mothers with a previous RTT child. These situations are discussed separately below.

Individuals with Suspected RTT

The clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of RTT changed patient management. Therefore, there is no direct evidence for the clinical utility of genetic testing in these patients.

Given that there is no specific treatment for RTT, making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. However, there are several potential ways in which adjunctive management might be changed following genetic testing after confirmation of the diagnosis:

- Further diagnostic testing may be avoided
- Referral to a specialist(s) may be made
- Heightened surveillance for Rett-associated clinical manifestations, such as scoliosis or cardiac arrhythmias may be performed

- More appropriate tailoring of ancillary treatments such as occupational therapy may be possible

Therefore, genetic testing for RTT syndrome in developmentally delayed female children, without a clear diagnosis, may offer some surveillance benefits as well as help to avoid unnecessary additional diagnostic testing.

Family Member and Prenatal RTT Testing

Genetic testing can be done in sisters of girls with RTT who have an identified *MECP2* pathogenic variant to determine if they are asymptomatic carriers of the disorder. However, this is an extremely rare possibility, since the disorder is nearly always sporadic. Testing of family members of individuals with RTT will therefore result in an extremely low yield. However, testing for a known familial Rett-syndrome-associated variant may aid mothers and sisters of affected individuals in reproductive decision-making.

Similarly, in cases of prenatal testing the risk of a family having a second child with the disorder is less than 1%, except in the rare situation where the mother carries the variant.[25] Therefore, for mothers without the Rett phenotype, it is extremely unlikely that prenatal testing will identify cases of RTT.

Section Summary

The clinical utility of genetic testing for RTT has not been established in the literature; however, genetic testing can confirm a diagnosis in patients with clinical signs and symptoms of Rett syndrome. A definitive diagnosis may help avoid further testing for other possible syndromes as well as alter surveillance and management of Rett associated conditions. While direct evidence of clinical utility for family member and prenatal testing is lacking, there may be some benefit in terms of reproductive decision making.

PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified which gave recommendations on when to perform *CDKL5* or *FOXG1* testing. However, studies have suggested that patients who are negative for *MECP2* variants and who have a strong clinical diagnosis of RTT should be considered for further screening of the *CDKL5* gene if there are early-onset seizures, or the *FOXG1* gene if there are congenital features (e.g., severe postnatal microcephaly).[1-3]

AMERICAN ACADEMY OF NEUROLOGY AND THE PRACTICE COMMITTEE OF THE CHILD NEUROLOGY SOCIETY[26]

In 2011, a quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society issued an evidence report on the genetic and metabolic testing of children with global developmental delay. The report concluded, “Girls with severe impairment may be appropriate for testing for *MECP2* mutations, regardless of whether the specific clinical features of Rett syndrome are present.”

AMERICAN ACADEMY OF PEDIATRICS

In 2019 the American Academy of Pediatrics (AAP) reaffirmed earlier their recommendation for *MECP2* testing to confirm a diagnosis of suspected Rett syndrome in females, especially when the diagnosis is unclear from symptoms alone.[27]

In 2020, the AAP published a Clinical Report Guidance on the identification, evaluation, and management of children with autism spectrum disorder which stated that "if patient is a girl, consider evaluation for Rett syndrome, *MECP2* testing.[28]

AMERICAN COLLEGE OF MEDICAL GENETICS

In 2013, ACMG updated their guideline for the genetic evaluation of autism spectrum disorders. Testing for *MECP2* variants is recommended as part of the diagnostic workup of females who present with an autistic phenotype.[29] Routine *MECP2* testing in males with autistic spectrum disorders is not recommended.

SUMMARY

There is enough research to show that genetic testing for variants in *MECP2*, *FOXG1* and/or *CDKL5* may be useful in confirming or excluding the diagnosis of Rett syndrome (RTT). Although there is no effective treatment for RTT, a definitive diagnosis can end a diagnostic workup for other possible diagnoses and may alter some aspects of management. Therefore, genetic testing of the *MECP2*, *FOXG1* and/or *CDKL5* genes for RTT may be considered medically necessary in select patients who meet the policy criteria.

There is enough research to show that genetic testing for Rett syndrome (RTT) variants in at-risk relatives of patients with RTT may help with reproductive decision-making. Therefore, targeted genetic testing of known familial RTT variants may be considered medically necessary for these individuals.

There is not enough research to show that genetic testing for Rett syndrome (RTT) can improve health outcomes or reproductive decision-making in situations that do not meet the policy criteria. Also, *MECP2*, *FOXG1* and *CDKL5* are the only genes that have been shown to cause RTT. Therefore, genetic testing for Rett syndrome is considered investigational for all other indications, including but not limited to prenatal screening and panel testing that includes genes other than *MECP2*, *FOXG1* and/or *CDKL5*.

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CODES

Codes	Number	Description
CPT	0234U	*MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81302	*MECP2 (methyl CpG binding protein 2)*(eg, Rett syndrome) gene analysis; full sequence analysis
	81303	;known familial variant
	81304	;duplication/deletion variants
	81404	Molecular pathology procedure, Level 5 – which includes *FOXG1* (*forkhead box G1*) (eg, Rett syndrome), full gene sequence
	81405	Molecular pathology procedure, Level 6 – which includes *CDKL5 (cyclin-dependent kinase-like 5)* (eg, early infantile epileptic encephalopathy), duplication/deletion analysis
	81406	Molecular pathology procedure, Level 7 – which includes *CDKL5 (cyclin-dependent kinase-like 5)* (eg, early infantile epileptic encephalopathy), full gene sequence
HCPCS	None	

Date of Origin: *May 2010*

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Effective: April 1, 2025

Next Review: January 2026
Last Review: February 2025

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

Disease-associated variants in the *DMD* gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases. The severe end of the spectrum includes the progressive muscle diseases Duchenne and Becker muscular dystrophy and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less and more severe forms, as well as identify individuals at risk of having affected offspring.

MEDICAL POLICY CRITERIA

Note: This policy does not address reproductive carrier screening for these disorders (see Cross References)

I. Genetic testing for *DMD* gene variants may be considered **medically necessary** if any of the following are met:

   A. In patients with signs and symptoms of a dystrophinopathy to confirm the diagnosis and direct treatment; or

   B. To confirm or exclude the need for cardiac surveillance in at-risk relatives (see Policy Guidelines).

C. Prenatal (fetal) genetic testing for fetal diagnosis if a parent is known to be a carrier or has a first- or second-degree relative who is affected or known to be a carrier.

II. Genetic testing for *DMD* gene variants is considered **not medically necessary** if the criteria above are not met.

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

POLICY GUIDELINES

Heterozygous individuals are at increased risk for cardiomyopathy and need routine cardiac surveillance and treatment.

At-risk relatives are defined as first- and second-degree relatives with two X chromosomes (e.g., sister, mother, daughter, aunt, etc).

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or disease-associated variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Date of blood draw for test
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, they are classified as Duchenne or Becker muscular dystrophy and when the heart is primarily affected, as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD), the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene.[1] The incidence of DMD is estimated to be one in 3,500 newborn male births,[2] and approximately one-third of DMD cases arise from de novo variants and have no known family history.[1] Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool from years two to five. Affected children present with gait problems, calf hypertrophy, positive Gower's sign, and difficulty climbing stairs. The affected child's motor status may plateau between three and six years of life with deterioration beginning at six to eight years. The majority of patients will be wheelchair bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (e.g., decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death.[1] Few individuals with DMD survive beyond the third decade.

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. Individuals remain ambulatory into their twenties. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-forties.

FEMALE CARRIERS

Females heterozygous for a *DMD* disease-associated variant can manifest symptoms of the disease.[3] An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from a mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy.[4] Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous individuals do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated *DMD* gene in the affected X chromosome.[5] In some cases, this compensation can be reversed by a non-random or skewed inactivation of X chromosome resulting in greater expression of the affected X chromosome and some degree of myopathic features.[6] Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome).[3]

CLINICAL DIAGNOSIS

DMD

The suspicion of DMD should be considered irrespective of family history and is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or after the discovery of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting

up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties in rising from the floor or in tip-toe walking, and pseudo hypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and commonly a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5,000 and 150,000 IU/L), is non-specific to DMD but is always present in affected patients.[1] Electromyography and nerve-conduction were traditional parts of the assessment of neuromuscular disorders, but now these tests are no longer believed to be necessary for the specific assessment of DMD.[7] An open skeletal muscle biopsy is needed when a negative test for deletions or duplications to the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

BMD

Becker muscular dystrophy (BMD) has a clinical picture similar to DMD but is milder than DMD and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5 to 100 times the normal level).

Molecular Diagnosis

DMD is the only gene in which variants are known to cause DMD, BMD and DMD-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males. *DMD*, the gene that codes for dystrophin is the largest known human gene[1] A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5,000 different reported disease-associated variants, as well as a high de novo variant rate.[8]

Treatment

There is no cure for Duchenne or Becker muscular dystrophy, and treatment is aimed at control of symptoms to improve quality of life. However, the natural history of the disease can be changed by several strategies such as corticosteroid therapy, proper nutrition or rehabilitative interventions. Glucocorticoids can slow the loss of muscle strength and may be started when a child is diagnosed or when muscle strength begins to decline.[7] The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways.[1] Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at two to five years of age although there has been no demonstrated benefit of earlier therapy, before five years of age.[1]

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted toward specific pathogenic variants.[9] Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, non-shifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Exon-skipping therapies using antisense oligonucleotides approved by the U.S. Food and Drug Administration include: eteplirsen (Exondys 51) for treatment for patients who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping, and golodirsen (Vyondys 53) \\pdxnas01\DataPdx1\Saturn\Groups\MedPol\1. Policy Work\Genetic Testing\gt69\Policy Drafts\2022 01_blankand viltolarsen (Viltepso) for patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping, and casimersen (Amondys 45), for patients who have a confirmed variant in the *DMD* gene that is amenable to exon 45 skipping. These approvals were based on improvements in the surrogate outcome of increased dystrophin production in skeletal muscle and benefits in clinical outcomes have not yet been established. A gene therapy, delandistrogene moxeparvovec-rokl (Elevidys), was also approved in 2023 to treat ambulatory children four to five years of age with DMD and a confirmed mutation in the DMD gene.

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review focuses on clinical validity and utility.

Clinical Validity

In male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy, the presence of a DMD familial variant is predictive of future developing clinical manifestations of a DMD-associated dystrophinopathy.[11]

Virtually all males with DMD/BMD have identifiable *DMD* disease-associated variants, indicating a high clinical sensitivity for genetic testing. In males with DMD and BMD, phenotypes are best correlated with the degree of expression of dystrophin, largely determined by the reading frame of the spliced message obtained from the deleted allele.

A reading frame is the way in which a messenger RNA sequence of nucleotides can be read as a series of base triplets and affects which protein is made. In DMD, dystrophin protein function is completely lost due to variants that disrupt the reading frame. Therefore, prematurely truncated, unstable dystrophins are generated. In contrast, patients with BMD have low levels of full-length dystrophin or carry in-frame variants that allow for the generation of partially functional proteins. This so-called reading frame rule explains the phenotypic differences between DMD and BMD patients. Since this rule was postulated in 1988,[12] thousands of variants have been reported for DMD and BMD, of which an estimated 90% fit this rule.[13]

Manjunath (2015) compared the sensitivity of multiplex ligation-dependant probe amplification (MLPA) and multiplex polymerase chain reaction (mPCR) in detecting deletions in 83 children with suspected DMD.[14] mPCR detected deletions in 60/83 (72.3%) of children, while MLPA in the same 83 samples detected deletions in 66/83 (79.5%) and duplications in 6/83 (6.5%), indicating that MLPA has the higher detection rate of the two techniques. Muscle biopsy and subsequent immunohistochemistry performed in the 11 MLPA-negative cases showed absent dystrophin staining in 4/83 (36.4%), indicating neither of these techniques are as sensitive as whole gene sequencing by NGS or deletion/duplication detection using a chromosomal microarray.

Clinical Utility

No studies were identified that reported on clinical utility. However, the clinical utility of testing for *DMD* gene variants for the index case includes:

- Establishing the diagnosis and initiating/directing treatment of the disease, such as glucocorticoids, evaluation by a cardiologist, avoidance of certain agents (e.g., botulinum toxin injections), and prevention of secondary complications (immunizations, reducing risk of fractures).
- Distinguishing between DMD and BMD.
- Avoidance of a muscle biopsy in the majority of cases.

The clinical utility of testing for *DMD* gene variants for at-risk relatives includes testing to identify heterozygous individuals to confirm or exclude the need for cardiac surveillance.

PRACTICE GUIDELINE SUMMARY

DUCHENNE MUSCULAR DYSTROPHY CARE CONSIDERATIONS WORKING GROUP

In 2010, an international working group comprised of 84 clinicians and scientists from government agencies, including the U.S. Centers for Disease Control and Prevention, and advocacy organizations provided recommendations for providing coordinated multidisciplinary

care in the diagnosis and treatment of DMD.[7] Per the working group, genetic testing should first be used to screen for deletions and duplications. If no deletion or duplication is detected, screening for single nucleotide variants should be performed. For patients diagnosed by genetic testing, muscle biopsy is optional to distinguish DMD from milder phenotypes.

In 2018, the DMD Care Considerations Working Group updated its Care Considerations recommendations.[15] Their recommendations for genetic testing utilization in DMD diagnosis remained similar to their 2010 recommendations, with a recommendation to first screen for deletions and duplications, followed by genetic sequencing if no deletion or duplication is detected. A muscle biopsy is only recommended if genetic testing does not confirm a clinical diagnosis and DMD is still considered likely. The working group also recommended genetic counseling to family members of an individual with DMD to establish who is at risk of being a carrier. Carrier testing is recommended for female relatives of a male who has been genetically confirmed to have DMD.

THE EUROPEAN MOLECULAR GENETICS QUALITY NETWORK AND EUROGENTEST

An international consortium of scientists conferred and developed the consensus-based, “Best Practice Guidelines on Molecular Diagnosis in DMD/BMD Muscular Dystrophies.” The guidelines recommend genetic testing when there is a clinical suspicion of a dystrophinopathy. In addition, the guidelines recommend to first screen for deletions and duplications. If no deletion or duplication is detected, but the clinical diagnosis is verified, the guidelines recommend screening for single nucleotide variants (SNVs).[9] In 2020, these guidelines were updated to summarize current recommended technologies and methodologies in DMD gene analysis.[16] The guideline's recommendations for testing are similar to the 2010 recommendations. In terms of an initial screen, a diagnostic test that detects whole-exon deletions or duplications should be offered to detect copy number variations. Use of RNA-based analysis is recommended in patients with a clinical diagnosis of dystrophinopathy but no copy number variations or small variants that were identified.

THE AMERICAN ACADEMY OF NEUROLOGY AND AMERICAN ASSOCIATION OF NEUROMUSCULAR AND ELECTRODIAGNOSTIC MEDICINE

The American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine guidelines (2015, reaffirmed in 2021) on evaluation, diagnosis and management of congenital muscular dystrophy (CMD) include the recommendation that, “when available and feasibly, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes.”[17] This is a level C recommendation, the lowest allowable recommendation level.

SUMMARY

There is enough research to show that genetic testing, including prenatal fetal testing, can improve health outcomes when dystrophinopathy is suspected and for at-risk relatives. Clinical guidelines based on research recommend testing of the *DMD* gene in patients that have signs and symptoms of Duchenne and/or Becker muscular dystrophy. Therefore, genetic testing for *DMD* gene disease-associated variants may be considered medically necessary to establish a diagnosis in an individual with clinical signs and symptoms

suggestive of a dystrophinopathy and in at-risk relatives. Similarly, prenatal fetal testing may be considered medically necessary when policy criteria are met.

Screening for *DMD* variants is not recommended for people without symptoms or who are not at-risk relatives. Therefore, genetic testing for *DMD* gene disease-associated variants is considered not medically necessary when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
	81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) --includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy), full gene sequence
HCPCS	None	

Table 1. Testing Strategy

To establish the diagnosis of a proband with DMD or BMD in a male with clinical findings that suggest a dystrophinopathy:

- Perform DMD genetic testing for deletion/duplication analysis first.
- If a copy number variant (CNV) is not identified, perform sequence analysis for a SNV.
- If a disease-causing DMD variant is identified, the diagnosis of a dystrophinopathy is established.
- In cases where a distinction between DMD and BMD is difficult, the reading frame “rule” states that the type of deletion/duplication (those that alter the reading frame [out-of-frame], which correlates with the more severe phenotype of DMD versus those that do not alter the reading frame [in-frame] which correlate with the milder BMD phenotype) can distinguish the DMD and BMD phenotypes with 91-92% accuracy.
- If no disease-causing DMD variant is identified, skeletal muscle biopsy is warranted for western blot and immunohistochemistry studies of dystrophin.

For carrier testing in at-risk female relatives:

- When the proband’s DMD disease-associated variant is known, test for that deletion/duplication or SNV using appropriate testing method.
- When an affected male is not available for testing, perform testing by deletion/duplication first and if no variant is identified, by sequence analysis.

Table 1. Testing Strategy
The evaluation of relatives at risk includes females who are the sisters or maternal female relatives of an affected male and females who are a first-degree relative of a known or possible carrier female.

Date of Origin: *January 2014*

Fetal Red Blood Cell Antigen Genotyping Using Maternal Plasma

Effective: April 1, 2025

Next Review: June 2025
Last Review: March 2025

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 use of cell-free fetal DNA in maternal blood has been proposed as a noninvasive method to determine fetal red blood cell antigen genotypes, including *RHD* genotype.

MEDICAL POLICY CRITERIA

Fetal red blood cell antigen genotyping, including but not limited to RhD, Fy^a (Duffy), K (Kell), C, c, and E antigens, using maternal plasma 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 Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA, Genetic Testing, Policy No 44

BACKGROUND

During pregnancy, antigen-negative individuals who are exposed to antigen-positive red blood cells (RBCs) can develop specific antibodies against those antigens, which can cross the placenta and cause fetal anemia. If undiagnosed and untreated, alloimmunization can cause

significant perinatal morbidity and mortality. Determining the antigen status, particularly the Rh status, of the fetus may guide subsequent management of the pregnancy. The use of cell-free fetal DNA in maternal blood has been proposed as a noninvasive method to determine fetal antigen genotype.

RED BLOOD CELL ANTIGENS

The surface of RBCs are covered with antigen molecules. These include the standard blood group antigens associated with ABO blood types, Rh antigens, and many others. These antigens can stimulate an immune response in individuals who do not produce the same antigens.

The (Rhesus) Rh system includes more than 100 antigen varieties found on RBCs. RhD is the most common and the most immunogenic. When people have the RhD antigen on their RBCs, they are considered RhD-positive; if their RBCs lack the antigen, they are considered RhD-negative. The RhD-antigen is inherited in an autosomal dominant fashion, and a person may be heterozygous (Dd) (~60% of Rh-positive people) or homozygous (DD) (approximately 40% of Rh-positive people). Homozygotes always pass the RhD antigen to their offspring, whereas heterozygotes have a 50% chance of passing the antigen to their offspring. A person who is RhD-negative does not have the Rh antigen. Although nomenclature refers to RhD-negative as dd, there is no small d antigen (i.e., they lack the *RHD* gene and the corresponding RhD antigen).

RhD-negative status varies among ethnic groups and is 15% in whites, 5 to 8% in African Americans, 5% to 8%, and 1% to 2% in Asians and Native Americans, respectively.

In the Caucasian population, almost all RhD-negative individuals are homozygous for a deletion of the *RHD* gene. However, in the African-American population, only 18% of RhD-negative individuals are homozygous for an *RHD* deletion, and 66% of RhD-negative African Americans have an inactive *RHD* pseudogene (*RHDψ*).[1] There are also numerous rare variants of the D antigen, which are recognized by weakness of expression of D and/or by absence of some of the epitopes of D. Some individuals with variant D antigens can make antibodies to one or more epitopes of the D antigen, if exposed to RhD-positive RBCs. In addition to *RHD* and *RHDψ* variants, variants in the homologous gene *RHCE* can produce C and E antigens. Other RBC antigens families include the Duffy, Kell, Kidd, Lewis antigens.

ALLOIMMUNIZATION

Alloimmunization refers to the development of antibodies in a patient whose blood cells are antigen-negative and who is exposed to antigen-positive red blood cells (RBCs). This most commonly occurs from fetal-placental hemorrhage and entry of fetal blood cells into the maternal circulation.

The management of a Rh-negative pregnant patient who is not alloimmunized and is carrying a known Rh-positive fetus or the fetal Rh status is unknown, involves administration of Rh immune globulin at standardized times during the pregnancy to prevent the formation of anti-Rh antibodies. If the patient is already alloimmunized, management involves monitoring the levels of anti-Rh antibody titers for the development of fetal anemia. Both noninvasive and invasive tests to determine fetal Rh status exist.

By 30 days of gestation, the RhD antigen is expressed on the red blood cell (RBC) membrane, and alloimmunization can occur when fetal Rh-positive RBCs enter maternal circulation, and

the Rh-negative mother develops anti-D antibodies.[2] Once anti-D antibodies are present in a pregnant woman's circulation, they can cross the placenta and cause destruction of fetal RBCs.

The production of anti-D antibodies in RhD-negative women is highly variable and significantly affected by several factors, including the volume of fetomaternal hemorrhage, the degree of the maternal immune response, concurrent ABO incompatibility, and fetal homozygosity versus heterozygosity for the D antigen. Therefore, although ~10% of pregnancies are Rh-incompatible, <20% of Rh-incompatible pregnancies actually lead to maternal alloimmunization.

Small fetomaternal hemorrhages of RhD-positive fetal RBCs into the circulation of an RhD-negative woman occurs in nearly all pregnancies, and incidence of fetomaternal hemorrhage increases as the pregnancy progresses: 7% in the first trimester, 16% in the second trimester, and 29% in the third trimester, with the greatest risk of RhD alloimmunization occurring at birth (15% to 50%). Transplacental hemorrhage accounts for almost all cases of maternal RhD alloimmunization.

Fetomaternal hemorrhage can also be associated with miscarriage, pregnancy termination, ectopic pregnancy, invasive in-utero procedures (e.g., amniocentesis), in utero fetal death, maternal abdominal trauma, antepartum maternal hemorrhage, and external cephalic version. Other causes of alloimmunization include inadvertent transfusion of RhD-positive blood and RhD-mismatched allogeneic hematopoietic stem-cell transplantation.

There are other antigens on RBCs in addition to RhD, including the Duffy (Fy^a,Fy^b) and Kell antigens, that can lead to alloimmunization, but these are much more rare.

Consequences of Alloimmunization

IgG antibody–mediated hemolysis of fetal RBCs, known as hemolytic disease of the fetus and newborn, varies in severity and can have a variety of manifestations. The anemia can range from mild to severe with associated hyperbilirubinemia and jaundice. In severe cases, hemolysis may lead to extramedullary hematopoiesis and reticuloendothelial clearance of fetal RBCs, which may result in hepatosplenomegaly, decreased liver function, hypoproteinemia, ascites, and anasarca. When accompanied by high-output cardiac failure and pericardial effusion, this condition is known as hydrops fetalis, which without intervention, is often fatal. Intensive neonatal care, including emergent exchange transfusion, is required.

Cases of hemolysis in the newborn that do not result in fetal hydrops can still lead to kernicterus, a neurologic condition observed in infants with severe hyperbilirubinemia due to the deposition of unconjugated bilirubin in the brain. Symptoms that manifest several days after delivery can include poor feeding, inactivity, loss of the Moro reflex, bulging fontanelle, and seizures. The 10% of infants who survive may develop spastic choreoathetosis, deafness, and/or mental retardation.

The result of disease from alloimmunization, hemolytic disease of the fetus or newborn, was once a major contributor to perinatal morbidity and mortality. However, with the widespread adoption of antenatal and postpartum use of Rh immune globulin in developed countries, the result has been a major decrease in frequency of this disease. In developing countries without prophylaxis programs, stillbirth occurs in 14% of affected pregnancies, and 50% of pregnancy survivors either die in the neonatal period or develop cerebral injury.[3]

Prevention of Alloimmunization

There are four currently in use Rh immune globulin products available in the U.S., all of which undergo micropore filtration to eliminate viral transmission.[3] To date, no reported cases of viral infection related to Rh immune globulin administration have been reported in the U.S.[3] Theoretically, the Creutzfeldt-Jakob disease (CJD) agent could be transmitted by the use of Rh immunoglobulin. Local adverse reactions may occur, including redness, swelling, and mild pain at the site of injection, and hypersensitivity reactions have been reported.

The American College of Obstetricians and Gynecologists (ACOG) and the American Association of Blood Banks (AABB) recommend the first dose of Rh_0(D) immune globulin (e.g., RhoGAM®) be given at 28 weeks' gestation, (or earlier if there's been an invasive event), followed by a postpartum dose given within 72 hours of delivery.

Diagnosis of Alloimmunization

The diagnosis of alloimmunization is based on detection of antibodies to specific RBC antiges in the maternal serum.

The most common test for determining antibodies in serum is the indirect Coombs test.[2] Maternal serum is incubated with known RhD-positive RBCs. Any anti-RhD antibody present in the maternal serum will adhere to the RBCs. The RBCs are then washed and suspended in Coombs serum, which is antihuman globulin. RBCs coated with maternal anti-RhD will agglutinate, which is referred to as a positive indirect Coombs test. The indirect Coombs titer is the value used to direct management of pregnant alloimmunized women.

Management of Alloimmunization during Pregnancy

A patient's first alloimmunized pregnancy involves minimal fetal or neonatal disease. Subsequent pregnancies are associated with more severe degrees of fetal anemia. Treatment of an alloimmunized pregnancy requires monitoring of maternal anti-D antibody titers and serial ultrasound assessment of middle cerebral artery peak systolic velocity of the fetus.

If severe fetal anemia is present near term, delivery is performed. If severe anemia is detected remote from term, intrauterine fetal blood transfusions may be performed.

DETERMINING FETAL RHD STATUS

ACOG recommends that all pregnant women should be tested at the time of their first prenatal visit for ABO blood group typing and Rh-D type and be screened for the presence of anti-RBC antibodies. These laboratory tests should be repeated for each subsequent pregnancy. The AABB also recommends that antibody screening be repeated before administration of anti-D immune globulin at 28 weeks' gestation, postpartum, and at the time of any event during pregnancy.

If the mother is determined to be Rh-negative, the paternal Rh status should also be determined at the initial management of a pregnancy. If paternity is certain and the father is Rh-negative, the fetus will be Rh-negative, and further assessment and intervention are unnecessary. If the father is RhD-positive, he can be either homozygous or heterozygous for the D allele. If he is homozygous for the D allele (i.e., D/D) then the fetus is RhD-positive. If the paternal genotype is heterozygous for Rh status or is unknown, determination of the Rh-status of the fetus is the next step.

Invasive and noninvasive testing methods to determine the Rh status of a fetus are available.

Invasive procedures use polymerase chain reaction (PCR) assays to assess the fetal cellular elements in amniotic fluid by amniocentesis or by chorionic villus sampling (CVS). Although CVS can be performed earlier in a pregnancy, amniocentesis is the preferred method because CVS is associated with disruption of the villi and the potential for larger fetomaternal hemorrhage and worsening alloimmunization if the fetus if RhD-positive. The sensitivity and specificity of fetal *RHD* typing by PCR are reported as 98.7% and 100%, respectively, with positive and negative predictive values of 100% and 96.9%, respectively.[4]

Noninvasive prenatal testing (NIPT) involves molecular analysis of cell-free fetal DNA (cffDNA) in the maternal plasma or serum. Lo (1998) showed that about 3% of cell-free DNA in the plasma of first trimester pregnant women is of fetal origin, with this percentage rising to 6% in the third trimester.[5] Fetal DNA cannot be separated from maternal DNA, but if the pregnant woman is RhD-negative, the presence of specific exons of the *RHD* gene, which are not normally present in the circulation of an RhD-negative patient, predicts an RhD-positive fetus. Measurement of cffDNA has been proposed as an alternative to obtaining fetal tissue by invasive methods, which are associated with a risk of miscarriage.[1]

The large quantity of maternal DNA compared to fetal DNA in the maternal circulation complicates the inclusion of satisfactory internal controls to test for successful amplification of fetal DNA. Therefore, reactions to detect Y chromosome-linked gene(s) can be included in the test, which will be positive when the fetus is a male.[1] When Y chromosome-linked genes are not detected, tests for polymorphisms may be performed to determine whether the result is derived from fetal but not maternal DNA.

REGULATORY STATUS

There are several tests available that include NIPT RBC antigen genotyping tests including:

- UNITY Fetal RhD NIPT (BillionToOne)
- UNITY Fetal Antigen NIPT (BillionToOne)
- Natera™ Fetal RhD NIPT (Natera™)
- SensiGene™ Fetal *RHD* Genotyping test (Sequenom)

There are currently no U.S. Food and Drug Administration (FDA)-cleared *RHD* genotyping tests. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[6] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease,

while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Fetal *RHD* genotyping is best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. Validation of the clinical use of any diagnostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review focuses on the clinical validity and utility of testing.

CLINICAL VALIDITY

For the evaluation of clinical validity, studies that reported on the accuracy of the marketed version of the technology, included a suitable reference standard, and described patient/sample clinical characteristics and selection criteria were considered for inclusion.

Systematic Reviews

A systematic review and meta-analysis by Yang (2019) the diagnostic accuracy of high-throughput cffDNA testing to determine fetal RhD status.[7] Study eligibility criteria for the review included a prospective cohort design, inclusion of women who were RhD-negative and not known to be sensitized, and the use of cord blood testing as a comparison standard. Eight studies were included, two of which were judged to be at high risk of bias. The results of the meta-analysis showed a false negative rate of 0.34% (95% confidence interval [CI] 0.15 to 0.76), and a false positive rate of 3.86% (95% CI 2.54 to 5.82) when inconclusive results were treated as positives, which dropped to 1.26% (95% CI 0.87 to 7.83) when inconclusive results were excluded.

Mackie (2017) published a systematic review and meta-analysis of studies on the diagnostic accuracy of cffDNA-based non-invasive prenatal testing.[8] Thirty of the 117 included cohort studies in the analysis evaluated RhD status. The overall sensitivity and specificity were 99.3% and 98.4% respectively. Real-time PCR exhibited higher sensitivity when compared to conventional PCR. There was no difference in specificity. Ten of the 30 studies reported inconclusive results.

Zhu (2014) published a meta-analysis of studies on the diagnostic accuracy of noninvasive fetal *RHD* genotyping using cell-free fetal DNA.[9] The investigators identified 37 studies conducted in RhD-negative pregnant women that were published by the end of 2013. The studies included a total of 11,129 samples, and 352 inconclusive samples were excluded. When all data were pooled, the sensitivity of fetal *RHD* genotyping was 99% and the specificity was 98%. Diagnostic accuracy was higher in samples collected in the first trimester (99.0%) than those collected in the second (98.3%) or third (96.4%) trimesters.

Nonrandomized Studies

A prospective study by Chitty (2014) was published evaluating the diagnostic accuracy of antenatal testing for fetal RhD status.[10] Samples from 2,288 Rh-negative women who initiated prenatal care before 24 weeks of gestation were analyzed using *RHD* genotyping. Overall, the sensitivity of the test was 99.34% and the specificity was 94.91%. The likelihood of correctly detecting RhD status in the fetus increased with gestational age, with high levels of accuracy after 11 weeks. For example, for samples taken before 11 completed weeks of gestation, the sensitivity was 96.85% and the specificity was 94.40%, and at 14 to 17 weeks' gestation, sensitivity was 99.67% and specificity was 95.34%. These findings of increased accuracy as pregnancies advanced differ from that of the Zhu (2014) meta-analysis, which found highest diagnostic accuracy in the first trimester.

A study published by Wikman (2012) reported the results of a prospective, population-based study involving 4,118 RhD-negative, non-alloimmunized pregnant women from 83 maternity care centers.[11] Median gestational age was 10 weeks (range 3 to 40 weeks), with 75.5% of patients undergoing testing in the first trimester, 18.8% in the second, 4.3% in the third, and 1.4% unknown. Extracted DNA samples from each woman were analyzed in triplicate. Reanalysis had to be performed in 211 (5.1%) cases with inconclusive results in the first analysis. A positive or negative fetal RhD was reported for 96% of the samples, with 165 (4%) remaining inconclusive. A second sample was then obtained from 147 of the 165 pregnancies with inconclusive results: 14 (0.8%) remained inconclusive, all resulting from a weak or silent maternal *RHD* gene. Blood group serology of the newborns was used as the gold standard, and blood group serology results were missing for 466 pregnancies, leaving 3,652 newborns for whom the validity of *RHD* genotyping could be assessed. The false-negative rate (*RHD* genotyping was Rh-negative, but newborn was determined to be Rh-positive) was 55 of 2,297 (2.4%) and the false-positive rate (*RHD* genotyping was Rh-positive, but newborn was determined to be Rh-negative) was 15 of 1,355 (1.1%). After exclusion of the samples obtained before the eighth week of gestation, the false-negative rate was 23 of 2,073 (1.1%) and the false-positive rate was 14 of 1,218 (1.1%). Both sensitivity and specificity were close to 99% if the samples were not collected before gestational week eight. The authors note that a limitation of their study was the lack of a positive control for fetal DNA.

Moise (2012) analyzed samples from 120 patients who were enrolled prospectively between May 2009 and July 2010 from multiple centers.[12] All patients were Rh-negative pregnant patients with no evidence of alloimmunization. Race/ethnicity was Caucasian/white (72.5%), African-American/black (12.5%), Hispanic/Latino (12.5%), Asian (0.8%), and other (1.7%). The samples were analyzed using the SensiGENE *RHD* test using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to detect control and fetal-specific DNA signals. The determination of fetal sex was: three Y-chromosome markers=male fetus, two markers=inconclusive, and one or no markers = female fetus. The algorithm for *RHD* determination was: pseudogene present=inconclusive, three *RHD* markers present = RhD-positive fetus, two markers present = inconclusive, one or no markers = RhD-negative fetus. The pregnant patients underwent planned venipunctures during three time periods in gestation: 11 to $13^{6/7}$, 16 to $19^{6/7}$, and 28 to $29^{6/7}$ weeks. Median gestational age of the first, second and third trimester samplings was 12.4 (range 10.6 to 13.9) weeks, 17.6 (16 to 20.9) weeks and 28.7 (27.9 to 33.9) weeks, respectively. Twenty-two samples (6.3% of the total samples; 2.5% of the patients) were deemed inconclusive. In 23% of these inclusive cases, there was an RhD-negative, female result, but there were an insufficient number of paternal SNVs detected to confirm the presence of fetal DNA. In the remaining 77% of the inconclusive results (4.8% of the total samples), the *RHD* ψ-pseudogene was detected, and the sample was deemed inconclusive. Erroneous results were observed for six of the samples

(1.7%) and included discrepancies in four *RHD* typings (1.1%) and two fetal sex determinations (0.6%) following data unblinding. Three cases of *RHD* typing were false positives (cffDNA was RhD-positive but neonatal serology RhD-negative) and one case was a false negative (cffDNA was RhD-negative but neonatal serology was RhD-positive). Accuracy for determination of the RhD status of the fetus was 99.1%, 99.1%, and 98.1%, respectively for each of the three consecutive trimesters of pregnancy, and accuracy of fetal sex determination was 99.1%, 99.1%, and 100%, respectively. The authors note, "the current test has not been validated for its ability to predict the zygosity of the fetus when the psi-pseudogene is detected because of limited number of pseudogene cases in conjunction with the challenge of assessing limited fetal copies against the high background of maternal DNA."

Bombard (2011) analyzed the performance of the SensiGene Fetal *RHD* Genotyping test in two cohorts using a retrospective study design. Cohort 1 used as a reference point the clinical RhD serotype obtained from cord blood at delivery. Samples from cohort 2 were originally genotyped at the Sequenom Center in Grand Rapids, Michigan and results were used for clinical validation of genotyping performed at the Sequenom Center in San Diego, California.[13]

In cohort 1, *RHD* genotyping was performed on 236 maternal plasma samples from singleton, nonsensitized pregnancies with documented fetal RhD serology. The samples were obtained at 11 to 13 weeks' gestation. Ethnic origin of the pregnant women was Caucasian (77.1%), African (19.1%), mixed race (3.4%) and South Asian (0.4%). Neonatal RhD phenotype, determined by serology at the time of birth, was positive in 69.1% of samples and negative in 30.9% of samples. In two (0.9%) of the 236 samples, there the results were classified as invalid. In the 234 (99.1%) samples with sufficient DNA extraction, the result was conclusive in 207 samples (88.5%); inconclusive in 16 samples (6.8%); and ψ-positive/*RHD* variant in 11 samples (4.7%). In the 207 samples with a conclusive result, the neonatal RhD phenotype was positive in 142 samples (68.6%) and negative in 65 samples (31.4%). The Fetal *RHD* Genotyping test correctly predicted the neonatal RhD phenotype in 201 of 207 samples for an accuracy of 97.1% (95% CI 93.5 to 98.8). In the 142 samples with RhD-positive fetuses, the test predicted that the fetus was positive in 138 and negative in four, for a sensitivity of prediction of RhD positivity of 97.2% (95% CI 93.0 to 98.9). In 63 of the 65 samples with RhD-negative fetuses, the Fetal *RHD* Genotyping test predicted that the fetus was negative and, in the remaining two, that it was positive, for a specificity for the prediction of RhD positivity of 96.9% (95% CI 89.5 to 99.1). The test predicted that the fetus was RhD-positive in 140 samples, of which, in 138 of these the prediction was correct, for a positive predictive value of 98.6% (95% CI 94.9 to 99.6). The test predicted that the fetus was RhD-negative in 67 samples, of which, in 63 of these the prediction was correct, for a negative predictive value for RhD-positive fetuses of 94.0% (95% CI 85.6 to 97.6). Cohort 1 samples were limited in the amount of sample available for analysis.

Cohort 2 consisted of 205 samples from 6 to 30 weeks' gestation. Testing was for the presence of *RHD* exon sequences 4, 5, 7, the ψ-pseudogene, and three Y-chromosome sequences (*SRY*, *DBY* and *TTTY2*), using MALDI-TOF MS (the *RHD* Genotyping laboratory developed test). The laboratory performing the assays for both cohorts was blinded to the sex and fetal *RHD* genotype. In cohort 2, the test correctly classified 198 of 199 patients, for a test accuracy of 99.5%, with a sensitivity and specificity for prediction of *RHD* genotype of 100.0% and 98.3%, respectively.

Other studies have replicated previous findings that fetal *RHD* genotyping can be accurately determined using cffDNA from maternal plasma, although not all Rh-positive fetuses are identified.[14-21]

The Unity Fetal Antigen™ test, which assesses RhD, K1, Fy^a, C, c, and E antigens, demonstrated 100% sensitivity and specificity in a validation study in 1,683 clinical samples.[22] Rego (2024) published a prospective validation study with samples from 156 patients with alloimmunized pregnancies.[23] Of these, 15.4% were Hispanic, 9.0% were non-Hispanic Black, 65.4% were non-Hispanic White, 4.5% were Asian, and 1.3% had more than one race/ethnicity. The authors reported 100% concordance between NIPT test results and neonatal genotype obtained from buccal swabs for 465 antigen calls: K1 (n=143), E (n=124), C (n=60), Fy^a (n=50), c (n=47), and D(RhD) (n=41). Neonatal phenotype was not assessed.

CLINICAL UTILITY

No published data are identified showing that this type of testing leads to improved health outcomes. This type of testing could lead to the avoidance of the use of anti-D immune globulin (e.g., RhoGAM) in Rh-negative mothers with Rh-negative fetuses. However, the false negative rate of the test, while low, is not zero, and a certain percentage of Rh-negative women will develop alloimmunization to Rh-positive fetuses. Other issues that still need to be defined include the optimal timing of testing during the pregnancy.

A systematic review by Runkel (2020) evaluated the evidence for the benefit of cffDNA testing for fetal RhD status in RhD-negative pregnant women and reported a lack of studies investigating patient-relevant outcomes.[24] They additionally performed a meta-analysis of diagnostic accuracy studies and reported a high sensitivity and specificity for the testing.

EVIDENCE SUMMARY

The clinical validity of fetal *RHD* genotyping is high, in that the test has shown a high degree of accuracy in correctly predicting fetal RhD status. However, the test does not identify all Rh-positive fetuses, which may lead to alloimmunization of the Rh-negative mothers in these cases. The current data that demonstrates how the results from cell-free fetal DNA analysis in maternal blood are used to alter treatment decisions and improve health outcomes compared to conventional testing are lacking. Therefore, the clinical utility of fetal *RHD* genotyping is unknown, and it is uncertain whether it will lead to improved health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN ASSOCIATION OF BLOOD BANKS (AABB)

AABB does not have specific practice guidelines or recommendations on the use of fetal *RHD* or other RBC antigen genotyping.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)

The American College of Obstetricians and Gynecologists Practice Bulletins 192 (2018) and 181 (2017) address management and prevention of RhD alloimmunization, respectively.[25, 26] The Bulletins note that although the detection of fetal RhD using molecular analysis of maternal plasma or serum can be assessed in the second trimester with an accuracy greater than 99%, it is not recommended nor widely used as a clinical tool.

SUMMARY

More research is needed to know how well fetal red blood cell (RBC) antigen genotyping with maternal plasma works for improving health outcomes compared to current standard of care. No clinical guidelines based on research recommend fetal RBC antigen genotyping with maternal plasma, including *RHD* genotyping. Therefore, fetal RBC antigen genotyping, including but not limited to RhD, Fy^a (Duffy), K (Kell), C, c, and E antigens, using maternal plasma is considered investigational.

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CODES

Codes	Number	Description
CPT	0488U	Obstetrics (fetal antigen noninvasive prenatal test), cellfree DNA sequence analysis for detection of fetal presence or absence of 1 or more of the Rh, C, c, D, E, Duffy (Fya), or Kell (K) antigen in alloimmunized pregnancies, reported as selected antigen(s) detected or not detected

	0494U	Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative
	0536U	Red blood cell antigen (fetal RhD), PCR analysis of exon 4 of RHD gene and housekeeping control gene GAPDH from whole blood in pregnant individuals at 10+ weeks gestation known to be RhD negative, reported as fetal RhD status
	81403	Molecular pathology procedure, Level 4 *RHD (Rh blood group, D antigen)* (eg, hemolytic disease of the fetus and newborn, Rh maternal/fetal compatibility), deletion analysis (eg, exons 4, 5 and 7, pseudogene), performed on cell-free fetal DNA in maternal blood (For human erythrocyte gene analysis of RHD, use a separate unit of 81403)
HCPCS	None	

Date of Origin: *June 2014*

Medical Policy Manual Genetic Testing, Policy No. 75

Genetic Testing for Macular Degeneration

Effective: September 1, 2024

Next Review: July 2025
Last Review: July 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

Age-related macular degeneration (AMD) is a complex disease involving both genetic and environmental influences. Testing for variants at certain genetic loci has been proposed to predict the risk of developing advanced AMD or to guide treatment.

MEDICAL POLICY CRITERIA

Genetic testing for macular degeneration is considered **investigational**.

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

CROSS REFERENCES

1. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

BACKGROUND

AGE-RELATED MACULAR DEGENERATION (AMD)

Macular degeneration, the leading cause of severe vision loss in people older than age 60 years, occurs when the central portion of the retina, the macula, deteriorates. Because the disease develops as a person ages, it is often referred to as age-related macular degeneration (AMD). AMD has an estimated prevalence of 1 in 2,000 people in the United States and affects individuals of European descent more frequently than African Americans in the United States.

There are two major types of AMD, known as the dry form and the wet form. The dry form is much more common, accounting for 85% to 90% of all cases of AMD, and it is characterized by the buildup of yellow deposits called drusen in the retina and slowly progressive vision loss. The condition typically affects vision in both eyes, although vision loss often occurs in one eye before the other. AMD is generally thought to progress along a continuum from dry AMD to neovascular wet AMD, with approximately 10 to 15% of all AMD patients eventually developing the wet form. Occasionally patients with no prior signs of dry AMD present with wet AMD as the first manifestation of the condition.

The wet form of AMD is characterized by the growth of abnormal blood vessels from the choroid underneath the macula, and is associated with severe vision loss that can rapidly worsen. The abnormal vessels leak blood and fluid into the retina, which damages the macula, leading to permanent loss of central vision.

Major risk factors for AMD include older age, cigarette smoking, cardiovascular diseases, nutritional factors, and certain genetic markers. Age appears to be the most important risk factor, as the chance of developing the condition increases significantly as a person gets older. Smoking is another established risk factor. Other factors that may increase the risk of AMD include high blood pressure, heart disease, a high-fat diet or one that is low in certain nutrients (such as antioxidants and zinc), and obesity. Observational data (n=17,174) from the European EYE-RISK Consortium suggest that the odds of AMD increases by at least 2 times in patients with both genetic risk and predisposing lifestyle factors (e.g., smoking and low dietary intake of vegetables, fruit, and fish).[1]

CLINICAL DIAGNOSIS OF AMD

AMD can be detected by routine eye exam, with one of the most common early signs being the presence of drusen or pigment clumping. An Amsler grid, a pattern of straight lines that resemble a checkerboard, may also be used. In an individual with AMD, some of the straight lines may appear wavy or missing.

If AMD is suspected, fluorescein angiography and/or optical coherence tomography (OCT) may be performed. Angiography involves injecting a dye into the bloodstream to identify leaking blood vessels in the macula. OCT captures a cross section image of the macula and aids in identifying fluid beneath the retina and in documenting degrees of retinal thickening.

TREATMENT OF AMD

There is currently no cure for macular degeneration, but certain treatments may prevent severe vision loss or slow the progression of the disease. For dry AMD, there is no medical treatment; however, changing certain lifestyle risks may slow the onset and progression of AMD. The goal for wet (advanced) AMD is early detection and treatment aimed at preventing the formation of new blood vessels, or sealing the leakage of fluid from blood vessels that have already formed. Treatment options include laser photocoagulation, photodynamic therapy, surgery, anti-angiogenic drugs, and combination treatments. Anti-angiogenesis drugs block the

development of new blood vessels and leakage from the abnormal vessels within the eye that cause wet macular degeneration and may lead to patients regaining lost vision. A large study performed by the National Eye Institute of the National Institutes of Health, the Age-Related Eye Disease Study (AREDS), showed that for certain individuals (those with extensive drusen or neovascular AMD in one eye) high doses of vitamins C, E, beta-carotene, and zinc may provide a modest protective effect against the progression of AMD.[2]

GENETICS OF AMD

It has been reported that genetic variants associated with AMD account for approximately 70% of the risk for the condition.[3]

More than 25 genes have been reported in association with an increased risk of developing AMD, discovered initially through family-based linkage studies, and subsequently through large-scale genome-wide association studies. Genes influencing several biological pathways, including genetic loci associated with the regulation of complement, lipid, angiogenic and extracellular matrix pathways, have been found to be associated with the onset, progression and bilateral involvement of early, intermediate and advanced stages of AMD.[4]

Loci based on common single nucleotide polymorphisms (SNPs) contribute to the greatest AMD risk:

- The long (q) arm of chromosome 10 in a region known as 10q26 contains two genes of interest, *ARMS2* and *HTRA1*. Changes in both genes have been studied as possible risk factors for the disease; however, because the two genes are so close together, it is difficult to tell which gene is associated with age-related macular degeneration risk, or whether increased risk results from variations in both genes.
- Common and rare variants in the complement factor H (*CFH*) gene.

Other confirmed genes in the complement pathway include *C2*, *C3*, *CFB* and *CFI*.[4] On the basis of large genome-wide association studies, high-density lipoprotein (HDL) cholesterol pathway genes have been implicated, including *CETP* and *LIPC*, and possibly *LPL* and *ABCA1*.[4, 5] The collagen matrix pathway genes *COL10A1* and *COL8A1,* apolipoprotein E *APOE* and the extracellular matrix pathway gene *TIMP3 and FBN2* have also been linked to AMD.[4] Genes involved in DNA repair (*RAD51B*) and in the angiogenesis pathway (*VEGFA*) have also been associated with AMD as have specific SNPs.[6] Recently Fang (2021) presented a systematic review on use of genetic biomarkers different than those mentioned above for early AMD and intermediate AMD, which are more reproducible and less invasive than the other classes of biomarkers. [7]

COMMERCIALLY AVAILABLE TESTING FOR AMD

Commercially available genetic testing for AMD is aimed at identifying those individuals who are at risk of developing *advanced* AMD.

Arctic Medical Laboratories offers Macula Risk PGx®, which uses patient clinical information (age, BMI, smoking history, education) and the patient's genotype for 15 genetic markers across 12 AMD-associated genes, in an algorithm to identify Caucasians at high risk for progression of early or intermediate AMD to advanced forms of AMD. A Vita Risk® report is also provided with vitamin recommendations based on the CFH/ARMS2 genotype.

Nicox offers Sequenom's RetnaGene™ AMD in North America, which evaluates the risk of a patient with early or intermediate AMD progressing to advanced choroidal neovascular disease (wet AMD) within 2, 5, and 10 years. The RetnaGene AMD test assesses the impact of 12 genetic variants (single nucleotide polymorphisms or SNPs) located on genes that are collectively associated with the risk of progressing to advanced disease in patients with early- or intermediate-stage disease (CFH/CFH region, C2, CRFB, ARMS2, C3), along with phenotype of disease, age, and smoking history. A risk score is generated, and the patient is categorized into one of three risk groups: low, moderate, or high risk.

ARUP laboratory offers testing for mutations in the *ARMS2* and *CFH* genes. deCode Complete includes testing for mutations in *CFH, ARMS2/HTRA1, C2, DFB*, and *C3* genes. 23andMe includes testing for *CFH, ARMS2, and C2*.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[8] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test indicating how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of the literature search was on evidence related to the ability of genetic test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

ANALYTIC VALIDITY

According to the manufacturer, the Macula Risk® PGx test is noted as having a 10-year predictive accuracy of 89.5%, with a sensitivity and specificity both > 80%.[9, 10] Data regarding the predictive accuracy of the RetnaGene™ AMD test was not identified in the peer-reviewed literature.

Genetic testing for single or multiple genes associated with advanced AMD may be requested through a number of laboratories which are typically validated in-house and are subject to CLIA regulatory standards.

CLINICAL VALIDITY

Current models for predicting AMD risk include various combinations of epidemiologic, clinical and genetic factors, and give areas under the curve (AUC) of approximately 0.8.[11-16] (By plotting the true and false positives of a test, an AUC measures the discriminative ability of the test, with a perfect test giving an AUC of 1). An analysis by Seddon (2015) demonstrated that a model of AMD risk that included age, gender, education, baseline AMD grade, smoking and body mass index had an AUC of 0.757.[14] The addition of the genetic factors SNPs in CFH, ARMS2, C2, C3 and CFB, increased the AUC to 0.821. In a 2015 report, Seddon included 10 common and rare genetic variants in their risk prediction model, resulting in an AUC of 0.911 for progression to advanced AMD.[17]

Klein (2011) evaluated macular phenotype, utilizing the Age-Related Eye Disease Study (AREDS) Simple Scale score, which rated the severity of AMD based on the presence of large drusen and pigment changes, to predict the rate of advanced AMD.[11, 18] This predictive model included age, family history, smoking, the AREDS Simple Scale score, presence of very large drusen, presence of advanced AMD in one eye, and genetic factors (CFH and ARMS2). The AUC was 0.865 without genetic factors included and 0.872 with genetic factors included.[11] Govindaiah (2021) reported that a prediction model for development of age-related macular degeneration using AREDS data had an area under the curve of 0.69 using genetic data only, 0.77 using genetic and sociodemographic data, and 0.92 using genetic, sociodemographic, and retinal imaging data.[19] Ajana (2021) also reported an area under the curve at five years of 0.92 for an age-related macular degeneration model that included clinical, genetic, and lifestyle factors.[20] de Breuk (2021) and the EYE-RISK consortium found that patients with late age-related macular degeneration had significantly higher genotype assay risk scores than patients with early or intermediate disease ($p<0.001$) or no disease ($p<0.001$) based on a European case-control population (n=4,740).[21] In addition to the biomarkers mentioned in this policy, a recent publication reported microRNAs, urinary proinflammatory cytokines, and proteins in the aqueous and vitreous humor; apolipoprotein A1 (APOA1), complement factor H R2 (CFHR2), and clusterin (CLUS) proteins, kallistatin (SERPINA4), lumican (LUM), and keratan (KERA) as an indication of early AMD.[7]

Although these risk models suggest some small incremental increase in the ability to assess risk of developing advanced AMD based on genetic factors, they do not demonstrate how results from testing alter treatment decisions or improve overall health outcomes.

CLINICAL UTILITY

The possible clinical utility of genetic testing for AMD can be divided into disease prevention, disease monitoring and therapy guidance, as discussed in more detail below.

Prevention

The clinical utility of predictive genetic testing for AMD rests in the availability of preventative therapies and interventions which go beyond good health practices (e.g., abstinence from smoking, balanced diet, exercise, nutrient supplements). In addition, once a preventive therapy was established, the optimal risk-benefit treatment strategy would need to be validated to ensure appropriate age-related AMD interventions. However, the only preventive measures currently available are high-dose antioxidants and zinc supplements which have been shown to reduce the progression of disease.[2, 22-25]

Monitoring

The clinical utility of genetic testing for AMD could also rest in the tests ability to identify a patient as high risk, which may increase the frequency of monitoring. This could include the use of home monitoring devices or the use of technology such as preferential hyperacuity perimetry to detect early or subclinical wet AMD. However, there is insufficient evidence demonstrating how more frequent monitoring of high-risk patients slows the progression of AMD or improves overall outcomes.[11]

Treatment

Finally, the clinical utility of genetic testing for AMD could also rest in the tests ability to identify patients who would benefit from specific gene-based treatment which may slow, halt, or resolve AMD symptoms. There is insufficient evidence demonstrating how genetic test results have been used to guide treatment decisions in patients with advanced AMD. A recent systematic review showed that anti-VEGF therapy may produce significant improvement at 12 months in patients with neovascular AMD.[26]. However, there have been no consistent associations between response to vitamin supplements or anti-VEGF (vascular endothelial growth factor) therapy and *VEGF* gene polymorphisms.[23, 24, 27-32]

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OPHTHALMOLOGY (AAO)

The 2014 American Academy of Ophthalmology (AAO) Task Force on Genetic Testing recommendations specific to genetic testing for complex eye disorders like AMD state that the presence of any one of the disease-associated variants is not highly predictive of the development of disease.[33] The AAO Task Force finds that in many cases, standard clinical diagnostic methods like biomicroscopy, ophthalmoscopy, tonography, and perimetry will be more accurate for assessing a patient's risk of vision loss from a complex disease than the assessment of a small number of genetic loci. AAO concludes that genetic testing for complex diseases will become relevant to the routine practice of medicine when clinical trials demonstrate that patients with specific genotypes benefit from specific types of therapy or surveillance; until such benefit can be demonstrated, the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

In 2019, AAO published a Preferred Practice Pattern on age-related macular degeneration, which noted that the routine use of genetic testing is not recommended at this time due to lack of prospective clinical evidence.[34]

AMERICAN SOCIETY OF RETINA SPECIALISTS[35]

The American Society of Retina Specialists (2017) published special correspondence on the use of genetic testing in the management of patients with AMD. The Society concluded that:

- While AMD genetic testing may provide information on progression from intermediate to advanced AMD, there is no clinical evidence that altering management of genetically higher risk progression patients results in better visual outcomes compared with lower risk progression patients.
- AMD genetic testing in patients with neovascular AMD does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor (VEGF) treatment and is therefore not recommended for this population.
- Currently, there is insufficient evidence to support the use of genetic testing in patients with AMD in regard to nutritional supplement recommendations.

SUMMARY

The current evidence is insufficient in demonstrating how genetic testing for age-related macular degeneration (AMD) improves treatment decisions or health outcomes. Currently, there are no preventive measures that can be undertaken, outside of good health practices. Therefore, genetic testing for AMD is considered investigational.

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CODES

Codes	Number	Description
CPT	0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
	81479	Unlisted molecular pathology procedure

Codes	Number	Description
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *July 2014*

Regence

Medical Policy Manual Genetic Testing, Policy No. 77

Genetic Testing for Heritable Disorders of Connective Tissue

Effective: September 1, 2024

Next Review: June 2025
Last Review: July 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

Heritable disorders of connective tissue have a high degree of clinical variability and phenotypes, often involving the cardiovascular, musculoskeletal, ocular, pulmonary, and gastrointestinal systems. Due to clinical overlap with other syndromes and disorders, diagnosis may be challenging.

MEDICAL POLICY CRITERIA

Note: Please see Cross References for individual gene and panel testing for genes not associated with connective tissue disorders.

I. Individual gene variant and targeted panel testing for connective tissue disorders (see Policy Guidelines) may be considered **medically necessary** when either of the following are met:
   A. To diagnose an individual with specific signs and symptoms of a connective tissue disorder; *or*
   B. Testing for an asymptomatic individual, when there is a known pathogenic variant in the family.

II. Individual gene variant testing and genetic panel testing for a connective tissue disorder is considered **not medically necessary** 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

HERITIBLE DISORDRS OF CONNECTIVE TISSUE

There are over thirty disorders of connective tissues with overlapping features. The most common are listed below with examples of frequently occurring symptoms (list is not exhaustive):

Disorder	Symptoms
Ehlers-Danlos syndrome (EDS), type IV, also referred to as vascular EDS (vEDS)	Arterial aneurysms, dissection, or rupture; intestinal rupture; uterine rupture during pregnancy; and family history of vEDS. Additionally, thin, translucent skin; facial characteristics including thin lips, micrognathia, narrow nose, and prominent eyes; acrogeria; carotid-cavernous sinus arteriovenous fistula; and hypermobility of small joints.
Loeys-Dietz syndrome (LDS)	Vascular, skeletal, cardiofacial, cutaneous, allergic/inflammatory disease, and ocular manifestations. Aortic root dilatation is seen in more than 95% of probands.
Marfan syndrome (MFS)	Mild to severe manifestations of the ocular, skeletal, and cardiovascular systems. Myopia; bone overgrowth and joint laxity; disproportionately long extremities for the size of the trunk; pectus excavatum or pectus carinatum; and varying degrees of scoliosis.
Heritable thoracic aortic disease	Manifestations of the ocular, neurological, cardiovascular, and pulmonary systems.

GENES COMMONLY TESTED FOR CONNECTIVE TISSUE DISORDERS

- *ACTA2*
- *COL3A1*
- *COL5A1*
- *COL5A2*
- *FBN1*
- *FBN2*
- *FLNA*
- *MYH11*
- *MYLK*
- *PLOD1*
- *SLC2A10*
- *SMAD3*
- *TGFB2*
- *TGFBR1*
- *TGFBR2*

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or variant(s) being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test:
    - History and physical/chart notes, including *specific* signs and symptoms observed, related to a *specific* connective tissue disorder
    - Known family history related to a specific connective tissue disorder, if applicable
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

BACKGROUND

CONNECTIVE TISSUE DISEASES

Individuals suspected of having a systemic connective tissue disease (CTD) like Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome (EDS), type IV usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these syndromes may share features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. Additional difficulties in the diagnosis of one of these syndromes may occur due to the age-dependent development of many of the physical manifestations of the syndrome (making the diagnosis more difficult in children); many show variable expression, and many features found in these syndromes occur in the general population (e.g., pectus excavatum, tall stature, joint hypermobility, mitral valve prolapse, nearsightedness). The identification of the proper syndrome is important to address its manifestations and complications, including the risk of aortic aneurysms and dissection.

Thoracic Aortic Aneurysms and Dissection

Most thoracic aortic aneurysms (TAAs) are degenerative and are often associated with the same risk factors as abdominal aortic aneurysms (e.g., atherosclerosis). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.[1]

Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically related TAA accounts for approximately 5% of TAA.[1] Some genetic syndromes associated with TAA have more aggressive rates of aortic expansion and are more likely to require intervention compared with sporadic TAA. MFS is the most common inherited form of syndromic TAA and thoracic aortic aneurysm dissection (TAAD). Other genetic, systemic CTDs associated with a risk of TAAD include Ehlers-Danlos syndrome (EDS) type IV, Loeys-Dietz syndrome (LDS), and arterial tortuosity syndrome.

Familial TAAD refers to patients with a family history of aneurysmal disease who do not meet criteria for a CTD.

Marfan Syndrome

MFS is an autosomal-dominant condition, in which there is a high degree of clinical variability of systemic manifestations, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease in multiple organ systems.[2] Despite the clinical variability, the principal manifestations involve the skeletal, ocular, and cardiovascular systems. Involvement of the skeletal system is characterized by bone overgrowth and joint laxity, disproportionately long extremities for the size of the trunk (dolichostenomelia), overgrowth of the ribs which can push the sternum in or out (pectus excavatum or carinatum, respectively), and scoliosis, which can be mild or severe and progressive. Ocular features include myopia, and displacement of the lens from the center of the pupil (ectopia lentis) is a feature seen in 60% of affected individuals. Cardiovascular manifestations are the major source of morbidity and mortality and include dilation of the aorta at the level of the sinuses of Valsalva, predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of a person with MFS can approximate that of the general population.

Diagnosis

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems and family history.[3] The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS.[3] The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some of the clinical manifestations, making the diagnosis in children more difficult, and for including some nonspecific physical manifestations or poorly validated diagnostic thresholds. The revised criteria are based on clinical characteristics in large patient cohort studies and expert opinions.[3] The revised criteria include several major changes, as follows. More weight is given to the two cardinal features of MFS—aortic root aneurysm and dissection and ectopia lentis. In the absence of findings that are not expected in MFS, the combination of these two features is sufficient to make the diagnosis. When aortic disease is present, but ectopia lentis is not, all other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to a “systemic score” that guides diagnosis. Second, a more prominent role has been given to molecular testing of *FBN1* and other relevant genes, allowing for the appropriate use when necessary. Third, some less specific manifestations of MFS were removed or given less weight in the diagnostic criteria. Fourth, the revised criteria formalized the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but shows unexpected findings, particularly if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on LDS, Shprintzen-Goldberg syndrome (SGS), and EDS vascular type. LDS and SGS have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin, and dura. EDS vascular type occasionally overlaps with MFS. Each of these conditions has a unique risk profile and management protocol.[3] Given the autosomal-dominant nature of inheritance, the number of physical findings needed to establish a diagnosis for a person with an established family history is reduced.

Genetic Testing

It is estimated that molecular techniques permit the detection of *FBN1* pathogenic variants in up to 97% of Marfan patients who fulfill Ghent criteria, suggesting that the current Ghent criteria have excellent specificity.[3]

FBN1 is the only gene for which pathogenic variants are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, while 25% have a de novo pathogenic variant. Over 1000 *FBN1* pathogenic variants that cause MFS have been identified. The following findings in *FBN1* molecular genetic testing should infer causality in making the diagnosis of MFS: a pathogenic variant previously shown to segregate in families with MFS and de novo pathogenic variants of a certain type (e.g., nonsense, certain missense variants, certain splice site variants, certain deletions and insertions).[2]

Most variants in the *FBN1* gene that cause MFS can be identified with sequence analysis (≈70% to 93%) and, although the yield of deletion and duplication analysis in patients without a defined coding sequence or splice site by sequence analysis is unknown, it is estimated to be about 30%. The most common testing strategy of a proband suspected of having MFS is sequence analysis followed by deletion and duplication analysis if a pathogenic variant is not identified.[2] However, the use of genetic testing for a diagnosis of MFS has limitations. More than 90% of pathogenic variants described are unique, and most pathogenic variants are not repeated among nongenetically related patients. Therefore, the absence of a known pathogenic variant in a patient in whom MFS is suspected does not exclude the possibility that the patient has MFS. No clear genotype-phenotype correlation exists for MFS and, therefore, the severity of the disease cannot be predicted from the type of variant.

Caution should be used when interpreting the identification of an *FBN1* variant, because other conditions with phenotypes that overlap with MFS can have an *FBN1* variant (e.g., MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopia lentis).

Treatment

Management of MFS includes both treatment of manifestations and prevention of complications, including surgical repair of the aorta depending on the maximal measurement, the rate of increase of the aortic root diameter, and the presence of progressive and severe aortic regurgitation.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of disorders that affect connective tissues and share common features characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. The defects in connective tissues can vary from mildly loose joints to life-threatening complications. All types of EDS affect the joints and many affect the skin, but features vary by type. In 2017, the Ehlers-Danlos Society published updated classification and diagnostic parameters based on expert consensus by the International EDS Consortium.[4] The new classification recognizes 13 subtypes, wherein all but one type has a known associated gene.

The different types of EDS include, among others, types I and II (classical and classical-like types), type III (cardiac-valvular), type IV (vascular type), and type VI (arthrochalasia form), all of which are inherited in an autosomal-dominant pattern except types II and III, which are autosomal-recessive. It is estimated that affected individuals with types I, II, or IV may inherit

the pathogenic variant from an affected parent 50% of the time, and about 50% have a de novo pathogenic variant.

Most types of EDS are not associated with aortic dilation, except the vascular type (also known as type IV), which can involve serious and potentially life-threatening complications. The prevalence of the vascular type IV may affect 1 in 250,000 people. Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by an aneurysm, arteriovenous fistulae or dissection, or may occur spontaneously. Such complications are often unexpected and may present as sudden death, stroke, internal bleeding, and/or shock. The vascular type is also associated with an increased risk of gastrointestinal perforation, organ rupture, and rupture of the uterus during pregnancy.

Diagnosis

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of two major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.[5] The presence of one or more minor clinical criteria supports the diagnosis but is insufficient to make the diagnosis by itself.

Genetic Testing

Pathogenic variants in the *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *PLOD1*, and *TNXB* genes cause EDS. The vascular type (type IV) is caused by pathogenic variants in the *COL3A1* gene.

Loeys-Dietz Syndrome

LDS is an autosomal-dominant condition characterized by 4 major groups of clinical findings, including vascular, skeletal, craniofacial, and cutaneous manifestations. Vascular findings include cerebral, thoracic, and abdominal arterial aneurysms and/or dissections. Skeletal findings include pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. The natural history of LDS is characterized by arterial aneurysms, with a mean age of death of 26 years and a high incidence of pregnancy-related complications, including uterine rupture and death. Treatment considerations take into account that aortic dissection tends to occur at smaller aortic diameters than MFS, and the aorta and its major branches can dissect in the absence of much if any, dilation. Patients with LDS require echocardiography at frequent intervals, to monitor the status of the ascending aorta, and angiography evaluation to image the entire arterial tree.

Genetic Testing

LDS is caused by pathogenic variants in the *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2,* and *SMAD3* genes.

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome is inherited in an autosomal recessive pattern and characterized by tortuosity of the aorta and/or large- and middle-sized arteries throughout the body. Aortic root dilation, stenosis, and aneurysms of large arteries are common. Other features of the syndrome include joint laxity and skin hyperextensibility.

Genetic Testing

The syndrome is caused by pathogenic variants in the *SLC2A10* gene.

Familial TAAD

Approximately 80% of familial TAA and TAAD is inherited in an autosomal-dominant manner and may be associated with variable expression and decreased penetrance of the disease-associated variant.

The major cardiovascular manifestations of familial TAAD (fTAAD) include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta, or both, and dissections of the thoracic aorta involving ascending or descending aorta.[6] In the absence of surgical repair of the ascending aorta, affected individuals have progressive enlargement of the ascending aorta, leading to acute aortic dissection. Presentation of the aortic disease and the age of onset are highly variable.

Diagnosis

Familial TAAD is diagnosed based on the presence of thoracic aorta pathology; absence of clinical features of MFS, LDS, or vascular EDS; and a positive family history of TAAD.

Genetic Testing

Familial TAAD is associated with 16 genes, including pathogenic variants in *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *SMAD3*, and two loci on other chromosomes, *AAT1* and *AAT2*. Rarely, fTAAD can also be caused by *FBN1* pathogenic variants. To date, only about 20% of fTAAD is accounted for by variants in known genes. Early prophylactic repair should be considered in individuals with confirmed pathogenic variants in the *TGFBR2* and *TGFBR1* genes and/or a family history of aortic dissection with minimal aortic enlargement.

Other Syndromes and Disorders

The following syndromes and conditions may share some of the features of the above CTDs, however, the list is not exhaustive.

Congenital Contractural Arachnodactyly (Beal Syndrome)

Congenital contractural arachnodactyly is an autosomal-dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers.[2] Other features may include “crumpled” ears, contractures of the knees and ankles at birth with improvement over time, camptodactyly, hip contractures, and progressive kyphoscoliosis. Mild dilatation of the aorta is rarely present. Congenital contractural arachnodactyly is caused by pathogenic variants in the *FBN2* gene.

MED12-Related Disorders

The phenotypic spectrum of *MED12*-related disorders is still being defined but includes Lujan syndrome and FG syndrome type 1.[7] Lujan syndrome and FG syndrome type 1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum. Individuals with Lujan syndrome share some physical features with MFS, in that they have Marfanoid features including tall and thin habitus, long hands and fingers, pectus excavatum, narrow palate, and joint hypermobility.[7] *MED12*-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

Shprintzen-Goldberg Syndrome

Shprintzen-Goldberg syndrome is an autosomal-dominant condition characterized by a combination of major characteristics that include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings.[8] *SK1* is the only gene for which pathogenic variants are known to cause Shprintzen-Goldberg syndrome.

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Homocystinuria is a rare metabolic disorder inherited in an autosomal recessive manner, characterized by an increased concentration of homocysteine, a sulfur-containing amino acid, in the blood and urine. The classical type is due to a deficiency of cystathionine beta-synthase. Affected individuals appear normal at birth but develop serious complications in early childhood, usually by age 3 to 4 years. Heterozygous carriers (1/70 of the general population) have hyperhomocysteinemia without homocystinuria; however, their risk for premature cardiovascular disease is still increased.

Overlap with MFS can be extensive and includes a Marfanoid habitus with normal to tall stature, pectus deformity, scoliosis, and ectopia lentis. Central nervous system manifestations include mental retardation, seizures, cerebrovascular events, and psychiatric disorders. Patients have a tendency for intravascular thrombosis and thromboembolic events, which can be life-threatening. Early diagnosis and prophylactic medical and dietary care can decrease and even reverse some of the complications. The diagnosis depends on the measurement of cystathionine beta-synthase activity in tissue (e.g., liver biopsy, skin biopsy).

REGULATORY STATUS

Commercially available, laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Several commercial laboratories currently offer targeted genetic testing, as well as next-generation sequencing panels that simultaneously analyze multiple genes associated with MFS, TAADs, and related disorders. Next-generation sequencing technology cannot detect large deletions or insertions, and therefore samples that are variant-negative after sequencing should be evaluated by other testing methodologies.

Ambry Genetics offers TAADNext, a next-generation sequencing panel that simultaneously analyzes 22 genes associated with TAADs, MFS, and related disorders. The panel detects variants in all coding domains and splice junctions of *ACTA2*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *MED12*, *MYH11*, *MYLK*, *NOTCH1*, *PLOD1*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4, TGFB2*, *TGFBR1*, *TGFBR2,* and *TGFBR3.* Deletion and duplication analyses are performed for all genes on the panel except *CBS, COL5A1*, *FLNA, SMAD4*, and *TGFB3.*

Prevention Genetics offers targeted familial variants testing, as well as “Marfan syndrome and related aortopathies next generation sequencing panel” testing, which includes 38 genes.

GeneDx offers the “Marfan/TAAD sequencing panel” and “Marfan/TAAD deletion/duplication panel,” which include variant testing for *ACTA2*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *MED12*, *MYH11*, *SKI*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1*, and *TGFBR2*.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[9] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

TESTING PATIENTS WITH SIGNS AND/OR SYMPTOMS OF A CONNECTIVE TISSUE DISEASE

The purpose of genetic testing of patients who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms (TAAs) when a diagnosis cannot be made clinically is to confirm a diagnosis and inform management decisions such as increased surveillance of the aorta, surgical repair of the aorta, when necessary, and surveillance for multisystem involvement in syndromic forms of thoracic aortic aneurysm and dissection (TAAD).

The potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. For example, increased surveillance of the aorta, surgical repair of the aorta, when necessary, and surveillance for multisystem involvement in syndromic forms of TAAD are initiated to detect and treat aortic aneurysms and dissections before rupture or dissection.

The potentially harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary surveillance of the aorta and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of an aortic aneurysm or dissection.

Analytic Validity

Evidence from multiple studies has indicated that the clinical sensitivity of genetic testing for CTDs is highly variable. This may reflect the phenotypic heterogeneity of the associated

syndromes and the silent, indolent nature of TAAD development. The true clinical specificity is uncertain because different CTDs are defined by specific disease-associated variants.

Clinical Validity

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified. However, given the nature of these disorders, randomized controlled trials are not expected to occur in the near future.

Clinical Utility

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, inferences are difficult to make about clinical utility. However, there is clear clinical benefit to early detection.

Establishing a definitive diagnosis can lead to:

- treatment of manifestations of a specific syndrome,
- prevention of primary manifestations,
- prevention of secondary complications,
- impact on surveillance,
- counseling on agents and circumstances to avoid,
- evaluation of relatives at risk, including whether to follow a relative who does or does not have the familial variant,
- pregnancy management, and
- future reproductive decision making.

Often, one of the CTDs that predisposes to severe progressing features has overlapping signs and symptoms of disorders that may not predispose to more severe diease. The overlapping phenotypic features of one of the syndromes associated with TAAD, for example, might made based on clinical criteria and evidence of an autosomal-dominant inheritance pattern by family history. However, there are cases in which the diagnosis cannot be made clinically because the patient does not fulfill necessary clinical criteria, the patient has an atypical presentation, and other CTDs cannot be excluded, or the patient is a child with a family history in whom certain age-dependent manifestations of the disease have not yet developed. In these circumstances, the clinical differential diagnosis is narrow, and single-gene testing or focused panel testing may be warranted, establishing the clinical usefulness of these types of tests. However, it is important to note that the incremental benefit of expanded NGS panel testing in these situations is unknown, and the VUS rate with these NGS panels is also unknown. Also, the more disorders that are tested in a panel, the higher the VUS rate is expected to be.

TARGETED FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS WITH A KNOWN FAMILIAL PATHOGENIC VARIANT ASSOCIATED CONNECTIVE TISSUE DISORDERS

Clinical Context and Test Purpose

The purpose of familial variant testing of asymptomatic individuals with a first-degree relative with a CTD is to screen for the family-specific pathogenic variant to inform management decisions (e.g., increased cancer surveillance) or to exclude asymptomatic individuals from increased surveillance of potential progressing symptoms. The following practice is being used for targeted testing of asymptomatic individuals with a first-degree relative with a CTD: standard clinical management without targeted genetic testing for a familial variant related to the known familial disorder.

The potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. An example would be increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD. These steps are initiated to monitor the development of aortic aneurysms and dissection and potentially repair them before rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased cancer surveillance.

The potentially harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary surveillance and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of aortic aneurysms or dissection.

Analytic Validity

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Same as the discussion in the previous Clinical Validity section for patients with sign and/or symptoms of a CTD.

Clinically Useful

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. No such trials were identified. No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified.

Evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. When a disease-associated variant of a CTD has been identified in a proband, testing of first-degree relatives can identify those who also have the familial variant and may develop the disorder. Depending on the severity of the CTD, these individuals may need initial evaluation and ongoing surveillance.

Alternatively, first-degree relatives who test negative for the familial variant could be excluded from ongoing surveillance.

Direct evidence of the clinical usefulness of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of individuals affected individuals with a CTD associated, in particular those that predispose to TAAD, a positive test for a familial variant confirms the diagnosis of the TAAD-associated disorder and results in ongoing surveillance of the aorta while a negative test for a familial variant potentially reduces the need for ongoing surveillance of the aorta.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision for children with Marfan syndrome.[10] This clinical report notes the following with regard to genetic testing:

- "Younger patients at risk for Marfan syndrome based on clinical features or a positive family history should be evaluated periodically until their growth is complete or preferably undergo appropriate genetic testing."
- "...genetic testing in Marfan syndrome has become an important part of the diagnosis and management of the condition."
- "For those suspected to have Marfan syndrome on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one should consider FBN1 testing"
- "Patients who fit clinical criteria for Marfan syndrome in whom no pathogenic variant is found in the FBN1 gene should continue to be followed according to the health supervision for Marfan syndrome. In addition, broader genomic testing should be considered in these individuals."
- "When a new diagnosis of Marfan syndrome is made in a child or adolescent, both parents and at-risk first-degree relatives should have physical, ophthalmologic, and cardiac evaluations as well as consideration of genetic testing. Similarly, when a new diagnosis of Marfan syndrome is made in a parent, all children should be screened for manifestations of Marfan syndrome."
- "Prenatal genetic testing for *FBN1* mutations may be helpful to confirm Marfan syndrome as well as reveal specific mutations in *FBN1* that may be more typically associated with this severe form and, therefore, reduced survivability."

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS

The American College of Medical Genetics and Genomics issued guidelines (2012) on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS).[11] The guidelines recommended the following:

> “If there is *no family history of MFS*, then the subject has the condition under any of the following four situations:

- A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
- A dilated aortic root and a mutation [pathogenic variant] in *FBN1* that is clearly pathologic
- A dilated aortic root and multiple systemic features … or
- Ectopia lentis and a mutation [pathogenic variant] in *FBN1* that has previously been associated with aortic disease."

"If there *is a positive family history of MFS* (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

- Ectopia lentis
- Multiple systemic features … or
- A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)"

The systemic features are weighted by a scoring system.

AMERICAN COLLEGE OF CARDIOLOGY AND AMERICAN HEART ASSOCIATION

Joint evidence-based guidelines (2022) from the American College of Cardiology (ACC) and American Heart Association (AHA) for the diagnosis and management of aortic disease include MFS, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:[12]

"Genetic testing is recommended for individuals with syndromic features, family history of TAD, and/or early age of disease onset. Thoracic aortic imaging is recommended for first-degree relatives of all individuals with TAD, regardless of age of onset, to detect asymptomatic aneurysms. Positive genetic testing should trigger gene-based management and cascade testing of at-risk relatives. When testing is negative or reveals variants of unknown significance, first-degree relatives should undergo screening aortic imaging."

Specific recommendations for genetic testing and screening of family members for TAD include the following:

- In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (i.e., mutations) is recommended.

- In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient's clinical management be informed by the specific gene and variant in the gene.

- In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e., cascade testing) is recommended. In family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended.

- In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging

(as per recommendation 4) of at-risk biological relatives (i.e., cascade testing) is recommended.

- In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging (as per recommendation 4) of first-degree relatives is recommended.

In 2020, the American Heart Association issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases.[13] Approaches for the evaluation of patients with a confirmed or suspected diagnosis of inherited cardiovascular disease, as well as individuals with secondary or incidental genetic findings are summarized in the statement. Briefly, the statement notes that:

- "Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family"
- "Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (ie, serve as major criteria) or warrant changes in clinical management (ie, are actionable) if they occur in certain genes in patients with certain diseases

SUMMARY

For individuals who have signs and/or symptoms of a heritable connective tissue disorder who receive testing for genes associated with these disorders, there is enough evidence to show that overall health outcomes may be improved. Confirming a diagnosis may lead to changes in clinical management. In those who do not have signs and/or symptoms of a heritable connective tissue disorder, but who have relatives with a known pathogenic variant associated with these disorders, overall health outcomes may also be improved. There is less evidence regarding this situation, yet early detection may lead to clinical management for manifestations known to develop in those with these disorders. Therefore, genetic testing for heritable connective tissue disorders may be considered medically necessary when criteria are met.

Due to a lack of research and clinical practice guidelines, individual gene and panel testing for connective tissue disorders in the absence of signs and/or symptoms of a heritable connective tissue disorder or a known pathogenic variant in the family is considered not medically necessary.

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CODES

Codes	Number	Description
CPT	81405	Molecular pathology procedure, Level 6
	81408	Molecular pathology procedure, Level 9
	81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
	81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
HCPCS	None	

Date of Origin: *June 2018*

Regence

Medical Policy Manual Genetic Testing, Policy No. 78

Invasive Prenatal Fetal Diagnostic Testing for Chromosomal Abnormalities

Effective: July 1, 2024

Next Review: April 2025
Last Review: June 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

Testing for chromosomal abnormalities, typically using chromosomal microarray (CMA), may be performed in the context of invasive prenatal fetal diagnostic testing or fetal tissue testing to confirm the presence of a pathogenic abnormality after it has been determined by prenatal screening that the fetus is at increased risk for a genetic condition.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address karyotyping, which may be considered medically necessary.
- Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to whole exome or genome sequencing and reproductive carrier testing.

Testing for chromosomal abnormalities (e.g., chromosomal microarray analysis) for fetal diagnosis may be considered **medically necessary** in the setting of invasive diagnostic prenatal fetal testing (i.e., not cell-free DNA testing), or for fetal tissue testing when an anomaly has been detected by ultrasound.

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

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - History and physical exam including any relevant diagnoses related to the genetic testing
    - Conventional testing and outcomes
    - Conservative treatments, if any
    - Date of sample collection

CROSS REFERENCES

1. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Noninvasive Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA, Genetic Testing, Policy No 44
4. Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Pol. No. 58
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
6. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
7. Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss, Genetic Testing, Policy No. 79
8. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81
9. Maternal Serum Analysis for Risk of Preterm Birth, Laboratory, Policy No. 75

BACKGROUND

The focus of this evidence review is on the use of CMA as an invasive diagnostic testing methodology in the prenatal (fetal) setting.

Invasive fetal diagnostic testing can include obtaining fetal tissue for karyotyping, fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA) testing, quantitative polymerase chain reaction (qPCR), next-generation sequencing (NGS), and multiplex ligation-dependent probe amplification (MLPA).

Genetic disorders are generally categorized into three main groups: chromosomal, single gene, and multifactorial. Single-gene disorders (also known as monogenic) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural.

Invasive prenatal testing refers to the direct testing of fetal tissue, typically by chorionic villus sampling (CVS) or amniocentesis. Invasive prenatal procedures are typically performed in pregnancies of women who have been identified as having a fetus at increased risk for a chromosomal abnormality, or if there is a family history of a single-gene disorder.

CHROMOSOMAL MICROARRAY ANALYSIS

CMA technology has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping) and, therefore, can result in potentially higher rates of detection of pathogenic chromosomal abnormalities. However, there are disadvantages to CMA, including the detection of variants of unknown clinical significance and the fact that it cannot detect certain types of chromosomal abnormalities, including balanced rearrangements.

CMA can identify abnormalities at the level of the chromosome and measures gains and losses of DNA segments (known as copy number variants [CNVs]) throughout the genome.

CMA analysis detects CNVs by comparing a reference genomic sequence (“normal”) with the corresponding patient sequence. Each sample has a different fluorescent label so that they can be distinguished, and both are co-hybridized to a sample of a specific reference (also normal) DNA fragment of known genomic locus. If the patient sequence is missing part of the normal sequence (deletion) or has the normal sequence plus additional genomic material within that genomic location (e.g., a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, standard CMA cannot detect balanced CNVs (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change.

CMA analysis uses thousands of cloned or synthesized DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. The prepared sample and control DNA are hybridized to the fragments on the slide, and CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. Array resolution is limited only by the average size of the fragment used and by the chromosomal distance between loci represented by the reference DNA fragments on the slide. High-resolution oligonucleotide arrays are capable of detecting changes at a resolution of up to 50 to 100 Kb.

TYPES OF CMA TECHNOLOGIES

There are differences in CMA technology, most notably in the various types of microarrays. They can differ first by construction; earliest versions were used of DNA fragments cloned from bacterial artificial chromosome. They have been largely replaced by oligonucleotide (oligos; short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of single nucleotide variants (SNVs, also known as single nucleotide polymorphisms, or SNPs) across the genome have some advantages as well. A SNV is a DNA variation in which a single nucleotide in the genomic sequence is altered. This variation can occur between two different individuals or between paired chromosomes from the same individual and may or may not cause disease. Oligo/SNV hybrid arrays have been constructed to merge the advantages of each.

The two types of microarrays both detect CNVs, but they identify different types of genetic variation. The oligo arrays detect CNVs for relatively large deletions or duplications, including whole chromosome duplications (trisomies), but cannot detect triploidy. SNV arrays provide a genome-wide copy number analysis, and can detect consanguinity, as well as triploidy and uniparental disomy.

Microarrays may be prepared by the laboratory using the technology, or more commonly by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of in-house developed and commercially available platforms prompted the American College of Medical Genetics (ACMG) to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

At this time, no guidelines indicate whether targeted or genome-wide arrays should be used or what regions of the genome should be covered. Both targeted and genome-wide arrays search the entire genome for CNVs, however, targeted arrays are designed to cover only clinically significant areas of the genome. The ACMG guideline for designing microarrays recommends probe enrichment in clinically significant areas of the genome to maximize detection of known abnormalities. Depending on the laboratory that develops a targeted array, it can include as many or as few microdeletions and microduplication syndromes as thought to be needed. The advantage, and purpose, of targeted arrays is to minimize the number of variants of unknown significance (VUS).

Whole genome CMA analysis has allowed the characterization of several new genetic syndromes, with other potential candidates currently under study. However, the whole genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and, to some extent, made available in public reference databases to aid in clinical interpretation relevance.

CLINICAL RELEVANCE OF CMA FINDINGS AND VUS

CNVs are generally classified as pathogenic (known to be disease-causing), benign, or a VUS.

A VUS is defined as a CNV that:

- has not been previously identified in a laboratory’s patient population, or
- has not been reported in the medical literature, or
- is not found in publicly available databases, or
- does not involve any known disease-causing genes.

To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (e.g., FISH, MLPA, PCR).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic.

- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication).
- The laboratory may establish a size cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 300 kb to 1 Mb.
- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign polymorphisms whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized; it established a public database containing deidentified whole genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including intellectual disability, autism, and developmental delay. As of June 2016, there were over 53,900 total cases in the database. Data are currently hosted on ClinGen (https://clinicalgenome.org/).

Use of the database includes an intra-laboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other variants, as well as any not consistent with the ISCA “known” pathogenic and “known” benign lists. The intra-laboratory conflict rate was initially about 3% overall; following release of the first ISCA curated track, the intra-laboratory conflict rate decreased to about 1.5%. An interlaboratory curation process, whereby a group of experts curates reported CNVs/variants across laboratories, is currently in progress.

The consortium recently proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defines levels of evidence (from the literature and/or ISCA and other public databases) that describe how well or how poorly detected variants or CNVs correlate with phenotype.

ISCA is also developing vendor-neutral recommendations for standards for the design, resolution, and content of cytogenomic arrays using an evidence-based process and an international panel of experts in clinical genetics, clinical laboratory genetics, genomics, and bioinformatics.

COMMERCIALLY AVAILABLE TESTS

Many academic and commercial laboratories offer CMA testing and sequencing-based tests in the prenatal setting. Many laboratories also offer reflex testing, which may be performed with microarray testing added if karyotyping is normal or unable to be performed (due to no growth of cells). The following is not inclusive; it is only an example of some laboratories that offer CMA and sequencing-based testing. The test should be cleared or approved by the Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendment–certified laboratory.

GeneDx offers prenatal CMA for copy number abnormalities in fetuses with ultrasound abnormalities. The targeted CMA includes oligonucleotide probes placed throughout the genome and within 100 common or novel microdeletion and microduplication syndromes, as well as those involving subtelomeric regions and any other intrachromosomal region greater

than 1.5 Mb. This array also contains SNV probes covering chromosomes known to contain uniparental disomy. Exon-level probe coverage is added to some genes associated with some monogenic disorders.

GeneDx also offers a whole genome array that contains oligonucleotide probes for areas throughout the genome and within more than 220 targeted regions. This array detects CNVs greater than 200 kb across the entire genome and between 500 bp and 15 kb in targeted regions. Approximately 65 genes associated with neurodevelopmental disorders are targeted at the exon level. This array also contains SNV probes throughout the genome to detect some types of uniparental disomy (UPD).

ARUP laboratory provides former Signature Genomics clients with prenatal tests, including targeted CMA with SNV coverage.

Many laboratories offer reflex testing, which may be performed with microarray testing added if karyotyping is normal of unable to be performed (due to no growth of cells).

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

There are many ethical considerations in testing a fetus for a condition that is of adult-onset. In general, there is consensus in the medical and bioethical communities that prenatal testing should not include testing for late-onset/adult-onset conditions, or for diseases for which there is a known intervention that would lead to improved health outcomes but would only need to be started after the onset of adulthood.

CMA is now considered standard of care for women undergoing invasive prenatal testing. Therefore, no further evidence will be added to this policy. Please see below for a summary of the current evidence.

SUMMARY OF EVIDENCE

The evidence for CMA testing in patients who are undergoing invasive diagnostic prenatal (fetal) testing includes systematic reviews, meta-analyses and prospective cohort and retrospective analyses of the diagnostic yield compared with karyotyping. Relevant outcomes reported are test accuracy and validity, and changes in reproductive decision making. CMA testing has been shown to have a higher rate of detection of pathogenic chromosomal

abnormalities than karyotyping. CMA testing is associated with a certain percentage of results that have unknown clinical significance; however, this can be minimalized by the use of targeted arrays and the continued accumulation of pathogenic variants in international databases.

The highest yield of pathogenic copy number variants by CMA testing has been found in fetuses with malformations identified by ultrasound. For studies that included all high-risk pregnancies (which were primarily because of abnormal ultrasound abnormalities), the range of pathogenic CNV detection was 2.6% to 7.8%, with a combination of all studies (n=1,800) being 5.0%. For pregnancies in which CMA was performed for other indications (advanced maternal age, abnormal Down syndrome screening test, parental anxiety), the range of pathogenic CNV detection was 0.5% to 1.6%, with a combination of all studies (n=10,099) being 0.9%.

Changes in reproductive decision making could include decisions regarding continuation of the pregnancy, enabling for timely treatment of a condition that could be treated medically or surgically either in utero or immediately after birth and birthing decisions. The American College of Obstetricians and Gynecologists recommends CMA testing in women who are undergoing an invasive diagnostic procedure. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS COMMITTEE ON GENETICS AND THE SOCIETY FOR MATERNAL FETAL MEDICINE

In December 2016 (reaffirmed in 2023), the American Congress of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine published a Committee Opinion (No. 682),[2] offering the following recommendations for the use of chromosomal microarray analysis in prenatal diagnosis:

- Chromosomal microarray analysis … can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities.
- Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype … therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.
- Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.

The American College of Obstetricians and Gynecologists (ACOG) published Practice Bulletin No. 162 in May 2016,[3] stating:

- In all patients at risk of aneuploidy or at risk of having a pregnancy affected by a genetic disorder, “karyotype or microarray analysis should be offered in every case, although preforming karyotype or microarray may not be necessary in a low risk patient.”
- “In patients with a major structural abnormality found on ultrasound examination, CVS or amniocentesis with chromosomal microarray should be offered.” Chromosomal microarray is now recommended as the primary test for these patients, replacing karyotyping.
- “Chromosomal microarray analysis should be available to women undergoing invasive diagnostic testing for any indication.”
- “If a structural abnormality is strongly suggestive of a particular aneuploidy in the fetus, karyotype analysis with or without FISH may be offered before chromosomal microarray analysis.”
- Chromosomal microarray analysis can be used to confirm an abnormal FISH test.

International Society for Prenatal Diagnosis:[4]

In 2018, the International Society for Prenatal Diagnosis, the Society for Maternal-Fetal Medicine, and the Perinatal Quality Foundation released a joint position statement on the use of prenatal exome and genome-wide sequencing for fetal diagnosis. This initial position statement was replaced in 2022. The 2022 position statement provides suggestions for clinical use, as described in the clinical indications below:

1. "The current existing data support that prenatal sequencing is beneficial for the following indications:
    a. A current pregnancy with a fetus having a major single anomaly or multiple organ system anomalies:
        i. For which no genetic diagnosis was found after CMA and a clinical genetic expert review considers the phenotype suggestive of a possible genetic etiology.
        ii. For which the multiple anomaly 'pattern' strongly suggests a single gene disorder with no prior genetic testing. As pES [prenatal exome sequencing] is not currently validated to detect all CNVs [copy number variants], CMA should be run before or in parallel with pES in this scenario.
    b. A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single or multiple anomalies:
        i. With a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA for the current or prior undiagnosed pregnancy. Point a.i. above also applies in these circumstances.
        ii. When such parents present for preconception counseling and no sample is available from the affected proband, or if a fetal sample cannot be obtained in an ongoing pregnancy, it is considered appropriate to offer sequencing for both biological parents to look for shared carrier status for autosomal recessive mutations that might explain the fetal phenotype. However, where possible, obtaining tissue from a previous abnormal fetus or child for pES is preferable.

2. There is currently no evidence that supports routine testing (including upon parental request) on fetal tissue obtained from an invasive prenatal procedure (amniocentesis, CVS, cordocentesis, other) for indications other than fetal anomalies.
    a. There may be special settings when prenatal sequencing in the absence of a fetal phenotype visible on prenatal imaging can be considered, such as with a strong family history of a recurrent childhood-onset severe genetic condition with no prenatal phenotype in previous children for whom no genetic evaluation was done and is not possible. Such scenarios should be reviewed by an expert multidisciplinary team preferentially in the context of a research protocol. If sequencing is done for this indication, it must be done as trio sequencing, using an appropriate analytical approach."

SUMMARY

There is enough research to show that testing for chromosomal abnormalities in the setting of invasive diagnostic prenatal fetal testing or ultrasound-detected fetal anomalies informs reproductive decision-making including decisions regarding continuation of the pregnancy, birthing decisions, and enabling for timely treatment of a condition that could be treated medically or surgically either in utero or immediately after birth. In addition, clinical practice guidelines recommend this testing in women who are undergoing invasive diagnostic prenatal fetal testing. Therefore, fetal testing for chromosomal abnormalities may be considered medically necessary when undergoing invasive diagnostic prenatal fetal testing or when a fetal anomaly has been detected by ultrasound.

REFERENCES

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2. American College of Obstetricians, Gynecologists Committee on Genetics. Committee Opinion No. 682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Dec [cited 5/24/2024]. 'Available from:' https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/12/microarrays-and-next-generation-sequencing-technology-the-use-of-advanced-genetic-diagnostic-tools-in-obstetrics-and-gynecology.
3. Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders. *Obstetrics and gynecology.* 2016;127(5):e108-22. PMID: 26938573
4. Van den Veyver IB, Chandler N, Wilkins-Haug LE, et al. International Society for Prenatal Diagnosis Updated Position Statement on the use of genome-wide sequencing for prenatal diagnosis. *Prenatal diagnosis.* 2022;42(6):796-803. PMID: 35583085

CODES

NOTE: The appropriate codes for reporting CMA are 81228 for CMA alone, and 81229 for CMA testing that includes single nucleotide polymorphism (SNP) analysis. It is not appropriate to report code 81422 for CMA.

Codes	Number	Description
CPT	0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities
	81405	Molecular Pathology Procedure Level 6
HCPCS	None	

Date of Origin: *April 2017*

Regence

Medical Policy Manual Genetic Testing, Policy No. 79

Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss

Effective: July 1, 2024

Next Review: April 2025
Last Review: May 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

Testing of products of conception for chromosomal abnormalities, including fetal tissue or placental tissue, may be performed to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (intrauterine fetal demise [IUFD]).

MEDICAL POLICY CRITERIA

Note: Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to, whole exome or genome sequencing, preimplantation diagnosis or screening, carrier screening, and single-gene testing.

I. Testing for chromosomal abnormalities (e.g., chromosomal microarray testing) in fetal tissue, a formed fetus, or placental tissue derived from the fetus may be considered **medically necessary** when any of the following Criteria are met:

   A. In cases of pregnancy loss at less than or equal to 20 weeks of gestation when there is a maternal history of recurrent pregnancy loss, defined as having two or more consecutive clinical pregnancy losses; or

   B. In all cases of pregnancy loss after 20 weeks of gestation.

II. Testing for chromosomal abnormalities in products of conception or for pregnancy loss is considered **investigational** when Criterion I. above is not met.

III. The use of next-generation sequencing (NGS) aneuploidy testing for products of conception or for pregnancy loss is considered **investigational**.

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

POLICY GUIDELINES

DEFINITIONS

Fetal tissue may consist of fetal tissue, a formed fetus, or placental tissue derived from the fetus, depending on the stage of pregnancy at the time of the fetal loss.

Early pregnancy loss or miscarriage is considered to be a pregnancy loss that occurred at or before 20 weeks of gestational age.[1, 2]

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   - History and physical exam including any relevant diagnoses related to the genetic testing
   - Conventional testing and outcomes
   - Conservative treatments, if any

CROSS REFERENCES

1. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Noninvasive Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA, Genetic Testing, Policy No 44
4. Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Pol. No. 58
5. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
6. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
7. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
8. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

PREGNANCY LOSS: ETIOLOGY AND EVALUATION

Early Pregnancy Loss

Pregnancy loss is common, occurring in at least 15% to 25% of recognized pregnancies. Most pregnancy loss occurs early in the pregnancy, most often by the end of the first trimester or early second trimester. Pregnancy loss that occurs before the 20th week of gestation is referred to as a spontaneous abortion, early pregnancy loss, or miscarriage. While a wide range of factors can lead to early pregnancy loss, genetic causes are thought to be the predominant cause: when products of conception (POC) are examined, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X.[2, 3] The increasing risk of trisomies with maternal age contributes to the increased risk of early pregnancy loss with increasing maternal age.

Recurrent pregnancy loss, defined by the American Society for Reproductive Medicine (ASRM) as two or more failed pregnancies, is less common, occurring in approximately 5% of women.[1] Recurrent pregnancy loss may be related to cytogenetic abnormalities, particularly balanced translocations, uterine abnormalities, thrombophilias, including antiphospholipid syndrome, and metabolic/endocrinologic disorders such as uncontrolled diabetes and thyroid disease. Estimates for the frequency of various underlying causes of recurrent pregnancy loss vary widely, with ranges from 2% to 6% for cytogenetic abnormalities, 8% to 42% for antiphospholipid antibody syndrome, and 1.8% to 37.6% for uterine abnormalities.[2] It is likely that the risk of cytogenetic abnormalities is lower in recurrent early pregnancy loss than in isolated spontaneous early pregnancy loss.

Clinicians and patients may undertake an evaluation for the cause of a single or recurrent early pregnancy loss for several reasons. The knowledge that an early pregnancy loss is secondary to a sporadic genetic abnormality may provide parents with reassurance that there was nothing that they did or did not do that contributed to the loss, although the magnitude of this benefit is difficult to quantify. For couples with recurrent pregnancy loss and evidence of a structural genetic abnormality in one of the parents, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. These therapies might be considered for couples with recurrent pregnancy loss without evidence of a structural genetic abnormality in one of the parents; guidelines on the management of recurrent pregnancy loss from ASRM state that “treatment options should be based on whether repeated miscarriages are euploid, aneuploidy, or due to an unbalanced structural rearrangement and not exclusively on the parental carrier status.” Finally, among patients FA who are found to have a potential nongenetic underlying cause of recurrent pregnancy loss, such as antiphospholipid syndrome, cytogenetic analysis of pregnancy losses may provide evidence that the miscarriages were not due to treatment failure.[4]

Genetic testing of POC, if possible, is recommended by several reproductive health organizations. A committee opinion from ASRM recommends that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents and states that karyotypic analysis of POC may be useful in the setting of ongoing therapy for recurrent pregnancy loss.[2] The National Society of Genetic Counselors convened a multidisciplinary Inherited Pregnancy Loss Working Group. It recommended that, for the genetic evaluation of couples with recurrent pregnancy loss, when possible, chromosomal analysis on fetal tissue from POC should be pursued.[3]

Late Pregnancy Loss

Fetal loss that occurs later in pregnancy, after 20 weeks of gestation, may be referred to as intrauterine fetal demise (IUFD), stillbirth, or intrauterine fetal death. In 2013, IUFD occurred in 5.96 of 1,000 births in the United States, representing about 60% of perinatal mortality. IUFD may be related to a range of disorders, including genetic disorders in the fetus, maternal infection, coexisting maternal medical disorders (e.g., diabetes, antiphospholipid antibody syndrome, heritable thrombophilias), and obstetric complications, although, in many cases, the precise cause is unidentifiable. Chromosomal or genetic abnormalities can be found in 8% to 13% of IUFD, most commonly aneuploidies. In one large series of IUFD (n=1,025), cytogenic abnormalities were detected in 11.9%.[5]

The American College of Obstetrics and Gynecology recommends that evaluation after an IUFD includes examination of the stillborn fetus, along with examination of the placenta and umbilical cord and genetic testing for all IUFD (after parental permission is obtained). Other evaluation should be based on maternal history and may include evaluation for thyroid disorders, systemic lupus erythematosus, and infections.[6]

Some motivations for evaluation for a cause of IUFD are similar to those for earlier pregnancy loss. Although both early and later pregnancy losses may cause grief for the mother and her family, IUFD can be particularly devastating. Information about the cause of the pregnancy loss may be important in counseling women about their recurrence risk. In low-risk women with an unexplained IUFD, the risk of recurrence is 7.8 to 10.5 of 1,000 live births, but this increases to 21.8 per 1,000 live births in women with a history of fetal growth restriction. Identification of a heritable genetic variant in a fetus may prompt testing in the parents; if a heritable variant is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

GENETIC ABNORMALITIES IN MISCARRIAGE AND IUFD

Genetic disorders are generally categorized into three main groups: single gene, chromosomal, and multifactorial. Single-gene disorders (also known as monogenic disorders) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural. Evidence about specific abnormalities in miscarriages and IUFD is somewhat limited. However, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X. For later pregnancy losses, aneuploidies are most common in the 8% to 13% of tested IUFD that have an identified chromosomal or genetic abnormality. Karyotypic abnormalities are identified in 6% to 12% of IUFD.[7] Rates of single-gene disorders in IUFD are less well-quantified. However, of stillborn fetuses who undergo autopsy, 25% to 35% are identified to have single or multiple malformations or deformations; of these, 25% have an abnormal karyotype, but other single-gene disorders are suspected to occur in a high proportion of stillborn fetuses with malformations.

Traditionally, genetic evaluation of the POC after a miscarriage is conducted by karyotyping of metaphase cells after cells are cultured in tissue. Karyotyping can identify whole chromosome aneuploidies and large structural rearrangements. However, only visible rearrangements are likely to be identified using this method (down to a resolution of 5 to 10 Mb), so smaller genetic variants may not be detected. In addition, karyotype requires culturing the target cells, which may fail or be infeasible, particularly for formalin-preserved samples. In addition, there is the potential for maternal cell contamination, which may occur if the POC tissue is not separated

from the maternal decidua before culturing, or if there is poor growth of noneuploid cells from the POC tissue, thereby allowing maternal cell overgrowth. The potential for maternal cell contamination makes it impossible to know if a normal female (46 XX) karyotype testing result is due to a normal fetal karyotype or a maternal karyotype. In one study that included 103 first trimester miscarriages, culture failure occurred in 25% of cases.[8]

CHROMOSOMAL MICROARRAY ANALYSIS TESTING

There has been interest in using alternative genetic testing methods, particularly array comparative genomic hybridization (aCGH), to detect chromosomal or other genetic abnormalities in the evaluation of miscarriages and IUFD.

Types of Chromosomal Microarray Analysis Technologies

Several types of microarray technology are in current clinical use, primarily aCGH and single-nucleotide polymorphism (SNP) microarrays. Comparative genomic hybridization (CGH) chromosomal microarray analysis (CMA) analysis detects copy number variants (CNVs) by comparing a reference genomic sequence with the patient ("unknown") sequence in terms of binding to a microarray of cloned (from bacterial artificial chromosomes) or synthesized DNA fragments with known sequences. The reference DNA and the unknown sample are labelled with different fluorescent tags, and both samples are cohybridized to the fragments of DNA on the microarray. Computer analysis is used to detect the array patterns and intensities of the hybridized samples. If the unknown sample contains a deletion or duplication of genetic material in a region contained on the reference microarray, the sequence imbalance is detected as a difference in fluorescence intensity.

In SNP-based CMA testing, a microarray of SNPs, which may include hundreds of thousands of SNPs, is used for hybridization. In contrast with aCGH, a reference genomic sequence is not used. Instead, only the "unknown" sample is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to provide information about copy numbers. In some cases, laboratories confirm CNVs detected on CMA with an alternative technique, such as fluorescence in situ hybridization or flow cytometry.

Microarrays also vary in breadth of coverage of the genome included. Targeted CMA provides coverage of the genome with a concentration of sequences in areas with known, clinically significant CNVs. In contrast, whole-genome CMA allows the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of undetermined significance.

CMA Compared with Karyotyping

CMA has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping), and therefore can result in potentially higher rates of detection of pathogenic chromosomal abnormalities. Array CGH can detect CNVs for larger deletions and duplications, including trisomies. However, CMA based on aCGH cannot detect balanced translocations or diploid, triploid, and tetraploid states, or sequence inversions because they are not associated with fluorescence intensity change. SNP-based CMA, in addition to detecting deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy.

CMA also has the advantage of not requiring successful cell culture, so it may be more likely to yield a result in cases where karyotyping is technically unsuccessful due to failed culture. In the case of testing of specimens from early miscarriage, CMA may also be used to rule out maternal cell contamination, if a fetal sample is compared with a maternal sample.

CMA has the disadvantage of higher rates of detection of variants of uncertain significance. The American College of Medical Genetics (ACMG) has published guidelines on the interpretation and reporting of CNVs in the postnatal setting. ACMG recommends that laboratories performing array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs determined to represent benign variation based on comparisons with internal and external databases.[9]

NEXT-GENERATION SEQUENCING

Next-generation sequencing (NGS) is a method that uses massively parallel sequencing of small fragments of DNA to allow the rapid sequencing of large stretches of DNA. NGS assays have been developed to detect aneuploidies.

COMMERCIALLY AVAILABLE TESTS

Natera Inc. (San Carlos, CA) offers the Anora ® miscarriage test, which uses a SNP-based array system for testing of POC. The test includes the company's proprietary "Parental Support Technology," which uses a DNA sample from one or both parents as a reference to the POC sample. This comparison can identify maternal cell contamination, uniparental disomy, and the parent of origin of a fetal chromosome abnormality. According to a description of the "Parental Support" algorithm,[10] the algorithm uses the

> "SNP array data to calculate the relative amounts of each of the two alleles at each SNP. At heterozygous loci, disomic chromosomes are expected to have SNP ratios of approximately 50%, trisomic chromosomes are expected to have SNP ratios of approximately 33% and 66%, and monosomic chromosomes are expected to have only homozygous loci. For each chromosome, the algorithm compares the observed SNP data to each of the expected alleles for the possible ploidy states and determines which is most likely."

According to the manufacturer's website, the test "is clinically validated to detect whole chromosome aneuploidy, triploidy, tetraploidy, uniparental disomy, and deletions and duplications greater than 5 Mb. Terminal deletions or duplications and clinically significant deletions and duplications down to 1 Mb are also reported."[11]

Arup Laboratories offers the Genomic SNP Microarray, Products of Conception, and the Mayo Clinic offers the Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue.[12, 13]

Multiple laboratories offer CMA testing for prenatal samples that is not specifically designed for testing of POC.

Igenomix offers a product-of-conception test that uses NGS technology for aneuploidy testing.[14]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The Anora® miscarriage test, the CombiSNP™ Array for Pregnancy Loss, the CombiBAC™ Array, and the GeneDx Whole Genome Chromosomal Microarray for Products of Conception, along with other chromosomal microarray analysis testing platforms currently available are LDTs available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[15] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

CHROMOSOMAL MICROARRAY ANALYSIS

The use of chromosomal microarray analysis (CMA) for the evaluation of products of conception and pregnancy loss has been established as standard of care primarily due to clinical consensus for the following situations:

- pregnancy loss after 20 weeks of gestation
- pregnancy loss less than or equal to 20 weeks of gestation when there is a maternal history of recurrent pregnancy loss

Therefore, evidence for the above indications with medical necessity criteria will no longer be reviewed. Only situations considered investigational will be reviewed for evidence.

Although the clinical validity of most diagnostic genetic tests are evaluated based on their ability to diagnosing clinically defined disease, for the purposes of assessment of POC, the diagnosis of a known chromosomal or genetic abnormality in the setting of pregnancy loss may serve as a surrogate end point. The results of CMA can be compared directly with karyotyping, but there is no independent reference standard that can be used to determine the performance characteristics of each test.

Diagnostic Accuracy of CMA

Martinez-Portilla (2019) published results from a systematic review and meta-analysis of seven studies assessing the added value of CMA over conventional karyotyping during a stillbirth work-up (i.e., fetal lose after 20 weeks of gestation).[16] The studies included 1,443 fetal losses, of which 903 (63%) were stillbirths with a normal karyotype. A total of 1,057 karyotyping and 701 CMA tests were performed. Results revealed a test success rate (i.e., rate of informative results) of 75% for conventional karyotyping versus 90% for CMA. The incremental yield of CMA over karyotyping was 4% (95% confidence interval [CI], 3 to 5%) for pathogenic CNVs and 8% (95% CI 4 to 17%) for VUS. In a subgroup analysis, the incremental yield of CMA for pathogenic CNVs was 6% (95% CI 4 to 10%) in structurally abnormal fetuses and was 3%

(95% CI 1 to 5%) for structurally normal fetuses. The authors concluded that CMA improves both test success rate and genetic abnormality detection when incorporated into a stillbirth workup as compared with conventional karyotyping. The risk of bias assessment judged two of the studies to have a high risk of bias - one in patient selection and the other in flow and timing. One other study had an unclear risk of bias for patient selection and in the reference standard.

In a 2017 systematic review, Pauta evaluated the added value of CMA analysis over karyotyping in early pregnancy loss.[17] Twenty-three studies were published between January 2000 and April 2017 that met the inclusion criteria. This included 5,520 pregnancy losses up to 20 weeks. When CMA and karyotyping were performed concurrently, informative results were provided by CMA in 95% (95% CI 94 to 96%) of cases and by karyotyping in 67% (95% CI 64 to 70%) of cases. The incremental yield of pathogenic CNV by CMA over karyotyping was 2%.

In 2014, Dhillon reported results from a systematic review and meta-analysis of studies that compared CMA with conventional karyotyping in the evaluation of miscarriage.[18] The authors included nine studies that reported results from CMA on POC following miscarriage alongside conventional karyotyping. Overall, there were 314 miscarriage samples in the included studies. One study was included that assessed 41 cases of spontaneous pregnancy loss <20 weeks of gestation, and two studies assessed first-trimester spontaneous miscarriage (n=14, 86). These studies were not analyzed separately for the others. In pooled analysis, the overall agreement between karyotype and CMA results was 86.0% (95% CI 77.0% to 96.0%), with high homogeneity across the studies (Cochrane Q, I^2=0.2%). CMA detected 13% (95% CI 8.0% to 21.0%) additional chromosomal abnormalities not detected by karyotyping (including both likely pathogenic variants and variants of uncertain significance [VOUS or VUS]). Conventional karyotyping detected 3% (95% CI 1.0% to 10.0%) additional abnormalities not detected by CMA. Among five studies that reported VOUS, the pooled chance of having a VOUS was 2% (95% CI 1.0% to 10.0%). This systematic review demonstrated good overall agreement between CMA and karyotype in the analysis of miscarriage specimens. However, the CI around the estimate of VOUS rate was large, indicating uncertainty regarding the true rate. Further research is required to determine whether CNVs found in POC are pathogenic or benign.

A number of additional studies not included in the above systematic reviews have compared CMA with karyotyping. Using a prospective design, Schilit (2022) reported on the efficacy of CMA testing in the evaluation of POC compared to available karyotype data.[19] There were 323 POC samples collected over a 42-month period. CMA analysis was performed using 2 different platforms: Affymetrix Cytoscan HD assay or Affymetrix Oncoscan assay. CMA was able to identify cytogenetic abnormalities in 47.4% (109/203) of first trimester losses and 10.9% (10/92) of second and third trimester losses. A total of 133 cases were evaluated by both CMA and karyotype. There was a 20% (9/45) discordance with CMA findings in samples with available karyotype data. Maternal cell overgrowth in the female karyotypes, and admixture due to multiple gestation may have limited karyotyping analysis. The most prevalent abnormalities reported overall were autosomal trisomies.

In another prospective study Lee (2021) compared the performance of karyotyping with CMA using both aCGH and SNV microarray to identify genetic abnormalities in miscarriage specimens.[20] Using a total of 63 specimens, genetic abnormalities were detected by at least one method in 49.2% of samples; the most common abnormality was single autosomal trisomy (71.0%). Using data from these 31 cases, the detection rate of genetic abnormalities was

higher with SNV microarray compared with aCGH (93.5% vs 77.4%, p=0.045) and was lowest with karyotyping (76.0%).

Dalton (2023) performed a retrospective secondary analysis of 393 stillbirth cases using CMA and birthweight data from a multi-site cohort to determine the relationship between fetal growth abnormalities and abnormal copy variants.[21] The small for gestational age outcome was significantly associated with abnormal copy variants (p=0.038). The large for gestational age outcome was not associated with abnormal copy number variants, but there may have been too few fetuses for adequate assessment (n=15). The authors note that 47% of the genetic abnormalities in the small for gestational age stillborn fetuses were detectable with CMA, not traditional karyotyping.

Popescu (2018) reported on a single-center prospective cohort study of 100 patients.[22] The study compared the percent of patients that learned a cause of recurrent pregnancy loss from the standard American Society for Reproductive Medicine (ASRM) evaluation, which included karyotyping, for recurrent miscarriage versus from ASRM evaluation plus CMA evaluation. Patients with two or more pregnancy losses. A definite or probable cause of pregnancy loss was identified in 95% of patients with ASRM plus CMA evaluation. The ASRM workup alone identified probable cause of pregnancy loss in 45% of patients whereas the CMA evaluation alone identified probable cause of pregnancy loss in 67% of patients. The final 5% of patients did not have a probable or definitive cause of pregnancy loss identified.

Lathi (2014) reported results from a comparison of a SNP-based array with informatics assistance (“Parental Support” algorithm previously described) with conventional karyotyping in 30 first-trimester miscarriage samples.[23] CMA was conducted using a single-nucleotide polymerase (SNP)–based microarray, which measures about 300,000 SNPs across the genome (approximately one SNP every 10 Kb). The “Parental Support” technique compares results from the POC sample with parental samples to determine the number and origin of each chromosome in the POC sample. On conventional karyotype, 63% of samples were chromosomally abnormal, with autosomal trisomies as the most common abnormality. All 46 XX samples on karyotype were confirmed to be from fetal tissue on microarray analysis. Four samples were discordant between CMA and karyotype, including one case of whole genome duplication and one balanced translocation, both of which would not be expected to be detected on microarray, and two additional discrepancies that were attributed to sampling error, tissue mosaicism, or culture artifact.

In 2006, Hu conducted genetic analysis by both CGH and karyotyping in 38 POC from early pregnancy losses.[24] Culture of chorionic villi and examination of metaphase chromosomes was attempted in all samples, but cytogenic analysis was technically successful in only 31 samples. Of the 31 samples successfully karyotyped, 14 were diagnosed to be aneuploidies, including four with trisomy 21, two each with trisomies 13 and 16, two with monosomy X, and one each with trisomies 7, 20, 18, and 3. An additional two cases of triploidy were detected. On CGH analysis, 17 aneuploidies were identified (14 of those found on the karyotyped samples, along with three cases in samples for which cell culture failed), along with one structural chromosomal abnormality. For the 31 samples that had both tests conducted, there was generally good concordance between the two approaches, with the exception that CGH did not detect the two cases of triploidy.

Yield of CMA in Pregnancy Loss

CMA in Early Pregnancy Loss

Several studies have assessed the use of CMA in the evaluation of pregnancy loss when standard karyotyping was unsuccessful/unavailable or have evaluated the incremental benefit of CMA in the detection of maternal cell contamination.

A study by Finley (2022) used SNP-CMA to evaluate 24,900 POC from various forms of pregnancy loss, including sporadic miscarriage or recurrent pregnancy loss.[25] Clinically significant chromosomal anomalies were found in 55.8%, while 1.8% had variants of uncertain significance and 42.4% had normal results. Autosomal trisomies were the most common anomies identified (36% of samples).

Lathi (2014) reported results of a retrospective analysis of the use of CMA in detecting maternal cell contamination on conventional karyotyping in 1,222 POC samples from first-trimester miscarriages that were evaluated at the Natera laboratory from January 2010 to August 2011.[10] The POC samples, along with maternal peripheral blood samples, were evaluated with a SNP-based CMA. When CMA results for the POC were 46 XX, a comparison with the maternal genotype fingerprint allowed investigators to determine if results were due to maternal cell contamination. On initial analysis, before comparison with the maternal genotype fingerprint, 48% of POC specimens were chromosomally abnormal, 37% were 46 XX, and 14% were 46 XY. Comparison with maternal bloody genotype indicated that 59% of the 46 XX results were due to maternal cell contamination. The authors suggested that the use of CMA may improve accurate detection of fetal chromosomal abnormalities.

Viaggi (2013) used a whole genome aCGH to evaluate 40 POC samples from first trimester miscarriages that had normal karyotypes to assess for the presence and prevalence of CNVs.[26] Frozen samples were evaluated with aCGH with a resolution of 100 Kb. CNVs were compared with those present in the Database of Genomic Variants (http://projects.tcag.ca/variation), Decipher (http://decipher.sanger.ac.uk), and the Database of Human CNVs (http://gvarianti.homelinux.net/gvarianti/index.php) to differentiate between benign CNVs and possibly pathogenic CNVs. Forty-five CNVs, corresponding to 22 different CNVs, were identified in 31 samples (31/40 [77.5%]). Thirty-one of the 45 CNVs identified (68%) were defined as common CNVs. When the CNVs were compared with control CNVs reported in the Database of Genomic Variants, seven CNV frequencies were considered statistically different from the control population.

Doria (2009) evaluated aCGH as part of a sequential protocol in the genetic evaluation of 232 spontaneous miscarriages or fetal deaths, 186 of which were from the first trimester, 24 from the second trimester, and 22 from the third trimester.[27] Tissue culture and karyotype was attempted on all specimens; samples that could not be karyotyped were tested with aCGH, followed by additional confirmation with fluorescence in situ hybridization (FISH) confirmation. Culture failure occurred in 25.4% of the cases. Of the 173 (74.6%) with valid karyotypes, 66 of 173 (38.2%) were abnormal: 62 of 66 with numerical abnormalities (single, double, or triple trisomies, monosomy X, polyploidy, or mosaicism), and five of 66 with structural abnormalities. Array CGH was performed in 58 of 59 cases with culture failure (1 case with insufficient DNA for CGH). Fifteen of the 58 cases were abnormal, with three cases of monosomy X, one case of XY with gain for X, seven cases of trisomy 15, two cases of trisomy 16, and one case each of trisomy 18 and 21. With the addition of FISH testing, four new cases of triploidy were detected. This study suggests that the use of aCGH increases the yield of testing of genetic testing of POC beyond that of standard karyotyping.

Benkhalifa (2005) evaluated 26 samples from first-trimester miscarriages that failed to divide in routine cytogenetic studies with array used CMA methods with array CGH.[28] The aCGH method used involved human genomic microarrays containing 2600 cloned areas spanning chromosome subtelomeric regions and critical areas spaced about 1 Mb along each chromosome. Of the 26 samples that failed to divide in routine cytogenetics, 15 had an abnormal genetic profile on aCGH. Abnormalities that are highly prevalent on routine karyotyping (trisomy 16, monosomy X, triploidy, which are estimated to account for >55% of cytogenetically abnormal findings in routine karyotyping) were relatively uncommon among the 15 abnormal samples, with instance of monosomy 16 and two instances of monosomy X.

A number of studies have reported outcomes from CMA of POC in various patient populations where karyotyping was not performed.

Gou (2020) evaluated POC using CMA in 222 specimens. There was a 40.54% overall detection rate for clinically significant chromosomal anomalies.[29] Of these, 53 (23.87%) were autosomal aneuploidy, 16 (7.21%) were sex chromosome aneuploidy, 5 (2.25%) were multiple aneuploidy, 4 (1.80%) were triploidy, and 12 (5.41%) were pathogenic copy number variants (pCNVs). Total chromosomal abnormality, autosomal aneuploidy, sex chromosome aneuploidy, multiple aneuploidy, and triploidy detection rates were higher in early versus late pregnancy loss, whereas the reverse was true for pCNV detection rate.

Wang (2016) reported on a prospective study assessing the clinical application of CMA testing for first-trimester pregnancy loss, successfully analyzing 551 fresh miscarriage specimens using single-nucleotide polymorphism (SNP) array.[30] Among the specimens, 2.9% (16/551) had significant maternal cell contamination and were excluded from the study. Clinically significant chromosomal abnormalities were identified in 295 (55.1%) cases, including 214 (40%) with aneuploidy, 40 (7.5%) with polyploidy, 19 (3.6%) with partial aneuploidy, 12 (2.2%) with pathogenic microdeletion/microduplication, and 10 (1.9%) with uniparental isodisomy (isoUPD). Variants of uncertain significance were obtained in 15 cases (2.8%). The authors concluded that SNP array is a reliable, robust, and high-resolution technology for genetic diagnosis of miscarriage in clinical practice.

Wou (2016) reported on a three-year retrospective study that analyzed tissue from products of conception and perinatal losses using QF-PCR and microarray. CMA was performed mostly in samples with normal QF-PCR results.[31] Of the 1071 informative specimens analyzed, 30.8% (n=330) were positive for chromosomal abnormalities, with 57.6% (n 190) of the abnormalities being detected by QF-PCR and 42.4% (n=140) by aCGH. In addition, high-resolution aCGH enabled an additional diagnostic yield of 36 cases of microdeletions and/or microduplications (10.9%) in specimens found to be abnormal by QF-PCR and 3.4% of all successfully analyzed specimens. Gestational age was known in 940 specimens. The study reported that the highest rate of chromosomal abnormalities (a combined analysis of QF-PCR and aCGH abnormalities) was observed in the first trimester (<12 weeks) with 67.6% being considered pathogenic. The difference in proportions of pathogenic findings across trimesters was statistically significant ($p < 0.001$) with the greater proportion of findings being in the first trimester.

Maslow (2015) evaluated the yield of SNP-based array for determining chromosome number in paraffin-fixed POC compared with a standard evaluation for couples with recurrent first-trimester pregnancy losses.[32] Eligible patients previously had analysis of chromosome number and screening tests recommended by the American Society for Reproductive Medicine (ASRM) for recurrent pregnancy loss, including parental karyotypes, maternal serum testing for

antiphospholipid antibodies, thyrotropin, and prolactin, and a uterine cavity evaluation via sonohysterogram or hysterosalpingogram. Forty-two women with a total of 178 first-trimester losses were included, with 62 paraffin-embedded POC samples available. SNP-based microarray was able to determine a fetal chromosome number in 44 of 62 (71%) of samples, 25 (57%) of which were noneuploid. Recurrent pregnancy loss screening was normal in 35 of 42 (83%) participants. The detection rate for any cause of pregnancy loss was significantly higher with SNP microarray (0.50; 95% CI 0.36 to 0.64) than with the ASRM-recommended recurrent pregnancy loss evaluation (0.17; 95% CI 0.08 to 0.31, p=0.002).

Romero (2015) reported on types of genetic abnormalities found on CMA in early pregnancy losses (<20 weeks of gestation) among 86 women.[33] Thirteen (14.9%) of POC samples were excluded because placental villi or fetal tissue could not be identified with certainty and nine were excluded due to complete maternal cell contamination, leaving a sample of 64 for analysis. The overall prevalence of aneuploidy and pathogenic CNV or VOUS was 43.8% (28/64). Excluding the two cases with VOUS, rates of pathogenic CNV or aneuploidy differed by gestational age: 9.1%, 69.2%, and 28.0% of pre-embryonic, embryonic, and fetal samples, respectively (p<0.01). Aneuploidy was the most common abnormality, occurring in 37.5% (24/64) cases.

Levy (2014) reported results of SNP microarray analysis of 2,447 consecutively received POC samples, of which 2,400 were fresh samples.[34] Of the fresh samples, 2392 (99.7%) were 20 weeks of gestation or less, and 1861 (77.6%) had no or negligible maternal cell contamination. The authors used a 10-Mb cutoff to estimate the threshold of detection for routine karyotyping in POC samples. At the resolution of conventional karyotyping, 1,106 (59.4%) showed classical cytogenetic abnormalities. Of the remaining 755 samples considered normal at the karyotype level, 33 (4.4%) had a CNV (microdeletion or microduplication); 12 (36.4%) were considered clinically significant and the remaining were considered VOUS.

In 2014, Mathur reported results from CMA testing in preserved POC samples from 58 women with 77 miscarriage specimens who were evaluated at a single recurrent pregnancy loss clinic.[35] All women had a history of recurrent pregnancy loss, defined as two or more ultrasound-documented miscarriages at less than 10 weeks of gestation. Samples were evaluated with CGH; if results were 46 XX, the genotype of the POC was compared with the maternal genotype at several highly polymorphic loci through microsatellite analysis (MSA) to determine if the 46 XX results were consistent with maternal cell contamination. Sixteen samples (21%) yielded uninformative results due to minimal pregnancy tissue (n=9), poor quality DNA (n=2), or confirmed maternal cell contamination (n=2). CGH was considered informative in 61 cases (79%), with 22 noneuploid and 39 euploid. Thirty-three of the euploid specimens were 46 XX, 11 of which were not sent for reflex MSA. The author concluded that CMA testing of preserved POC is technically feasible, including in cases where karyotyping had failed due to cell growth failure, which had occurred in eight samples evaluated.

Warren (2009) conducted a prospective case series to evaluate results from aCGH in POC from 35 women who had pregnancy loss between 10 and 20 weeks of gestation with either normal karyotype (n=9) or no conventional cytogenetic testing (n=26).[36] Thirty-five samples were from fresh tissue obtained at the time of pregnancy loss when dilatation and curettage was performed; the remainder was from paraffin-embedded tissue. Samples were assessed with a whole genome bacterial artificial chromosome array chip. Clones that demonstrated copy number changes in the fetal tissue were compared against known copy number change regions in the Database of Genomic Variants, and the internal database of apparently benign

copy number changes maintained by the University of Utah CGH laboratory. When CNVs were detected, parental samples were assessed with the same array chip, and CNVs present in fetal tissue but not parental DNA were defined as de novo CNVs. Samples with de novo CNVs on the bacterial artificial chromosome chip were further analyzed with an oligonucleotide microarray chip with an average resolution of 6.4 Kb for more accurate characterization. DNA was successfully isolated in 30 cases (all from the fresh tissue samples). De novo CNVs were detected in six of the 30 (20%) cases using the bacterial artificial chromosome array and confirmed in four of 30 (13%) cases using the oligonucleotide array.

CMA in IUFD

The use of CMA for evaluating products of conception for IUFD is documented in a number of large nonrandomized studies. In studies that used CMA on samples that had been previously found to have normal karyotypes, approximately 13% were found to have pathogenic results via CMA testing.[37, 38]

In a large study that compared CMA with karyotype in the evaluation of 532 cases of IUFD.[39] Of the karyotypes attempted, 375 (70.5%) yielded a result. Of those, 31 of 375 (8.3%) were classified as abnormal, with trisomy 21 (n=9), trisomy 18 (n=8), trisomy 13 (n=2), and monosomy X (n=5) representing the most common abnormalities. CMA yielded results in 465 (87.4%) of samples, significantly more than were successful karyotyped ($p<0.001$). Of those, 32 (6.9%) were aneuploidy, 12 (2.6%) were considered a pathogenic variant, and 25 (5.4%) were considered a VOUS. Nine pathogenic variants on CMA were detected in stillbirths with normal karyotypes. CMA detected aneuploidy in seven cases of the 157 in which karyotyping was unsuccessful.

Section Summary

The evidence related to the validity of CMA testing of products of conception comes primarily from studies that compared genetic testing results from CMA with conventional karyotype, and from several studies that evaluated the yield of CMA in patients with a normal or unsuccessful karyotype. These studies suggest that CMA has good concordance with karyotype for detection of aneuploidy and is more likely to yield results than conventional karyotyping given the need for cell culture for karyotyping. Studies on the yield of testing in early pregnancy losses suggests that aneuploidies are the most common abnormality detected, CMA may detect abnormalities not detected on karyotype. Relatively few studies have reported CMA outcomes in late pregnancy losses, but they suggest that CMA is more likely to yield a result than conventional karyotyping.

Changes in Patient Management and Outcomes Following CMA

Changes in management that could result from CMA testing include changes in additional testing to evaluate for causes of a pregnancy loss or changes in the management of future pregnancies, such as the decision to undertake preimplantation genetic testing. No empirical studies identified evaluated changes in management that occurred as a result of CMA testing in miscarriage or IUFD.

One argument for genetic evaluation (karyotype or CMA) in POC in cases of recurrent pregnancy loss is that an abnormal genetic evaluation would potentially forestall an evaluation for other causes of recurrent pregnancy loss, which might include assessment of the uterine cavity, thyroid function testing, and testing for antiphospholipid antibodies. In the study by

Maslow (described above), the yield of testing using a SNP microarray in recurrent pregnancy loss was higher than the yield of other recommended testing (some of which are potentially invasive).[32]

Several potential health-related outcomes result from CMA testing POC in pregnancy loss. These outcomes are the same for both early and late pregnancy loss. Knowledge of the cause of the loss may lead to reduced parent distress or anxiety. For couples with recurrent pregnancy loss, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. No studies identified reported whether the use of CMA is associated with changes in parental mental health outcomes or management of future successful pregnancies.

Section Summary

Although there are several ways in which CMA of fetal tissue in early pregnancy loss may change management and outcomes, including leading to changes in diagnostic testing, reduced parental distress, or preimplantation genetic diagnosis, no studies identified directly demonstrated changes in outcomes.

NEXT-GENERATION SEQUENCING ANEUPLOIDY TESTING

Tamura (2021) evaluated 279 cases of spontaneous abortion for aneuploidy using NGS.[40] Chorionic villi were separated from the POC for analysis. Seven samples were also analyzed with G-banding karyotyping. Of these, five were analyzed (one was excluded for culture failure and one for maternal cell contamination) and all were consistent with G-banding. Of the 279 cases analyzed with NGS, 61 (21.9%) were normal karyotype, 186 (66.7%) showed chromosomal abnormality, and 32 (11.5%) did not show distinct chorionic villi in POC specimens. Of the cases with abnormal findings, there were 172 (61.6%) cases of aneuploidy (autosomal trisomy and sex chromosome aneuploidy), 8 (2.9%) cases of segmental aneuploidy (duplication and deletion), and 6 (2.2%) cases of mosaicism, indicating that more than half of the cases in this study were chromosomally abnormal.

Xu (2020) compared the performance of traditional G-banding karyotyping with NGS for detecting common trisomies in POC.[41] A total of 28 miscarriage samples were tested via high-resolution G-banding karyotyping and NGS, while 20 samples were analyzed with NGS alone. Multiplex PCR was also used to monitor maternal cell contamination (MCC), chromosomal status, and sex. NGS identified all 21 abnormalities which were found in karyotype examination. Specificity and sensitivity of NGS combined with multiplex PCR was 100% for both normal (7/7) and abnormal (21/21) results.

Fan (2020) evaluated 1,010 POC from first-trimester pregnancy loss with NGS for chromosomal abnormalities.[42] Four samples were excluded to due maternal cell contamination. Benign CNVs were considered to be normal chromosomal variants. Chromosomal variants were detected in 634 cases. Of these, 383 were aneuploidy (60.4%), 44 were polyploidy (6.9%), 35 were mosaicisms (5.5%), 19 were benign CNVs (3.0%), 52 were pathogenic CNVs (8.2%), and 101 were VOUS CNVs (16%). Advanced maternal age was associated with a sharp increase in frequency of aneuploidy, both for sporadic abortion (with 71 of 121 age ≥35 presenting with aneuploidy vs. 155 of 432 for under 35) and for recurrent miscarriage (with 49 of 104 age ≥35 presenting with aneuploidy vs. 108 of 349 for under 35).

SUMMARY OF EVIDENCE

The evidence for testing for chromosomal abnormalities (e.g., CMA) in fetal tissue in individuals who have pregnancy loss suggests that it has a high rate of concordance with karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA detects a substantial number of abnormalities in patients with normal karyotypes, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of unknown significance in CMA testing of miscarriage samples are not well characterized. Potential benefits from identifying a genetic abnormality in a miscarriage or intrauterine fetal demise include reducing emotional distress for families, altering additional testing that is undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. The potential for clinical utility for CMA testing of fetal tissue in pregnancy loss is parallel to that for obtaining a karyotype of fetal tissue in pregnancy loss, which is recommended by a number of organizations. While no studies identified directly demonstrated whether or how patient management is changed based on CMA testing of POC from early or late pregnancy losses, or how patient outcomes are improved, the available evidence suggests that, for pregnancy loss at 20 weeks gestation or less in recurrent pregnancy loss, and after 20 weeks gestation in pregnancy loss, CMA would be expected to perform as well as or better than standard karyotyping.

The evidence for the use of next-generation sequencing (NGS) aneuploidy testing of fetal tissue in individuals who have pregnancy loss is limited. While there is some research to suggest that it performs similarly to karyotyping, sample sizes are small, and more research is needed to know for sure.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGISTS

In 2016 (and reaffirmed in 2023), the American College of Obstetrics and Gynecologists Committee (ACOG) on Genetics and the Society for Maternal-Fetal Medicine published a joint committee opinion (No. 682) on the use of CMA testing in obstetrics and gynecology, stating the following:[43]

> “Chromosomal microarray analysis of fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities.”

In 2020, ACOG also published an obstetric care consensus on the management of stillbirth.[44] The consensus states that microarray analysis, incorporated into the stillbirth evaluation, "improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping [strong recommendation; high-quality evidence]." As such, the authors of the consensus recommend microarray as the preferred method of stillbirth evaluation; however, "due to cost and logistics concerns, karyotype may be the only method readily available for some patients."

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2012, the American Society for Reproductive Medicine issued a committee opinion on the evaluation and treatment of recurrent pregnancy loss.[2] The statement makes the following conclusions about the evaluation of recurrent pregnancy loss:

- "Evaluation of recurrent pregnancy loss can proceed after two consecutive clinical pregnancy losses."
- Assessment of recurrent pregnancy loss focuses on screening for genetic factors, which may include peripheral karyotype of the parents.
- "Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss."

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

In 2023, the Royal College of Obstetricians and Gynaecologists issued guidelines on the evaluation and treatment for recurrent first-trimester and second-trimester miscarriage.[45] The guidelines make the following recommendations related to karyotyping in recurrent miscarriage:

- "Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s)." (Grade of evidence D [evidence level 3 or 4; or extrapolated from studies rated as 2+]; evidence level 4 [expert opinion]).
- "Parental peripheral blood karyotyping should be offered for couples in whom testing of pregnancy tissue. reports an unbalanced structural chromosomal abnormality [Grade D] or there is unsuccessful or no pregnancy tissue available for testing." (Grade of evidence D; Evidence level 3 [nonanalytical studies, e.g., case reports, case series]).

SUMMARY

The research on chromosomal abnormality testing of fetal tissue is limited. However, practice guidelines recommend such testing for pregnancy loss for certain individuals. Therefore, this testing may be considered medically necessary in cases of pregnancy loss at less than or equal to 20 weeks of gestation when there is recurrent pregnancy loss or pregnancy loss after 20 weeks of gestation.

There is not enough research to show that testing for chromosomal abnormalities in fetal tissue is helpful for individuals that do not meet the policy criteria. Clinical guidelines only recommend testing for pregnancy loss at less than or equal to 20 weeks of gestation when there is recurrent pregnancy loss, or if there is pregnancy loss after 20 weeks of gestation. Therefore, this testing is considered investigational when policy criteria are not met.

There is not enough research to show that the use of next-generation sequencing (NGS) aneuploidy testing of fetal tissue for pregnancy loss improves health outcomes. No clinical guidelines based on research recommend this method of testing for pregnancy loss. Therefore, this testing is considered investigational.

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CODES

NOTE: The appropriate codes for reporting CMA are 81228 for CMA alone, and 81229 for CMA testing that includes single nucleotide polymorphism (SNP) analysis. It is not appropriate to report code 81422 for CMA.

Codes	Number	Description
CPT	0252U	Fetal aneuploidy short tandem–repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy

Codes	Number	Description
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities
	81479	Unlisted molecular pathology procedure
	88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
	88299	Unlisted cytogenetic study
HCPCS	None	

Date of Origin: *April 2017*

Regence

Medical Policy Manual Genetic Testing, Policy No. 80

Genetic Testing for Epilepsy

Effective: January 1, 2025

Next Review: October 2025
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

There are numerous rare epileptic syndromes associated with global developmental delay and/or cognitive impairment that occur in infancy or early childhood and that may be caused by single-gene pathogenic variants. Genetic testing is commercially available for a large number of genes that may be related to epilepsy.

MEDICAL POLICY CRITERIA

Note: This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (e.g., Rett syndrome, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

I. Single gene and targeted panel testing for genetic epilepsy syndromes (see Policy Guidelines, Table PG1) may be considered **medically necessary** for individuals suspected of having a genetic epilepsy syndrome when all of the following are met (A. - D.):

   A. Infantile or childhood onset of seizures (younger than 18 years of age at onset); and

B. Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities; and

C. EEG and neuroimaging by CT or MRI have been performed with no evidence of structural anomalies; and

D. No other clinical syndrome has been identified that would explain the patient's symptoms.

II. Single gene and targeted panel testing for genetic epilepsy syndromes to determine *reproductive carrier status* in prospective parents may be considered **medically necessary** when one or more of the following are met for the epilepsy syndrome being tested:

A. There is at least one first- or second-degree relative diagnosed; or

B. Reproductive partner is known to be a carrier.

III. Epilepsy syndrome genetic testing for reproductive carrier status is considered **not medically necessary** when Criterion II. is not met.

IV. Genetic testing to diagnose genetic epilepsy syndromes is considered **not medically necessary** for patients who do not have severe seizures affecting daily functioning and/or interictal EEG abnormalities, and for patients that have not had EEG and neuroimaging (CT or MRI), or when another clinical syndrome has been identified that would explain a patient's symptoms.

V. Genetic testing to diagnose genetic epilepsy syndromes is considered **investigational** for patients with seizure onset in adulthood (age 18 and older).

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

POLICY GUIDELINES

INFANTILE- AND EARLY-CHILDHOOD-ONSET EPILEPSY SYNDROMES

Variants in a large number of genes have been associated with early-onset epilepsies. Some of these are summarized in Table PG1.

Table PG1: Single-Genes Associated With Epileptic Syndromes

Syndrome	Associated Genes
Dravet syndrome	*SCN1A*, *SCN9A*, *GABRA1*, *STXBP1*, *PCDH19*, *SCN1B*, *CHD2*, *HCN1*
Epilepsy limited to females with mental retardation	*PCDH19*
Epileptic encephalopathy with continuous spike-and-wave during sleep	*GRIN2A*
Genetic epilepsy with febrile seizures plus	*SCN1A, SCN9A*
Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)	*KCNQ2*, *SLC25A22*, *STXBP1*, *CDKL5*, *ARX*
Landau-Kleffner syndrome	*GRIN2A*
West syndrome	*ARX*, *TSC1*, *TSC2*, *CDKL5*, *ALG13*, *MAGI2*, *STXBP1*, *SCN1A*, *SCN2A*, *GABA*, *GABRB3*, *DNM1*
Glucose transporter type 1 deficiency syndrome	*SLC2A1*
Neuronal Ceroid-Lipofuscinoses	*PPT1, TPP1, CLN3, CLN5, CLN6, MFSD8, CLN8, CTSD, DNAJC5, CTSF, ATP13A2, GRN, KCTD7*

Syndrome	Associated Genes
Other syndromes	*KCNQ3, GABRG2, GABRD, CHRNA4, CHRNB2, CHRNA2, KCNT1, DEPDC5, CRH, TBC1D24, EFHC1, POLG* *ASAH1, FOLR1, SCN8A, SYNGAP1, SYNJ1, SLC13A5*

This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (e.g., Rett syndrome, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or mutation(s) being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test:
    - History and physical/chart notes, including *specific* signs and symptoms observed, related to a *specific* epileptic syndrome
    - Known family history related to a specific epileptic syndrome, if applicable
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Cytochrome p450 Genotyping, Genetic Testing, Policy No. 10
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Genetic Testing for Mental Health Conditions, Genetic Testing, Policy No. 53
4. Chromosomal Microarray Analysis (CMA) and Next-generation Sequencing Panels for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies, Genetic Testing, Policy No. 58
5. Genetic Testing for Methionine Metabolism Enzymes, including MTHFR, for Indications Other than Thrombophilia, Genetic Testing, Policy No. 65
6. Genetic Testing for Rett Syndrome, Genetic Testing, Policy No. 68
7. Whole Exome and Whole Genome Sequencing, Genetic Testing, Policy No. 76
8. Acthar H.P. Gel, repository corticotropin injection, Medication Policy Manual, Policy No. dru316

BACKGROUND

EPILEPSY

Epilepsy is defined as the occurrence of two or more unprovoked seizures. It is a common

neurologic disorder, with approximately 3% of the population developing the disorder over their entire lifespan.[1]

Classification

Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, i.e., the type of seizures that occur. The International League Against Epilepsy (ILAE) developed the classification system that is widely used for clinical care and research purposes (see Table 1).[2] Classification of seizures can also be done on the basis of age of onset: neonatal, infancy, childhood, and adolescent/adult.

Table 1. Classification of Seizure Disorders by Type

Seizures Disorders
Partial (focal seizures)
Simple partial seizures (consciousness not impaired)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms or signs
With psychic symptoms (disturbance of higher cerebral function)
Complex partial (with impairment of consciousness)
Simple partial onset followed by impairment of consciousness
Impairment of consciousness at outset
Partial seizures evolving to secondarily generalized seizures
Generalized seizures
Nonconvulsive (absence)
Convulsive
Unclassified seizures

Adapted from Berg (2010).[2]

More recently, the concept of genetic epilepsies has emerged as a way of classifying epilepsy. Many experts now refer to “genetic generalized epilepsy” as an alternative classification for seizures previously called “idiopathic generalized epilepsies.” The ILAE report, published in 2010, offers the following alternative classification (see Table 2).[2]

Table 2. Alternative Classifications

Classification	Condition Definition
Genetic epilepsies	Conditions in which the seizures are a direct result of a known or presumed genetic defect(s). Genetic epilepsies are characterized by recurrent unprovoked seizures in patients who do not have demonstrable brain lesions or metabolic abnormalities. In addition, seizures are the core symptom of the disorder, and other symptomatology is not present, except as a direct result of seizures. This is differentiated from genetically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.
Structural/metabolic	Conditions having a distinct structural or metabolic condition that increases the likelihood of seizures. Structural conditions include a variety of central nervous system abnormalities such as stroke, tumor or trauma, and metabolic conditions include a variety of encephalopathic abnormalities that predispose to seizures. These conditions may have a genetic etiology, but the genetic defect is associated with a separate disorder that predisposes to seizures.
Unknown cause	Conditions for which the underlying etiology for the seizures cannot be determined and may include both genetic and nongenetic causes.

For this evidence review, the ILAE classification is most useful. The review focuses on the category of genetic epilepsies in which seizures are the primary clinical manifestation. This

category does not include syndromes that have multiple clinical manifestations, of which seizures may be one. Examples of syndromes that include seizures are Rett syndrome and tuberous sclerosis. Genetic testing for these syndromes will not be assessed herein, but may be included in separate reviews that specifically address genetic testing for that syndrome.

Genetic epilepsies can be further broken down by type of seizures. For example, genetic generalized epilepsy refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.[1 3] These syndromes are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as development delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.[2] A partial list of severe early-onset epilepsy syndromes is as follows:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy or polymorphic myoclonic epilepsy in infancy)
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Nocturnal frontal lobe epilepsy
- GEFS+ syndrome (generalized epilepsies with febrile seizures plus)
- EIEE syndrome (early infantile epileptic encephalopathy with burst suppression pattern)
- West syndrome
- Ohtahara syndrome.

Dravet syndrome falls on a spectrum of *SCN1A*-related seizure disorders, which includes febrile seizures at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures at the severe end. The spectrum may be associated with multiple seizure phenotypes, with a broad spectrum of severity; more severe seizure disorders may be associated with cognitive impairment, or deterioration.[4] Ohtahara syndrome is a severe early-onset epilepsy syndrome characterized by intractable tonic spasms, other seizures, interictal electroencephalography abnormalities, and developmental delay. It may be secondary to structural abnormalities but has been associated with variants in the *STXBP1* gene in rare cases. West syndrome is an early-onset seizure disorder associated with infantile spasms and the characteristic electroencephalography finding of hypsarrhythmia. Other seizure disorders presenting early in childhood may have a genetic component but are characterized by a more benign course, including benign familial neonatal seizures and benign familial infantile seizures.

Genetic Etiology

Most genetic epilepsies are primarily believed to involve multifactorial inheritance patterns. This follows the concept of a threshold effect, in which any particular genetic defect may increase the risk of epilepsy, but is not by itself causative.[5] A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of

epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or particular combinations of genes, probably increase the risk by a greater amount. However, it is not well- understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Early-onset epilepsy syndromes may be single-gene disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are currently being frequently discovered.[6]

Some of the most common genes associated with genetic epileptic syndromes are listed in Table 3.

Table 3. Selected Genes Most Commonly Associated With Genetic Epilepsy

Genes	Physiologic Function
KCNQ2	Potassium channel
KCNQ3	Potassium channel
SCN1A	Sodium channel α-subunit
SCN2A	Sodium channel α-subunit
SCN1B	Sodium channel β-subunit
GABRG2	γ-aminobutyrate A-type subunit
GABRRA1	γ-aminobutyrate A-type subunit
GABRD	γ-aminobutyrate subunit
CHRNA2	Acetylcholine receptor α2 subunit
CHRNA4	Acetylcholine receptor α4 subunit
CHRNB2	Acetylcholine receptor β2 subunit
STXBP1	Synaptic vesicle release
ARX	Homeobox gene
PCDH19	Protocadherin cell-cell adhesion
EFHC1	Calcium homeostasis
CACNB4	Calcium channel subunit
CLCN2	Chloride channel
LGI1	G-protein component

Adapted from Williams and Battaglia, 2013.[1]

For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include generalized epilepsies with febrile seizures plus syndrome (associated with *SCN1A*, *SCN1B*, and *GABRG2* variants), Dravet syndrome (associated with *SCN1A* variants, possibly modified by *SCN9A* variants), and epilepsy and intellectual disability limited to females (associated with *PCDH19* variants). Ohtahara syndrome has been associated with variants in STXBP1 in cases where patients have no structural or metabolic abnormalities. West syndrome is often associated with chromosomal abnormalities or tuberous sclerosis or may be secondary to an identifiable infectious or metabolic cause, but when there is no underlying cause identified, it is thought to be due to a multifactorial genetic predisposition.[7]

Targeted testing for individual genes is available. Several commercial epilepsy genetic panels are also available. The number of genes included in the tests varies widely, from about 50 to over 450. The panels frequently include genes for other disorders such as neural tube defects, lysosomal storage disorders, cardiac channelopathies, congenital disorders of glycosylation, metabolic disorders, neurologic syndromes, and multisystemic genetic syndromes. Some panels are designed to be comprehensive while other panels target specific subtypes of epilepsy. Chambers (2016) reviewed comprehensive epilepsy panels from seven U.S.-based

clinical laboratories and found that between 1% and 4% of panel contents were genes not known to be associated with primary epilepsy.[8] Between 1% and 70% of the genes included on an individual panel were not on any other panel.

Treatment

The condition is generally chronic, requiring treatment with one or more medications to adequately control symptoms. Seizures can be controlled by antiepileptic medications in most cases, but some patients are resistant to medications, and further options such as surgery, vagus nerve stimulation, and/or the ketogenic diet can be used.[9]

Pharmacogenomics

Another area of interest for epilepsy is the pharmacogenomics of antiepileptic medications. There are a wide variety of these medications, from numerous different classes. The choice of medications, and the combinations of medications for patients who require treatment with more than one agent is complex. Approximately one-third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication.[10] These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the clinical phenotype of seizures but has a large trial-and-error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in detecting genetic markers that identify patients likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

Of note, genotyping for the *HLA-B**1502 allelic variant in patients of Asian ancestry, prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions, is recommended by the U.S. Food and Drug Administration labeling for carbamazepine.[11]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Commercially available genetic tests for epilepsy are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

This evidence review does not address testing for genetic syndromes that have a wider range of symptomatology (e.g., neurofibromatosis, tuberous sclerosis) or genetic syndromes

associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

The genetic epilepsies are discussed in two categories: the rare epileptic syndromes that may be caused by a single-gene variant and are classified as epileptic encephalopathies and the epilepsy syndromes that are thought to have a multifactorial genetic basis.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

EARLY-ONSET EPILEPSY AND EPILEPTIC ENCEPHALOPATHIES

Numerous rare syndromes have seizures as their primary symptom which generally present in infancy or early childhood and may be classified as epileptic encephalopathies. Many are thought to be caused by single-gene variants. The published literature on these syndromes generally consists of small cohorts of patients treated in tertiary care centers, with descriptions of genetic variants that are detected in affected individuals.

Table 4 lists some of these syndromes, with the putative causative genetic variants.

Table 4. Early-Onset Epilepsy Syndromes Associated With Single-Gene Variants

Syndrome	Implicated Genes
Dravet syndrome (severe myoclonic epilepsy of infancy)	*SCN1A*
Early infantile epileptic encephalopathy	*STXBP1*
Generalized epilepsy with febrile seizures plus (GEFS+)	*SCN1A*, *SCN2A*, *SCN1B*, *GABRG2*
Epilepsy and mental retardation limited to females (EFMR)	*PCDH19*
Nocturnal frontal lobe epilepsy	*CHRNA4*, *CHRNB2*, *CHRNA2*

Other less commonly reported single-gene variants have been evaluated in childhood-onset epilepsies and in early-onset epileptic encephalopathies, including *ASAH1*, *FOLR1*, *GRIN2A*, *SCN8A*, *SYNGAP1*, and *SYNJ1* variants in families with early-onset epileptic encephalopathies[13] and *SLC13A5* variants in families with pedigrees consistent with autosomal recessive epileptic encephalopathy.[14]

The purpose of genetic testing in patients who have epileptic encephalopathies is to determine the etiology of the epilepsy syndrome thereby possibly limiting further invasive investigation (e.g., epilepsy surgery), define prognosis, and help guide therapy.

The potential beneficial outcomes of primary interest would be improvement in symptoms (particularly reduction in seizure frequency), functioning, and quality of life. Genetic diagnosis may also limit further invasive investigations into seizure etiology that have associated risks and resource utilization, e.g., a genetic diagnosis may spare patients the burden and morbidity of unnecessary epilepsy surgery.

The potential harmful outcomes are those resulting from a false test result. False-positive test results can lead to initiation of unnecessary treatment and adverse effects from that treatment. False-negative test results could lead to unnecessary surgeries.

Analytic Validity

Assessment of analytic validity focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

The literature on the clinical validity of genetic testing for these rare syndromes is limited and, for most syndromes, the clinical sensitivity and specificity are not defined. Dravet syndrome is probably the most well studied, and some evidence on the clinical validity of *SCN1A* variants is available. The clinical sensitivity has been reported to be in the 70% to 80% range.[15 16] In a 2006 series of 64 patients, 51 (79%) were found to have *SCN1A* pathogenic variants.[16] Among eight infants who met clinical criteria for Dravet syndrome in a 2015 population-based cohort, six had a pathogenic *SCN1A* variant, all of which were *de novo*.[17]

A number of studies have reported on the genetic testing yield in cohorts of pediatric patients with epilepsy, typically in association with other related symptoms. Table 6 summarizes examples of diagnostic yield in children with epileptic encephalopathy.

Table 6. Genetic Testing Yields in Pediatric Patients with Epilepsy

Study (Year)	Population	Genetic Testing	Results
Burk (2024)[18]	736 patients with epilepsy	Microarray (n=366) and targeted epilepsy gene panel (n=370)	• Diagnostic yield: 7.7% with microarray and 41.9% with targeted epilepsy gene sequencing • Diagnostic yield was greater in patients with infantile seizure onset
Charouf (2024)[19]	49 children with unexplained epilepsy with neurodevelopmental delay and/or medically intractable	Whole-exome or whole-genome sequencing	• Diagnostic yield: 68.9% overall (27 of 38 for whole-exome sequencing and 4 of 7 for whole-genome sequencing)
Gerik-Celebi (2024)[20]	100 children with epilepsy	Targeted gene panel and whole-exome sequencing	• Diagnostic yield: 33% • 11 Novel variants were identified in *WDR45, ARX, PCDH19, SCN1A, CACNA1A, LGI1, ASPM, MECP2, NF1, TSC2*, and *CDK13*.
Kim (2024)[21]	57 patients with unexplained pediatric-onset epilepsy	Targeted gene panel and/or whole-exome sequencing	• Diagnostic yield: 32.4% overall, 36.9% with clinical exome sequencing, 29.9% with epilepsy gene panel • Diagnostic yield differed across syndromes: 87.2% (Dravet syndrome), 60.7% (early infantile developmental epileptic encephalopathy), 21.8% (West syndrome), and 4.8% (myoclonic-atonic epilepsy) • Frequently implicated genes: *SCN1A* (n=49), *STXBP1* (n=15), *SCN2A* (n=14), *KCNQ2* (n=13), *CDKL5* (n=11),

Study (Year)	Population	Genetic Testing	Results
			CHD2 (n=9), *SLC2A1* (n=9), *PCDH19* (n=8), *MECP2* (n=6), *SCN8A* (n=6), and *PRRT2* (n=5)
Majethia (2024)[22]	161 children with epilepsy	Microarray, epilepsy panel, or whole-exome sequencing	• Diagnostic yield: 52% definitive molecular diagnosis • Genetic variants identified in 53 epilepsy-associated genes
Krygier (2023)[23]	127 patients with monogenic epilepsy	Targeted gene panel and/or whole-exome sequencing	• Diagnostic yield: molecular diagnosis established in 36% of cases • Alterations in six genes detected in 48% of positive cases: *SCN1A, MECP2, KCNT1, KCNA2, PCDH19, SLC6A1, STXBP1,* and *TPP1*
Witzel (2023)[24]	304 patients with epilepsy	Single and trio exome sequencing, targeted gene panel	• Diagnostic yield: pathogenic variants identified in 22% of patients
Bayanova (2023)[25]	20 children with epilepsy onset before age three	Whole genome sequencing	• Diagnostic yield: pathogenic and likely pathogenic variants identified in 70% of patients • Genes with novel variants: *KCNQ2, CASK, WWOX, MT-CO3, GRIN2D, and SLC12A5*
Ko (2023)[26]	1,213 children with neurodevelopmental disorders, 168 of whom had epilepsy	Whole exome sequencing	• Diagnostic yield: 39.3% of patients with neurodevelopmental disorders received genetic diagnosis • Epilepsy-associated variants identified in 77% of patients with epilepsy
Pinto (2023)[27]	110 children with epilepsy	Next-generation sequencing, targeted gene panel	• Diagnostic yield: 34% pathogenic results overall • 54% of pathogenic variants identified in *SCN1A, SCN2A, MECP2, KCNT1, PCDH19, SPTAN1, CACNA1A,* and *UBE3A*
Scheffer (2023)[28]	103 children and infants with developmental and epileptic encephalopathies	Epilepsy panel, singleton exome sequencing	• Diagnostic yield: 35% of patients had genetic etiology • 29% of patients had pathogenic or likely pathogenic variants, 38% had variants of unknown significance, and 33% were negative on exome analysis • *KCNQ2, CDKL5, SCN1A, and STXBP1* were the most frequently identified genes
Jiang (2021)[29]	221 children with epilepsy	Whole exome sequencing	• Diagnostic yield: 64.5% of patients with epilepsy and developmental delay/intellectual disability; 18.9% of patients with only epilepsy (p<.0001) • 48 of 87 variants detected were novel • Genes with novel variants: *NCL, SEPHS2, PA2G4, SLC35G2, MYO1C, GPR158,* and *POU3F1*
Kim (2021)[30]	59 patients with infantile-onset epilepsy and prior negative targeted gene panel testing	Whole exome sequencing	• Diagnostic yield: 8% more than with targeted gene panel testing • Genes with pathogenic/likely pathogenic variants: *FARS2, YWHAG, KCNC1, DYRK1A, SMC1A, OGT,* and *FGF12*

Study (Year)	Population	Genetic Testing	Results
			• Newly associated genes: *YWHAG*, *KCNC1*, and *FGF12*
Palmer (2021)[31]	30 patients with developmental and epileptic encephalopathies with prior negative genetic testing	Whole exome sequencing	Diagnostic yield: • 53% in 15 patients with prior exome sequencing (20% had complex structural variants) • 68% in 15 patients with prior multigene panel testing
Salinas (2021)[32]	55 patients with developmental and epileptic encephalopathies with prior negative genetic testing	Targeted multigene panel testing, whole exome sequencing	• Diagnostic yield: 38% at baseline, 53% after a mean of 29 months (based on new literature) • Genes with novel variants: *CHD2, COL4A1, FOXG1, GABRA1, GRIN2B, HNRNPU, KCNQ2, MECP2, PCDH19, SCN1A, SCN2A, SCN8A, SLC6A1, STXBP1,* and *WWOX*
Sun (2021)[33]	73 infants with epileptic encephalopathies including West syndrome and Dravet syndrome	Whole exome sequencing	• Diagnostic yield: 46.6%, most commonly SCN1A variants • Genes with novel variants: *CACNA1E* and *WDR26*
Gall (2021)[34]	211 patients 24 to 60 months of age with firs unprovoked seizure at/after 24 months and at least one additional finding	Epilepsy panel	• Genetic diagnosis established in 20.4% • Predominant molecular diagnosis was neuronal ceroid lipofuscinosis type 2
Lee (2021)[35]	105 children with various seizure types	Whole exome sequencing, microarray, single gene testing, targeted multigene panel testing	Diagnostic yield: • 35.71% with whole exome sequencing • 8.33% with microarray • 18.60% with single gene testing • 19.23% with targeted multigene panel testing
Mitta (2020)[36]	82 children with infantile-onset developmental-epileptic encephalopathies	Epilepsy panel	Diagnostic yield: • 31.7% overall with pathogenic/likely pathogenic variants • 50% for Ohtahara syndrome • 13.3% for West syndrome • 67% for epilepsy of infancy with migrating partial seizures due to CACNA1A and KCNT1 variants
Lee (2020)[37]	24 patients with Dravet syndrome	Targeted panel with 40 epilepsy genes	Disease-causing variants (SCN1A and PCDH19) identified in 75% of patients
Lee (2020)[38]	48 patients with early-onset epileptic encephalopathies with burst suppression	Epilepsy panel	Diagnostic yield was 64.6% overall The most common involved genes were: • STXBP1 (27.1%) • KCNQ2 (10.4%) • SCN2A (10.4%) • DEPDC5 (6.3%) • CASK (2.1%) • CDKL5 (2.1%) • GNAO1 (2.1%) • SLC6A8 (2.1%)

Study (Year)	Population	Genetic Testing	Results
			• LIS1 (2.1%)
Lee (2020)[39]	116 patients with early-onset epilepsy (before age 2 years) and normal brain imaging	Next-generation sequencing targeted gene panel	Disease-causing variants (most commonly SCN1A and PRRT2) identified in 34.5% of patients
Stödberg (2020)[40]	116 children with epilepsy onset before the age of 2 years and	Whole exome sequencing/next-generation sequencing	An epilepsy syndrome was diagnosed in 54% of patients (34% structural causes, 20% genetic causes). Diagnostic yield with whole exome sequencing/next-generation sequencing was 58% (of 26 patients).
Angione (2019)[41]	77 patients with a potential diagnosis of epilepsy with myoclonic-atonic seizures	Microarray, epilepsy panel, or WES	• 6 of 37 microarrays identified copy number variants • 2 of 51 panel tests identified pathogenic or likely pathogenic variants (in SCN1A and GABRG2) • 3 of 6 WES tests identified variants that were believed to explain the phenotype
Balciuniene (2019)[42]	151 patients with idiopathic epilepsy	Sequence and copy number analysis of 100 epilepsy genes; reflex to exome sequencing	Diagnostic yield: • 15.3% overall from initial testing • 17.9% including exome sequencing • 38.6% in patients with epilepsy onset in infancy (age 1-12 months) Diagnostic findings reported in: • SCN1A (n=4) • PRRT2 (n=3) • STXBP1 (n=2) • IQSEC2 (n=2) • ATP1A2, ATP1A3, CACNA1A, GABRA1, KCNQ2, KCNT1, SCN2A, SCN8A, DEPDC5, TPP1, PCDH19, and UBE3A (all n = 1)
Yang (2019)[43]	733 patients with epilepsy onset by one year of age	Exome sequencing or targeted sequencing (2742 gene panel)	Diagnostic yield: • 26.7% for targeted sequencing • 42% for exome sequencing • 48.7% of diagnostic findings related to 12 genes
Jang (2019)[44]	112 patients with seizure onset before 12 months with unknown cause	Deep targeted sequencing with a custom-designed capture probe	Diagnostic yield: • 47.3% overall • 61.5% in patients with neonatal onset • 50.0% in patients with early infantile onset
Symonds (2019)[45]	333 patients presenting with epilepsy by 36 months of age	104-gene epilepsy panel	• 25% of patients had a diagnostic genetic finding. • Most common single-gene epilepsies were PRRT2, SCN1A, KCNQ2, and SLCA1
Esterhuizen (2018)[46]	22 infants with provisional diagnosis of DS	Target resequencing of DS-associated genes	Disease-causing variants (SCN1A and PCDH) identified in 45.5% of patients
Peng (2018)[47]	273 pediatric patients with drug-resistant epilepsy	WES, epilepsy panel, or clinical WES panel	93 likely disease-causing variants found in 31.5% of patients: • SCN1A (24.4%) • TSC2 (8.1%) • SCN8A (5.8%)

Study (Year)	Population	Genetic Testing	Results
			• CDKL5 (5.8%)
Staněk (2018)[48]	151 unrelated patients with severe childhood epilepsy	Epilepsy panel of 112 genes	Diagnostic yield: 25.8% overall • 61.9% in patients with seizure onset within the first four weeks of life • 35.8% in patients with seizure onset between four weeks and 12 months of age • 11.1% in patients with seizure onset between 12 and 36 months of age • 15.6% in patients with seizure onset after 36 months of age
Kothur (2018)[49]	105 patients with epilepsy of unknown cause	Epilepsy panel of 71 genes or 47 genes	Diagnostic yield: 28.5% overall • 52% of early onset including Ohtahara syndrome patients • 60% of Dravet syndrome patients • 26% of epileptic encephalopathy not otherwise specified • 0% of generalized epilepsy patients
Berg (2017)[50]	327 infants and young children with newly diagnosed with epilepsy	Various forms	Diagnostic yield: 40.4% overall • 44.1% of 59 with karyotyping • 17.0% of 188 with microarrays • 27.2% of 114 with epilepsy panels • 33.3% of 33 with whole exome sequencing • 20% of 20 with mitochondrial panels
Moller (2016)[51]	216 patients with epileptic encephalopathy phenotypes or familial epilepsy	Epilepsy panel of 46 genes	Diagnostic yield: 23% patients overall • 32% of patients with epileptic encephalopathies • 57% of patients with neonatal-onset epilepsies • 3% variants of uncertain significance
Trump (2016)[52]	400 patients with early-onset seizures and/or severe developmental delay	Epilepsy and development delay panel of 46 genes	Diagnostic yield: 18% patients overall • 39% in patients with seizure onset within first two mo of life
Wirrell (2015)[53]	81 patients with infantile spasms and no obvious cause at diagnosis	Various forms	Diagnostic yield: • 0% for karyotyping • 11.3% of 62 for aCGH • 33.3% of three for targeted chromosomal SNV analysis • 11.1% of nine for targeted single-gene analysis • 30.8% of 26 for epilepsy gene panels
Mercimek-Mahmutoglu (2015)[54]	110 patients with epileptic encephalopathies	aCGH, NGS	Diagnostic yield: • 2.7% for aCGH • 12.7% for targeted NGS
Hrabik (2015)[55]	147 children with epilepsy	SNV microarray	• Diagnostic yield: 7.5% clinically significant abnormal results

aCGH: array comparative genomic hybridization; NGS: next-generation sequencing; SNV: single-nucleotide variant.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

For the early-onset epilepsies that may have a genetic component, interventions to reduce the risk of having an affected offspring may be a potential area for clinical utility. Genetic counseling and consideration of preimplantation genetic testing combined with *in vitro* fertilization are available options. For Dravet syndrome, most pathogenic variants are sporadic, making the clinical utility of testing for the purposes of counseling parents and intervening in future pregnancies low. However, when there is a familial disease with a pathogenic variant present in one parent, then preimplantation genetic testing may reduce the likelihood of having an affected offspring. For other syndromes, the risk in subsequent pregnancies for families with one affected child may be higher, but the utility of genetic counseling is not well-established in the literature.

Another potential area of clinical utility for genetic testing may be in making a definitive diagnosis and avoiding further testing. For most of these syndromes, the diagnosis is made by clinical criteria. However, there may be significant overlap across syndromes regarding seizure types. It is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be made by clinical criteria.

There is no direct evidence of utility, i.e., there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to the efficacy of treatment without genetic testing.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence could be constructed to demonstrate the utility of genetic testing for epileptic encephalopathies. As mentioned, the differential diagnosis of infants presenting with clinical features of epileptic encephalopathies cannot always be made by phenotype alone; however, treatment may differ depending on the diagnosis. For Dravet syndrome, the seizures are often refractory to common medications. Some experts have suggested that diagnosis of Dravet syndrome may, therefore, prompt more aggressive treatment, and/or avoidance of certain medications known to be less effective (e.g., carbamazepine).[16 56] Also, some experts suggest that patients with Dravet syndrome may be more susceptible to particular AEDs, including clobazam and stiripentol.[4] In contrast, the usual medical treatment of infantile spasms is hormonal therapy with corticotropin (adrenocorticotropic hormone),[57-59] and usual first-line treatment of Lennox-Gastaut is sodium valproate.[60] Therefore, confirming the specific diagnosis leads to changes in therapy expected to improve outcomes.

Krygier (2024) reported diagnostic yield (Table 6) and investigated the treatment impact of whole-exome or multigene panel sequencing in 127 patients with suspected monogenic epilepsy.[23] Fifty-three of 127 patients developed pharmacoresistant epilepsy, 19 of whom (36%) had a single-gene etiology identified. Genetic diagnosis led to a change in anti-seizure management in 15 of 46 cases (33%). Most of these patients had *SCN1A*-related epilepsy (7 of 15), who benefited from receiving fist-line and add-on therapy for Dravet syndrome and/or stopping carbamazepine for focal seizures. Specific treatments were also implemented for patients with *GLUT1* deficiency syndrome (ketogenic diet and withdrawal of anti-seizure medication), pyridoxine-dependent epilepsy (large daily supplements of pyridoxine), creatine transporter deficiency (supplementation with creatine), and neuronal ceroid lipofuscinosis (enzyme replacement therapy). One patient with a pathogenic *TSC1* variant became seizure-free after switching to monotherapy with vigabatrin, and one patient with a *GRIN2A* splice-site variant began supplementation with L-serine.

Scheffer (2023) reported diagnostic yield (Table 6) and assessed treatment impact of exome sequencing in 103 children and infants with developmental and epileptic encephalopathies.[28] 13 of 36 patients with a known genetic cause for their condition had management implications. These included treatment for the underlying biochemical abnormality (one patient with *SLC2A1*), choice of antiseizure medication (four patients with *KCNQ2*, three with *SCN1A*, two with *SCN8A*, and one with *SCN2A*), choice of other medication (one patient with *ATP1A3*), and screening for disease-related complications (one patient with *COL4A1*).

In an international, cross-sectional, retrospective study, McKnight (2022) evaluated the association of genetic diagnoses with clinical management and outcomes for epilepsy patients.[61] 418 patients with epilepsy, regardless of sociodemographic features or age, whose genetic test results indicated a pathogenic or likely pathogenic variant in at least one gene were included. Genetic diagnosis was associated with changes in clinical management for 208 patients (49.8%) and usually (81.7% of the time) within three months of receiving the result. The most common clinical management changes were addition of a new medication (78 [21.7%]), initiation of medication (51 [14.2%]), referral of a patient to a specialist (48 [13.4%]), vigilance for subclinical or extra-neurological disease features (46 [12.8%]), and cessation of a medication (42 [11.7%]). Follow-up information was gathered for 167 patients at a mean follow-up time of 584 days. 125 (74.9%) reported positive outcomes, 108 (64.7%) reported reduction or elimination of seizures, 37 (22.2%) had decreases in the severity of other clinical signs, and 11 (6.6%) had reduced medication adverse effects. A few patients reported worsening of outcomes, including a decline in their condition (20 [12.0%]), increased seizure frequency (6 [3.6%]), and adverse medication effects (3 [1.8%]). No clinical management changes were reported for 178 patients (42.6%).

Boonsimma (2022) reported the diagnostic yield and treatment impact of exome sequencing in a cohort of 103 unrelated patients with pharmacoresistant epilepsy presenting during infancy at a center in Thailand.[62] The testing identified a molecular cause in 64 patients (62%) and a partial cause in two patients. Eight of these patients had specific treatment associated with the disorder, including six patients with pyridoxine-dependent epilepsy. Management changes were made for 43% of the patients as a result of the testing.

A single-center retrospective study by Hoelz (2020) described the effect of next-generation sequencing on clinical decision-making among children with epilepsy.[63] Testing was performed a mean of 3.6 years after symptom onset. Most of the patients had epileptic encephalopathy (40%) followed by focal epilepsy (33%) and generalized seizures (18%). Sixteen patients (18%) who underwent testing had a pathogenic or likely pathogenic gene identified. Subsequently, 10 of these 16 patients (63%) had changes in their clinical management, including medications (n=7), diagnostic testing (n=8), or avoiding future surgical procedures (n=2).

Ream (2014) retrospectively reviewed a single center’s use of clinically available genetic tests in the management of pediatric drug-resistant epilepsy.[64] The study included 25 newly evaluated patients with pediatric drug-resistant epilepsy. Fourteen (56%) of tested patients had epileptic encephalopathies; 17 (68%) had generalized epilepsy syndromes. Of the 25 patients in the newly evaluated group, 15 had positive findings on genetic testing (defined as a “potentially significant” result), with 10 of the 15 considered to be diagnostic (consisting of variants previously described to be disease-causing for epilepsy syndromes or variants predicted to be disease-causing.) The genetic testing yield was higher in patients with epileptic encephalopathies (p=0.005) and generalized epilepsy (p=0.028). Patients with a clinical

phenotype suggestive of an epilepsy syndrome were more likely to have positive results on testing: both patients with Dravet syndrome phenotypes had pathologic variants in SCN1A; three of nine patients with Lennox-Gastaut syndrome had identified variants (one with a CDKL5 variant, one with an SCL9A6 variant, one with both SCN1A and EFHC1 variants). Two (6.9%) patients had diagnostic variants not suspected based on their clinical phenotypes. In eight (27.6%) patients, genetic test results had potential therapeutic implications. However, only one patient had significantly reduced seizure frequency; the patient received stiripentol following a positive SCN1A variant test.

Section Summary: Early-Onset Epilepsy Syndromes and Epileptic Encephalopathies

For early-onset epilepsy syndromes and epileptic encephalopathies, the diagnostic yield is highest for Dravet syndrome (70% to 80%). The yield in epileptic encephalopathies and early infancy onset is between 30% and 60% in the studies reporting in those subsets. There is no direct evidence of the clinical utility of genetic testing. However, a chain of evidence can be constructed to demonstrate the utility of genetic testing for early-onset epilepsy syndromes and epileptic encephalopathies. The differential diagnosis of infants presenting with clinical features of epileptic encephalopathies cannot always be made by phenotype alone, and genetic testing can yield a diagnosis in some cases. Management differs depending on the differential diagnosis so correct diagnosis is expected to improve outcomes.

PRESUMED GENETIC EPILEPSY

Most genetic epilepsy syndromes present in childhood, adolescence, or early adulthood. They include generalized or focal and may be convulsant (grand mal) or absence type. They are generally thought to have a multifactorial genetic component.

The purpose of genetic testing in patients who are presumed to have genetic epilepsy is to determine etiology of the epilepsy syndrome and thereby possibly limit further invasive investigation (e.g., epilepsy surgery), define prognosis, and help guide therapy.

Analytic Validity

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

The literature on clinical validity includes many studies that have reported on the association between various genetic variants and epilepsy. A large number of case-control studies have compared the frequency of genetic variants in patients who have epilepsy with the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of SNVs associated with epilepsy across the entire genome. No studies were identified that reported on the clinical sensitivity and specificity of genetic variants in various clinically defined groups of patients with epilepsy. In addition to these studies on the association of genetic variants with the diagnosis of epilepsy, numerous other studies have evaluated the association between genetic variants and pharmacogenomics of AEDs.

<u>Diagnosis of Epilepsy</u>

McKnight (2022) conducted targeted gene panel testing (range, 89 to 189 genes) using next-generation sequencing in a cohort of 2,008 adults with epilepsy.[65] Diagnosis occurred in 10.9% of patients, and 55.5% of these diagnoses led to changes in clinical management. Diagnostic yield was highest among individuals who first experienced seizure activity during infancy (29.6%) and among females with developmental delay or intellectual disability (19.6%). Patients with treatment-resistant epilepsy had a diagnostic yield of 13.5% and 57.4% of diagnoses led to changes in clinical management. The most common genes associated with a diagnosis were *SCN1A* and *MECP2*. The most common genes associated with changes in clinical management were *SCN1A*, *DEPDC5*, *PRRT2*, *PCDH19*, and *TSC1.* Nondiagnostic and negative genetic findings were common (70.1% and 19.0%, respectively).

Zacher (2021) reported genetic testing results in 150 adult/elderly individuals (age range 18 to 84 years) with neurodevelopmental disorders with epilepsy.[66] Pathogenic or likely pathogenic variants were identified in 71 individuals (47.3%). The yield was 58.3% in individuals with anecdotal evidence of exogenic early-life events (e.g., nuchal cord, complications at delivery) with alleged/unproven association to the disorder. Causative variants were identified by conventional karyotyping in three individuals (2.0%), CMA in 24 individuals (16%), and NGS in 50 individuals. Causative variants were identified using exome sequencing in 13 of the 71 individuals in whom exome sequencing was performed. The most common diagnosis was 15q13.3 microdeletion syndrome (4 of 150 individuals, 2.7%).

Alsubaie (2020) evaluated the diagnostic yield of whole exome sequencing among 420 patients at a single center in Saudi Arabia.[67] Epilepsy was the reason for testing in 15.4% (n=65) patients. Whole exome sequencing confirmed the diagnosis of epilepsy in 14 patients (positive yield of 21.5%) with variants in the following genes: ARID1B, UGDH, KCNQ2, PAH, PARS2, ARHGEF9, CNA2, CASK, SLC23A3, TBCD, QARS, CBL, GABRB2, and SUOX. Genetic test results were inconclusive in 15 of the 65 patients with epilepsy (23%). Thirty patients with negative whole exome sequencing results underwent comparative genomic hybridization, which identified four additional variants (positive yield of 13.3%).

Minardi (2020) published a single-center analysis of 71 adult patients (age range: 21 to 65 years) with developmental and epileptic encephalopathies of unknown etiology who underwent whole exome sequencing.[68] Almost all patients (90.1%) had prior negative genetic tests. The analysis identified 24 variants that were considered pathogenic or likely pathogenic. The variants were: DYNC1, ZBTB20, CACNA1, DYRK1A, ANKRD11, GABRG2, KCNB1, KCNH5, SCN1A, GABRB2, YWHAG, STXBP1, PRODH, LAMB1, PNKP, APC2, RARS2, KIAA2022, and SMC1A. No clinical characteristics were significantly different between patients with pathogenic variants and patients with variants of unknown clinical significance; however, sample sizes were small. In half of the diagnosed cases (n=9), clinical management changed after diagnosis, including medication selection, additional testing, and reproduction-related decisions.

Johannesen (2020) reported the diagnostic yield for genetic testing in a group of 200 adult (age 18 to 80 years) epilepsy patients, 91% of whom were comorbid for intellectual disability.[69] A genetic diagnosis was made in 46 patients (23%). Of those, 48% were found to have a variant in *SCN1A, KCNT1,* or *STXBP1*. Variants were also found in *SLC2A1, ATP6A1V, HNRNPU, MEF2C,* and *IRF2BPL*. Treatment changes based on genetic results were made in 17% of patients with a genetic diagnosis.

Borlot (2019) published a single center retrospective study that reported the diagnostic yield of a commercial epilepsy gene panel in adults with chronic epilepsy and intellectual disability.[70]

Of the 64 patients tested, 14 (22%) were found to have pathogenic or likely pathogenic variants in the following genes: *SCN1A, GABRB3, UBE3A, KANSL1, SLC2A1, KCNQ2, SLC6A1, HNRNPU, STX1B, SCN2A, PURA,* and *CHD2*. The results of genetic testing led to a change in diagnosis in 57% of patients with identified pathogenic or likely pathogenic variants.

Hesse (2018) published a retrospective analysis of 305 patients (age range under one to 69 years old with 88% <18 years old) referred for genetic testing with a targeted epilepsy panel between 2014 and 2016.[71] Positive yield was 15.1%, with pathogenic, likely pathogenic, predicted deleterious mutations identified in 46 individuals. Twenty-nine distinct genes were present, and known pathogenic variants were identified in seven genes (*BRAF, DPYD, GABRG2, PAX6, SCN1A, SLC2A1,* and *SLC46A1*).

Lindy (2018) published an industry sponsored analysis of 8,565 consecutive individuals with epilepsy and/or neurodevelopmental disorders who underwent genetic testing with multigene panels.[72] Positive results were reported in 1,315 patients (15.4%), and, of 22 genes with high positive yield, *SCN1A* (24.8%) and *KCNQ2* (13.2%) accounted for the greatest number of positive findings. Results found 14 distinct genes with recurrent pathogenic or likely pathogenic (P/LP) variants (most commonly in *MECP2, KCNQ2, SCN1A, SCN2A, STXBP1,* and *PRRT2*). Greater than 30% of positive cases had parental testing performed; all variants found in *CDKL5, STXBP1, SCN8A, GABRA1,* and *FOXG1* were de novo, however, 85.7% of variants in *PRRT2* were inherited. No P/LP variants were found in *ATP6AP2*, *CACNB4, CHRNA2, DNAJC5, EFHC1, MAGI2,* and *SRPX2*.

Miao (2018) published an analysis of 141 Chinese patients under 14 years of age with epilepsy who underwent genotype and phenotype analysis using an epilepsy-associated gene panel between 2015 and 2017.[73] Certain diagnoses were obtained in 39 probands (27.7%); these causative variants were related to 21 genes. The most frequently mutated gene was *SCN1A* (5.6%), but others included *KCNQ2, KCNT1, PCDH19, STXBP1, SCN2A, TSC2,* and *PRRT2*. The treatments for 18 patients (12.8%) were altered based on their genetic diagnosis and on genotype-phenotype analysis.

Butler (2017) published a retrospective analysis of epilepsy patients screened using a 110-gene panel between 2013 and 2016; 339 unselected individuals (age range 2.5 months to 74 years, with more than 50% under five years old) were included.[74] Pathogenic and likely pathogenic variants were identified in 62 patients (18%), and another 21 individuals (6%) had potentially causative variants. *SCN1A* (n=15) and *KCNQ2* (n=10) were the frequently identified potentially causative variants. However, other genes in which variants were identified in multiple individuals included *CDKL5, SCN2A, SCN8A, SCN1B, STXBP1, TPP1, PCDH19, CACNA1A, GABRA1, GRIN2A, SLC2A1,* and *TSC2*. The study was limited by the lack of clinical information available for approximately 20% of participants.

Tan and Berkovic (2010) published an overview of genetic association studies using records from Epilepsy Genetic Association Database.[75] Reviewers identified 165 case-control studies published between 1985 and 2008. There were 133 studies that examined the association between 77 different genetic variants and the diagnosis of epilepsy. Approximately half (65/133) focused on patients with genetic generalized epilepsy (GGE). Most studies had relatively small sample sizes, with a median of 104 cases (range, 8 to 1361) and 126 controls (range, 22-1390). There were fewer than 200 case patients in 80% of the studies. Most did not show a statistically significant association. Using a cutoff of p less than 0.01 as the threshold for significance, 35 studies (21.2%) reported a statistically significant association. According to

standard definitions for genetic association, all associations were in the weak-to-moderate range, with no associations considered strong.

In 2014, the International League Against Epilepsy Consortium on Complex Epilepsies published a meta-analysis of GWAS studies for all epilepsy and two epilepsy clinical subtypes, GGE and focal epilepsy.[76] The authors combined GWAS data from 12 cohorts of patients with epilepsy and controls (ethnically matched to cases) from population-based datasets, for a total of 8,696 cases and 26,157 controls. Cases with epilepsy were categorized as having GGE, focal epilepsy, or unclassified epilepsy. For all cases, loci at 2q24.3 (*SCN1A*) and 4p15.1 (*PCDH7*, which encodes a protocadherin molecule) were significantly associated with epilepsy ($p=8.71\times10^{-10}$ and 5.44×10^{-9}, respectively). For those with GGE, a locus at 2p16.1 (*VRK2* or *FANCL*) was significantly associated with epilepsy ($p=9.99\times10^{-9}$). No SNVs were significantly associated with focal epilepsy.

Some of the larger GWAS are described here. The EPICURE Consortium published one of the larger GWAS of GGE in 2012.[77] It included 3020 patients with GGE and 3954 control patients, all of European ancestry. A two-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million SNVs. In the discovery phase, 40 candidate SNVs were identified that exceeded the significance for the screening threshold (1×10^{-5}), although none reached the threshold defined as statistically significant for GWAS (1×10^{-8}). After stage 2 analysis, four SNVs identified had suggestive associations with GGE on genes *SCN1A*, *CHRM3*, *ZEB2*, and *NLE2F1*.

A second GWAS with a relatively large sample size of Chinese patients was also published in 2012.[78] Using a similar two-stage methodology; this study evaluated 1087 patients with epilepsy and 3444 matched controls. Two variants were determined to have the strongest association with epilepsy. One was on the *CAMSAP1L1* gene and the second was on the *GRIK2* gene. There were several other loci on genes suggestive of an association that coded for neurotransmitters or other neuron function.

In addition to the individual studies reporting general genetic associations with epilepsy, a number of meta-analyses have evaluated the association of particular genetic variants with different types of epilepsy. Most have not shown a significant association. For example, Cordoba (2012) evaluated the association between *SLC6A4* gene variants and temporal lobe epilepsy in 991 case patients and 1202 controls and failed to demonstrate a significant association on combined analysis.[79] Nurmohamed (2010) performed a meta-analysis of nine case-control studies that evaluated the association between the *ABC1* gene variants and epilepsy.[80] It included 2454 patients with epilepsy and 1542 control patients. No significant associations were found. One meta-analysis that did report a significant association was published by Kauffman (2008).[81] They evaluated the association between variants in the *IL1B* gene and temporal lobe epilepsy and febrile seizures, using data from 13 studies (1866 patients with epilepsy, 1930 controls). Combined analysis showed a significant relation between one SNV (511T) and temporal lobe epilepsy, with a strength of association considered modest (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.1 to 2.0; p=0.01). Another meta-analysis reporting a positive association was published by Tang (2014).[82] The authors evaluated the association between the *SCN1A* IVS5N+5GNA variant and susceptibility to epilepsy with febrile seizures. The analysis included six studies with 2719 cases and 2317 controls. There was a significant association between *SCN1A* variant and epilepsy with febrile seizures (A vs G: OR=1.5; 95% CI 1.1 to 2.0).

Prognosis of Epilepsy

A smaller body of literature has evaluated whether specific genetic variants are associated epilepsy phenotypes or prognosis. Van Podewils (2015) evaluated the association between sequence variants in *EFHC1* and phenotypes and outcomes in 38 probands with juvenile myoclonic epilepsy, along with three family members.[83] Several *EFHC1* gene variants, including *F229L*, *R294H*, and *R182H*, were associated with earlier onset of generalized tonic-clonic seizures (66.7% vs 12.5%, OR=13, p=0.022), high risk of status epilepticus (p=0.001), and decreased risk of bilateral myoclonic seizures (p=0.05).

Pharmacogenomics of Antiepileptic Medications

Pharmacogenomic of AED Response

Lin (2021) conducted a prospective study of 96 children less than two years of age with epilepsy and neurodevelopmental disability.[84] A genetic cause of epilepsy was present in 28 children, while the remaining 68 children did not have an identified genetic cause. The incidence of drug-resistant epilepsy was 42.8% in patients with a genetic cause and 13.2% in patients without a genetic cause. Risk of drug-resistant epilepsy was significantly higher in the genetic group compared to the non-genetic group (adjusted OR 6.50, 95% CI 2.15 to 19.6, p=0.03). Specific genes associated with drug-resistant epilepsy included *TBC1D24*, *SCN1A*, *PIGA*, *PPP1CB*, and *SZT2*.

Numerous case-control studies have reported on the association between various genetic variants and response to medications in patients with epilepsy. The Epilepsy Genetic Association Database identified 32 case-control studies of 20 different genes and their association with medication treatment.[75] The most common comparison was between responders to medication and nonresponders. Some of the larger representative studies are discussed next.

Li (2015) conducted a meta-analysis of 28 articles reporting on 30 case-control studies to evaluate the association between the *ABCB1* gene C3435T variant and AED resistance.[85] The included studies had a total of 4124 drug-resistant epileptic patients and 4480 control epileptic patients for whom drug treatment was effective. In a pooled random-effects model, the 3435C allele was not significantly associated with drug resistance, with a pooled odds ratio of 1.07 in an allele model (95% CI 0.95 to 1.19; p=0.26) and 1.05 in a genotype model (95% CI 0.89 to 1.24; p=0.55).

Kwan (2008) compared the frequency of SNVs on the *SCN1A*, *SCN2A*, and *SCN3A* genes in 272 drug-responsive patients and 199 drug-resistant patients.[86] Twenty-seven candidate SNVs were evaluated, selected from a large database of previously identified SNVs. One SNV identified on the *SCN2A* gene (rs2304016) had a significant association with drug resistance (OR=2.1; 95% CI 1.2 to 3.7; p<0.007).

Jang (2009) compared the frequency of variants on the *SCN1A*, *SCN1B*, and *SCN2B* genes in 200 patients with drug-resistant epilepsy and 200 patients with drug-responsive epilepsy.[87] None of the individual variants tested showed a significant relation with drug resistance. In a further analysis for gene-gene interactions associated with drug resistance, the authors reported a possible interaction of two variants, one on the *SCN2A* gene and the other on the *SCN1B* gene, though falling below their cutoff for statistical significance (p=0.055).

Other representative studies that have reported associations between genetic variants and AED response are summarized in Table 7.

Table 7: Genetic Variants and Antiepileptic Drug Response

Study	Population	Genes	Overview of Findings
Feria-Romero[88]	55 children: 32 with controlled epilepsy and 23 with drug-resistant epilepsy	• *SCN1A* • *CYP2C9* • *CYP2C19* • *CYP2D6* • *CYP3A4* • *CYP2B6*	Polymorphisms significantly associated with drug-resistant epilepsy (p=0.021): • *SCN1A*: T1025C (rs10497275), C2177A (rs10198801), and G32431A/C/T, G32432A, G32433A (rs67636132) • *CYP2D6*: C100T (rs1065852) • *CYP3A4*: C313T (rs2242480) • Number of missense variants significantly higher in drug-resistant epilepsy (p=0.014)
Song (2020)[89]	83 adults with epilepsy in China receiving sustained-release valproic acid monotherapy	CYP2C19	• Valproic acid concentration to dose ratios were significantly lower in EMs (3.33±1.78) compared to IMs (4.45±1.42) and PMs (6.64±1.06) • Valproic acid concentrations were significantly correlated with CYP2C19*2 and CYP2C19*3, but the CYP2C9*13 allele was not
Zhao (2020)[90]	245 children with epilepsy in China receiving levetiracetam alone or in combination with other medications (classified as drug-resistant [n=117] or drug-responsive [n=128])	*ABCB1* (C1236T, G2677T/A, and C3435T variants)	• Significantly higher levetiracetam concentrations were observed in patients with the following: 2677 genotypes GT, TT, GA, and AT compared to GG carriers (p=0.021), and 3435-TT compared to CC and CT carriers (both p<0.005) • No significant difference in variants among drug-resistant and drug-responsive patients
Lu (2017)[91]	124 epileptic Chinese patients receiving OXC monotherapy	• *UGT1A4* 142T>G (rs2011425) • *UGT1A6* 19T>G (rs6759892) • *UGT1A9* 1399C>T (rs2741049) • *UGT2B15* 253T>G (rs1902023)	• *UGT1A9* variant allele 1399C>T had significantly lower monohydroxylated derivative plasma concentrations (TT 13.28 mg/L, TC 16.41 mg/L vs CC 22.24 mg/L, p<0.05) and poorer seizure control than noncarriers (p=0.01)
Hashi (2015)[92]	50 epileptic adults treated with stable clobazam dose	*CYP2C19*	• Clobazam metabolite N-desmethylclobazam serum concentration:dose ratio was higher in PMs (median, 16,300 [ng/mL]/[mg/kg/d]) than in EMs (median, 1760 [ng/mL]/[mg/kg/d]) or IMs (median, 4640 [ng/mL]/[mg/kg/d]) • Patients with EM or IM status had no change in seizure frequency with clobazam therapy
Ma (2015)[93]	184 epileptic patients receiving OXC monotherapy and 156 healthy volunteers	• *SCN1A* c.3184A>G (rs2298771) • *SCN2A* c.56G>A (rs17183814) • *SCN2A* IVS7-32A>G (rs2304016) • *ABCC2* 3972C>T (rs3740066) • *ABCC2* c.1249G>A (rs2273697) • *UGT2B7* c.802T>C (rs7439366)	• *SCN1A* IVS5-91G>A, *UGT2B7* c.802T>C, and *ABCC2* c.1249G>A variants showed significant associations with oxcarbazepine maintenance doses • Patients with the *ABCC2* c.1249G>A allele variant more likely to require higher oxcarbazepine maintenance doses than noncarriers (p=0.002,

Study	Population	Genes	Overview of Findings
			uncorrected), which remained significant after Bonferroni correction
Guo (2015)[94]	483 Chinese patients with genetic generalized epilepsies	• *KCNJ10*	• Frequency of rs12402969 C allele and the CC+CT genotypes were higher in the drug-responsive patients than that in the drug-resistant patients (9.3% vs 5.6%, OR=1.7, 95% CI 1.1 to 2.9, p=0.026)
Ma (2014)[95]	453 epileptic patients, classified as drug-responsive (n=207) or drug-resistant (n=246)	• *SCN1A* c.3184A>G (rs2298771) • *SCN2A* c.56G>A (rs17183814) • *SCN2A* IVS7-32A>G (rs2304016) • *ABCC2* 3972C>T (rs3740066) • *ABCC2* c.1249G>A (rs2273697)	• *SCN1A* IVS5-91G>A AA genotype more prevalent in drug-resistant than drug-responsive patients receiving multidrug therapy (OR=3.41; 95% CI 1.73 to 6.70; p<0.001, uncorrected) • *SCN1A* IVS5-91G>A AA more prevalent in drug-resistant than drug-responsive patients receiving carbamazepine/OXC (OR=3.55; 95% CI 1.62 to 7.78; p=0.002, uncorrected) • *ABCC2* c.1249G>A GA genotype and allele A significantly associated with drug response (OR=2.14; 95% CI 1.23 to 3.71; p=0.007; OR=2.05; 95% CI 1.31 to 3.19; p=0.001, respectively, uncorrected)
Radisch (2014)[96]	229 epileptic patients treated with carbamazepine monotherapy	*ABCC2:* variant rs717620 (-24G4A), rs2273697 (c.1249G4A) and rs3740067	• *ABCC2* variants not associated with time to first seizure or time to 12-mo remission
Yun (2013)[97]	38 epileptic patients treated with carbamazepine monotherapy	• *EPHX1* c.337T>C • *EPHX1* c.416A>G • *SCN1A* IVS5-91G>A • *CYP3A4*1G*	• Patients *EPHX1* c.416A>G genotypes had higher adjusted plasma carbamazepine concentrations vs those with wild-type genotype (p<0.05) • Other studied variants not associated with carbamazepine pharmaco-resistance
Taur (2014)[98]	115 epileptic patients treated with phenytoin, phenobarbital, and/or carbamazepine	• *ABCB1* (c.3435T) • *CYP2C9* (416C>T) • *CYP2C9* (1061A>T) • *CYP2C19* (681G>A) • *CYP2C19* (636G>A)	• *ABCB1* C3435T genotype and allele variants significantly associated with drug response (OR=4.5; 95% CI 1.04 to 20.99; OR=1.73; 95% CI 1.02 to 2.95, respectively)

CI: confidence interval; EM: extensive metabolizer; IM: intermediate metabolizer; OR: odds ratio; OXC: oxcarbazepine; PM: poor metabolizer.

Several meta-analyses evaluating pharmacogenomics were identified. Haerian (2010) examined the association between SNVs on the *ABCB1* gene and drug resistance in 3231 drug-resistant patients and 3524 controls from 22 studies.[99] Reviewers reported no significant relation between variants of this gene and drug resistance (combined OR=1.06; 95% CI 0.98 to 1.14; p=0.12). There was also no significant association for subgroup analysis by ethnicity.

In a separate meta-analysis, Sun (2014) evaluated eight studies evaluating the association between variants in the multidrug resistance 1 (*MDR1*) gene and childhood medication-refractory epilepsy, including 634 drug-resistant patients, 615 drug-responsive patients, and 1052 healthy controls.[100] In the pooled analysis, the *MDR1* C3435T variant was not significantly associated with risk of drug resistance.

Shazadi (2014) assessed the validity of a gene classifier panel consisting of five SNVs for predicting initial AED response and overall seizure control in two cohorts of patients with newly diagnosed epilepsy.[101] A cohort of 115 Australian patients with newly diagnosed epilepsy was used to develop the classifier from a sample of 4041 SNVs in 279 candidate genes via a *k*-nearest neighbor machine learning algorithm, resulting in a 5-SNV classifier. The classifier was validated in two separate cohorts. One cohort included 285 newly diagnosed patients in Glasgow, of whom a large proportion had participated in randomized trials of AED monotherapy. Drug-response phenotypes in this cohort were identified by retrospectively reviewing prospectively collected clinical trial and/or hospital notes. The second cohort was drawn from patients who had participated in the Standard and New Epileptic Drugs (SANAD) trial, a multicenter RCT comparing standard with newer AEDs. The trial included 2400 patients, of whom 520 of self-described European ancestry who provided DNA samples were used in the present analysis. The *k*-nearest neighbor machine model derived from the original Australian cohort did not predict treatment response in either the Glasgow or the SANAD cohorts. Investigators redeveloped a *k*-nearest neighbor machine learning algorithm based on SNV genotypes and drug responses in a training dataset (n=343) derived from the SANAD cohort. None of the five SNVs used in the multigenic classifier was independently associated with AED response in the Glasgow or the SANAD cohort after correction for multiple tests. When applied to a test dataset (n=148) derived from the SANAD cohort, the classifier correctly identified 26 responders and 52 nonresponders but incorrectly identified 26 nonresponders as responders (false positives) and 44 responders as nonresponders (false negatives), corresponding to a positive predictive value of 50% (95% CI 32.8% to 67.2%) and a negative predictive value of 54% (95% CI 41.1% to 66.7%). In a cross-validation analysis, the 5-SNV classifier was significantly predictive of treatment responses among Glasgow cohort patients initially prescribed either carbamazepine or valproate (positive predictive value, 67%; negative predictive value, 60%; corrected p=0.018), but not among those prescribed lamotrigine (corrected p=1.0) or other AEDs (corrected p=1.0). The 5-SNV classifier was significantly predictive of treatment responses among SANAD cohort patients initially prescribed carbamazepine or valproate (positive predictive value, 69%; negative predictive value, 56%; corrected p=0.048), but not among those prescribed lamotrigine (corrected p=0.36) or other AEDs (corrected p=0.36).

Pharmacogenomics of AED Adverse Events

Many AEDs have a relatively narrow therapeutic index, with the potential for dose-dependent or idiosyncratic adverse events. Several studies have evaluated genetic predictors of adverse events from AEDs, particularly severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Chung (2014) evaluated genetic variants associated with phenytoin-induced severe cutaneous adverse events (SJS/TEN, drug reactions with eosinophilia and systemic symptoms) and maculopapular exanthema.[102] This GWAS included 60 cases with phenytoin-related severe cutaneous adverse events and 412 population controls, and was followed by a case-control study of 105 cases with phenytoin-related severe cutaneous adverse events (61 with SJS/TEN, 44 with drug reactions with eosinophilia and systemic symptoms), 78 cases with maculopapular exanthema, 130 phenytoin-tolerant control participants, and 3655 population controls from Taiwan, Japan, and Malaysia. In the GWAS analysis, a missense variant of *CYP2C9*3* (rs1057910) was significantly associated with phenytoin-related severe cutaneous adverse events (OR=12; 95% CI 6.6 to 20; $p=1.1\times10^{-17}$). In a case-control comparison between the subgroups of 168 patients with phenytoin-related cutaneous adverse events and

130 phenytoin-tolerant controls, *CYP2C9*3* variants were significantly associated with SJS/TEN (OR=30; 95% CI 8.4 to 109; $p=1.2\times10^{-19}$), drug reactions with eosinophilia and systemic symptoms (OR=19; 95% CI 5.1 to 71; $p=7.0\times10^{-7}$), and maculopapular exanthema (OR=5.5; 95% CI 1.5 to 21; p=0.01).

He (2014) conducted a case-control study to evaluate the association between carbamazepine-induced SJS/TEN and 10 SNVs in the *ABCB1*, *CYP3A4*, *EPHX1*, *FAS*, *SNC1A*, *MICA*, and *BAG6* genes.[103] The study included 28 cases with carbamazepine-induced SJS/TEN and 200 carbamazepine-tolerant controls. The authors reported statistically significant differences in the allelic and genotypic frequencies of *EPHX1* c.337T>C variants between patients with carbamazepine-induced SJS/TEN and carbamazepine-tolerant controls (p=0.011 and p=0.007, respectively). There were no significant differences between SJS/TEN cases and carbamazepine-tolerant controls for the remaining SNVs evaluated.

Wang (2014) evaluated the association between *HLA* genes and cross-reactivity of cutaneous adverse drug reactions to aromatic AEDs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital).[104] The study included 60 patients with a history of aromatic AED-induced cutaneous adverse drug reactions, including SJS/TEN and maculopapular eruption, who were reexposed to an aromatic AED, 10 of whom had a recurrence of the cutaneous adverse drug reaction on re-exposure (cross-reactive group). Subjects tolerant to re-exposure were more likely to carry the *HLA-A**2402 allele than cross-reactive subjects (OR=0.13; 95% CI 0.015 to 1.108; p=0.040). Frequency distributions for testing other *HLA* genes did not differ significantly between groups.

Prediction of Sudden Unexplained Death in Epilepsy

Sudden unexplained death in epilepsy (SUDEP) is defined as a sudden, unexpected, nontraumatic, and nondrowning death in patients with epilepsy, excluding documented status epilepticus, with no cause of death identified following comprehensive postmortem evaluation. It is the most common cause of epilepsy-related premature death, accounting for 15% to 20% of deaths in patients with epilepsy.[105] Given uncertainty related to the underlying causes of SUDEP, there has been interested in identifying genetic associations with SUDEP.

Bagnall (2014) evaluated the prevalence of sequence variations in the *PHOX2B* gene in 68 patients with SUDEP.[105] Large polyalanine repeat expansions in the *PHOX2B* gene are associated with congenital central hypoventilation syndrome, a potentially lethal autonomic dysfunction syndrome, but smaller *PHOX2B* expansions may be associated with nocturnal hypoventilation. In a cohort of patients with SUDEP, one patient was found to have a 15-nucleotide deletion in the *PHOX2B* gene, but no *PHOX2B* polyalanine repeat expansions were found.

Coll (2016) evaluated the use of a custom resequencing panel including genes related to sudden death, epilepsy, and SUDEP in a cohort of 14 patients with focal or generalized epilepsy and a personal or family history of SUDEP, including two postmortem cases.[106] In four cases, rare variants were detected with complete segregation in the *SCN1A*, *FBN1*, *HCN1*, *SCN4A*, and *EFHC1* genes, and in one case a rare variant in *KCNQ1* with an incomplete pattern of inheritance was detected. New potential candidate genes for SUDEP were detected: *FBN1*, *HCN1*, *SCN4A*, *EFHC1*, *CACNA1A*, *SCN11A*, and *SCN10A*.

Bagnall (2016) performed an exome-based analysis of rare variants related to cardiac arrhythmia, respiratory control, and epilepsy to search for genetic risk factors in 61 SUDEP

cases compared with 2936 controls.[107] Mean epilepsy onset of the SUDEP cases was 10 years and mean age at death was 28 years. De novo variants, previously reported pathogenic variants, or candidate pathogenic variants were identified in 28 (46%) of 61 SUDEP cases. Four (7%) SUDEP cases had variants in common genes responsible for long QT syndrome and a further nine (15%) cases had candidate pathogenic variants in dominant cardiac arrhythmia genes. Fifteen (25%) cases had variants or candidate pathogenic variants in epilepsy genes; six cases had a variant in *DEPDC5*. *DEPDC5* (p=0.00015) and *KCNH2* (p=0.0037) were highly associated with SUDEP. However, using a rare variant collapsing analysis, no gene reached criteria for genome-wide significance.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There is a lack of evidence on the clinical utility of genetic testing for the genetic epilepsies. Association studies are insufficient evidence to determine whether genetic testing can improve the clinical diagnosis of GGE. There are no studies reporting the accuracy regarding sensitivity, specificity, or predictive value; therefore, it is not possible to determine the impact of genetic testing on diagnostic decision making.

The evidence on pharmacogenomics has suggested that genetic factors may play a role in the pharmacokinetics of antiepileptic medications. However, how genetic information might be used to tailor medication management in ways that will improve efficacy, reduce adverse events, or increase the efficiency of medication trials is not yet well-defined.

Section Summary: Presumed Genetic Epilepsy

The evidence on genetic testing for genetic epilepsies is characterized by a large number of studies that have evaluated associations between many different genetic variants and the various categories of epilepsy. The evidence on the clinical validity of testing for the diagnosis of epilepsy is not consistent in showing an association between any specific genetic variant and any specific type of epilepsy. Where associations have been reported, they are not of strong magnitude and, in most cases, have not been replicated independently or through the available meta-analyses. Because of the lack of established clinical validity, the clinical utility of genetic testing for the diagnosis of genetic epilepsies is also lacking. Several studies have reported associations between a number of genes and response to AEDs or AED adverse events. How this information should be used to tailor medication management is not yet well-defined, and no studies were identified that provide evidence for clinical utility.

SUMMARY OF EVIDENCE

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test accuracy and validity, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for *SCN1A* disease-associated variants is high (≈80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing are not well-defined. However, studies reporting on the overall testing yield in populations with epileptic encephalopathies and early-onset epilepsy

have reported detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have presumed genetic epilepsy who receive testing for genetic variants associated with genetic epilepsies, the evidence includes prospective and retrospective cohort studies describing testing yields. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For most genetic epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic variants and the risk of epilepsy is uncertain. Despite a large body of literature on associations between genetic variants and epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic variants and AED treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy. The largest number of these studies is related to AED pharmacogenomics, which has generally reported some association between variants in a number of genes (including *SCN1A*, *SCN2A*, *ABCC2*, *EPHX1*, *CYP2C9*, *CYP2C19*) and AED response. Similarly, genetic associations between a number of genes and AED-related adverse events have been reported. However, no empirical evidence on the clinical utility of testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY AND CHILD NEUROLOGY SOCIETY

The American Academy of Neurology and Child Neurology Society published joint guidelines on the diagnostic assessment of children with status epilepticus.[108] These guidelines were reviewed and reaffirmed in 2016. With regard to whether genetic testing should be routinely ordered for children with status epilepticus, the guidelines stated: “There is insufficient evidence to support or refute whether such studies should be done routinely.”

INTERNATIONAL LEAGUE AGAINST EPILEPSY

In 2015, the International League Against Epilepsy issued a report with recommendations on the management of infantile seizures, which included the following related to genetic testing in epilepsy[59]:

- “Genetic screening should not be undertaken at a primary or secondary level of care, as the screening to identify those in need of specific genetic analysis is based on tertiary settings.”
- “Standard care should permit genetic counseling by trained personnel to be undertaken at all levels of care (primary to quaternary).”
- “Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation).”

- "Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown."

SUMMARY

DIAGNOSIS

Research shows that for patients with infantile- or early-childhood-onset epilepsy genetic testing can aid with diagnosis. For Dravet syndrome, genetic testing for *SCN1A* can identify about 80% of patients. For other early-onset epilepsies, studies report detection rates ranging from 7.5% to 57%. A positive test result may lead to targeted medication management and avoidance of other diagnostic tests. Overall, genetic testing for epilepsy syndromes can improve health outcomes for these patients and therefore may be considered medically necessary when criteria are met.

For patients who do not have severe seizures affecting daily functioning and/or interictal EEG abnormalities, and for patients that have not had EEG and neuroimaging (CT or MRI), or when another clinical syndrome has been identified that would explain a patient's symptoms, genetic testing is unlikely to be informative. Clinical guidelines based on evidence do not recommend genetic testing in these situations. Therefore, this testing is considered not medically necessary.

While some adult-onset epilepsies may have a genetic component, there is not enough research to show that genetic testing can improve health outcomes for these patients. Evidence linking genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy is limited. In addition, clinical practice guidelines do not recommend genetic testing for adult-onset epilepsies. Therefore, this testing is considered investigational.

REPRODUCTIVE CARRIER TESTING

There is enough research to show that reproductive carrier testing for patients that are at increased risk of being asymptomatic carriers of genetic epilepsy syndromes can help to inform reproductive decision-making. Therefore, testing in these individuals may be considered medically necessary.

There is enough research to show that targeted reproductive carrier testing for genetic epilepsy syndromes is unlikely to improve health outcomes and inform reproductive decision-making in individuals that are not at increased risk of being carriers of the disorder. Therefore, reproductive carrier testing for genetic epilepsy syndromes is considered not medically necessary when individuals do not have an affected first- or second-degree relative and the reproductive partner is not known to be a carrier.

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107. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Annals of neurology.* 2016;79(4):522-34. PMID: 26704558
108. Riviello JJ, Jr., Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2006;67(9):1542-50. PMID: 17101884

CODES

Codes	Number	Description
CPT	0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81189	;full gene sequence
	81190	;known familial variant(s)
	81401	Molecular pathology procedure, Level 2
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *October 2018*

Regence

Medical Policy Manual Genetic Testing, Policy No. 81

Reproductive Carrier Screening for Genetic Diseases

Effective: January 1, 2025

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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 purpose of reproductive carrier screening is to identify asymptomatic individuals who are heterozygous for serious or lethal single-gene disorders, in order to evaluate the risk of conceiving an affected child and inform reproductive decisions.

MEDICAL POLICY CRITERIA

Notes:

- This policy is not intended to address preimplantation genetic testing, prenatal fetal testing, or diagnostic genetic testing (see Cross References section).
- This policy applies only if there is not a separate Medical Policy that outlines specific criteria for carrier testing. If a separate policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy (see Cross References section).
- Carrier screening with the UNITY Screen™ (BillionToOne) is reviewed in Genetic Testing, Policy No 44 (see Cross References section) due to the reflex single-gene non-invasive prenatal testing of the fetus.

I. Reproductive carrier screening for the following genes in adults, either as individual genes or in a panel test (see Policy Guidelines 2 section), may be considered **medically necessary**:

A. *ABCC8* for familial hyperinsulinism

B. *ACADM* for medium-chain acyl-CoA-dehydrogenase deficiency

C. *ASPA* for Canavan disease

D. *BCKDHA*, *BCKDHB* for maple syrup urine disease

E. *BLM* for Bloom syndrome

F. *CFTR* for cystic fibrosis

G. *DHCR7* for Smith-Lemli-Opitz syndrome

H. *DMD* for Duchenne and Becker muscular dystrophies

I. *ELP1* (also known as *IKAP*, *IKBKAP*, *TOT1*) for familial dysautonomia/Riley-Day syndrome

J. *FANCC* for Fanconi anemia group C

K. *FMR1* for fragile X syndrome

L. *G6PC* for glycogen storage disease type 1A

M. *GALT* for galactosemia

N. *GBA* for Gaucher disease

O. *HBA* for α-thalassemia

P. *HBB* for β-thalassemia, sickle cell anemia

Q. *HEXA* for Tay-Sachs disease

R. *MCOLN1* for mucolipidosis IV

S. *PAH* for phenylketonuria

T. *SMN1*, *SMN2* for spinal muscle atrophy

U. *SMPD1* for Niemann-Pick disease type A

V. *TMEM216* for Joubert syndrome 2

II. Risk-based reproductive genetic carrier testing (see Policy Guidelines 1 section) for other specific autosomal recessive or X-linked diseases may be considered **medically necessary** for adults when all of the following criteria (A and B) are met for all included genes and conditions (see Criterion IV. for larger panels):

A. There is an increased risk for affected offspring, due to any of the following:

1. One or both reproductive partners have a first- or second-degree relative who is affected (see Policy Guidelines 3 section); OR
2. Reproductive partner is known to be a carrier; OR
3. One or both reproductive partners are members of a population known to have a carrier rate that exceeds 1/200 for recessive disorder(s) or a disease

prevalence that exceeds 1/40,000 for X-linked disorders (see Policy Guidelines 3 section).

B. All of the following criteria are met:

1. The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity;
2. Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;
3. An association of the marker with the disorder has been established and the genetic test has adequate clinical validity to guide clinical decision making.

III. Risk-based reproductive genetic carrier screening for specific autosomal recessive or X-linked diseases that does not meet any of the above criteria is considered **not medically necessary,** including screening of children.

IV. Non-risk-based carrier screening panels for X-linked and autosomal recessive disorders (not based on ethnic or familial/partner risk) may be considered **medically necessary** when all of the following criteria are met for all included genes and conditions (see Policy Guidelines 2 section):

A. The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity; and

B. Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing; and

C. An association of the marker with the disorder has been established and the genetic test has adequate clinical validity to guide clinical decision making; and

D. The carrier rate is estimated to exceed 1/200 for recessive disorders or the disease prevalence is estimated to exceed 1/40,000 for X-linked disorders (see Policy Guidelines 3 section).

V. Non-risk-based carrier screening panels that do not meet Criterion IV are considered **investigational**.

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

POLICY GUIDELINES

POLICY GUIDELINES 1

Risk-based carrier screening refers to screening an individual specifically for disorders for which their offspring are known to be at increased risk compared to the general population. This increased risk may be due to ethnic background, family or personal history of a disorder, or a reproductive partner who is known to be a carrier.

Non-risk-based carrier screening refers to carrier screening that is performed in the absence of any specific increased risk. This is the most commonly requested type of screening.

POLICY GUIDELINES 2

Examples of panel tests that may be medically necessary according to Criterion I. (if all genes are listed in Criterion I.) or Criterion IV. include, but are not limited to, the following tests:

- Ashkenazi Jewish Diseases, 16 Genes (ARUP)
- Beacon ACOG/ACMG Female Carrier Screening Panel (Fulgent)
- Beacon Focus Panel (Fulgent)
- Horizon 4 and 14 Panels
- Inheritest® CF/SMA Panel (Labcorp, Integrated Genetics)
- Inheritest® Core Panel (Labcorp, Integrated Genetics)
- Inheritest® Carrier Screen, Society-guided Panel (Labcorp, Integrated Genetics)
- Invitae Core Carrier Screen (Invitae)
- Foresight® Fundamental and Fundamental Plus Panels (Myriad)
- Prenatal Carrier Panel (CFvantage, Fragile X, SMA) (Quest Diagnostics)
- QHerit™ 24-gene carrier panel (Quest Diagnostics)

POLICY GUIDELINES 3

- First-degree relatives include a biological parent, brother, sister, or child
- Second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.

If there is no family history of, or other form of increased risk for a disease, such as ethnicity, carrier screening is not recommended when the carrier rate is less than 1% in the general population, according to the American College of Obstetrics and Gynecology. Disorders with carrier rates in the general population that exceed 1% include, but are not limited to, cystic fibrosis (*CFTR* gene) and spinal muscular atrophy (*SMN1* gene). The American College of Medical Genetics and Genomics (ACMG) has recommended testing for recessive disorders with an estimated carrier frequency of 1/200 and X-linked disorders with a prevalence of at least 1/40,000 (see Tables in the ACMG Practice Resource).

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
   - o History and physical exam
   - o Conventional testing and outcomes

- Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic Testing for Alzheimer's Disease, Genetic Testing, Policy No. 01
2. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. Genetic Testing for FMR1 and AFF2 Variants (Including Fragile X and Fragile XE Syndromes), Genetic Testing, Policy No. 43
5. Noninvasive Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA, Genetic Testing, Policy No 44
6. Genetic Testing for α-Thalassemia, Genetic Testing, Policy No. 52
7. Genetic Testing for Primary Mitochondrial Disorders, Genetic Testing, Policy No. 54
8. Chromosomal Microarray Analysis (CMA) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder or Congenital Anomalies, Genetic Testing, Policy No. 58
9. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
10. Genetic Testing for Rett Syndrome, Genetic Testing, Policy No. 68
11. Genetic Testing for Duchenne and Becker Muscular Dystrophy, Genetic Testing, Policy No. 69
12. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
13. Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss, Genetic Testing, Policy No. 79
14. Maternal Serum Analysis for Risk of Preterm Birth, Laboratory, Policy No. 75

BACKGROUND

There are more than 1,300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children.[1] Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in childhood. See Appendix I for a glossary of terms related to carrier screening.

CARRIER SCREENING

Carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child "to provide … information to optimize pregnancy outcomes based on … personal preferences and values."[2] Risk-based carrier screening is performed in individuals having an increased risk based on population carrier prevalence, and personal or family history. Conditions selected for screening can be based on ethnicities at high risk (e.g., Tay-Sachs disease in Ashkenazi Jews) or may be pan-ethnic (e.g., screening for cystic fibrosis carriers). Ethnicity-based screening for some conditions has been offered for decades and, in some cases, has reduced the prevalence of diseases. For example, a 90% reduction in Tay-Sachs disease followed introduction carrier screening in the 1970s in the United States and Canada.[3] In addition, the U.S. population has become increasingly ethnically intermarried[4, 5]—a phenomenon the American College of Obstetricians and Gynecologists (ACOG) noted when offering a recommendation in 2005 for pan-ethnic cystic fibrosis carrier screening.[6]

While methods for carrier screening of conditions individually may have been onerous in the past, contemporary molecular techniques including next-generation sequencing allow simultaneously identifying carriers of a wide range of disorders efficiently and inexpensively.

CARRIER SCREENING PANELS

Non-targeted carrier panels may be used to screen individuals or couples for disorders and range in size from two to hundreds of genes. The disorders included many large screening panels may also span a range of disease severity or phenotype. Arguments for carrier screening using large panels include potential issues in assessing ethnicity, ability to identify more potential conditions, efficiency, and cost. However, there are possible downsides of screening individuals at low risk, including a potential for incorrect variant ascertainment and the consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (e.g., due to variable expressivity and uncertain penetrance). The list of conditions included in carrier screening panels is not standardized. Although these panels generally include conditions assessed in risk-based screening, they often include many conditions that not routinely evaluated and for which there are no existing professional guidelines.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

A number of commercially available genetic tests exist for carrier screening. They range from testing for individual diseases, to small panels designed to address testing based on ethnicity as recommended by practice guidelines (American College of Obstetricians and Gynecologists, American College of Medical Genetics and Genomics), to large panels that test for numerous diseases.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

RISK-BASED CARRIER SCREENING

The purpose of carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child and to inform reproductive decisions.

Risk-based carrier screening is typically based on disease and carrier risk determined by family history, ethnicity, and race. Screening is recommended when carrier rates in a population approach or exceed those judged to offer clinical utility.

This evidence review applies only if there is no separate evidence review that outlines specific criteria for carrier screening. If a separate evidence review exists, then criteria for medical necessity in that evidence review supersede the evidence herein.

Clinical Validity

The clinical validity of a carrier screening test is evaluated by its ability to predict carrier status. Clinical validity is influenced by carrier prevalence, penetrance, expressivity, and environmental factors.[1] Different variants in the same gene can result in different phenotypes (allelic heterogeneity) in most genetic disorders and impact clinical validity. The clinical sensitivity and predictive value of different assay methods (e.g., next-generation sequencing [NGS], microarray) vary depending on the proportion of known pathogenic variants evaluated. For example, clinical sensitivities for disorders in the previously mentioned Jewish panel ranged from 90% to 99% for all but Usher syndrome type 1F (62%). Clinical sensitivity will also vary according to the number of known variants tested. Additionally, not all testing strategies rely solely on genetic testing—for example, biochemical testing for hexosaminidase A may be the initial test to screen for Tay-Sachs carrier status. Finally, following a negative carrier screening test, the estimated residual risk of being a carrier reflects both the pretest probability, that is, the estimated carrier prevalence in the population, and the sensitivity and specificity of the test. Consequently, limitations in clinical validity are quantified in residual risk estimates.

Clinical Utility

The clinical utility of carrier screening is defined by the extent to which reproductive decision making or choices are informed, increasing “reproductive autonomy and choice”[1]. Evidence to support the clinical utility carrier screening for conditions with the highest carrier rates e.g., Tay-Sachs disease, CF) among specific ethnic groups is robust concerning the effect on reproductive decision making.[3, 8-10] For example, early studies of Tay-Sachs carrier screening in Ashkenazi Jews demonstrated a marked impact on reproductive decisions[8, 10] and, after more than four decades of ethnicity-based carrier screening, most Tay-Sachs disease cases occur in non-Jewish individuals.[9] As another example, a 2014 systematic review of CF carrier screening found that while individual carrier status “did not affect reproductive intentions or behaviors,” most couple carriers terminated affected fetuses.[11] Similarly, a 2023 systematic review that included studies of both targeted and non-targeted carrier screening found that carriers of conditions classified as having a more severe impact were more likely to terminate pregnancy or opt for in vitro fertilization with preimplantation genetic testing.[12]

A 2023 Canadian Health Technology Assessment reviewed 107 studies on carrier screening programs for cystic fibrosis, fragile X syndrome, hemoglobinopathies, thalassemia, and spinal muscular atrophy in individuals considering or already pregnant.[13] The findings indicated that carrier screening likely influences reproductive decisions (GRADE: Moderate) and may reduce anxiety in pregnant individuals, though evidence was uncertain (GRADE: Very low). The main reproductive decision reported was whether at-risk couples opted for prenatal diagnostic testing to confirm if pregnancy was affected. Most individuals with confirmed affected pregnancies chose termination. For future pregnancies, some individuals opted for natural conception with potential termination, while others chose in vitro fertilization with preimplantation genetic testing. With regards to preconception carrier screening, few studies assessed plans for in vitro fertilization, prenatal testing, adoption, or pregnancy avoidance.

CARRIER SCREENING PANEL TESTING

The purpose of carrier screening panel testing in asymptomatic individuals is to identify those who are heterozygous for any of a large number of serious or lethal single-gene disorders, with the purpose of evaluating the risk of conceiving an affected child and to inform reproductive decisions.

Clinical Validity

For conditions where pathogenic variants would be included in a risk-based genotyping carrier test, clinical validity should be similar or approach that of the targeted test. Outside those defined variants (or when genotyping includes only others with strong evidence supporting pathogenicity), for the purposes of carrier screening pathogenicity, penetrance, and expressivity together with disease severity require accurate definition. Subsumed in clinical validity is the effect of a condition's severity on quality of life, impairments, and the need for intervention.

The ACOG (2017) Committee Opinion No. 690 included the following related to large carrier screening panels, also known as expanded carrier screening:[17]

"Expanded carrier screening does not replace previous risk-based screening recommendations."

Based on consensus, characteristics of included disorders should meet the following criteria:

- Carrier frequency ≥1/100
- Well-defined phenotype
- Detrimental effect on the quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life
- Not be primarily associated with a disease of adult-onset

The ACOG opinion provided a detailed example of a panel that includes testing for 22 conditions that meet these criteria: α-thalassemia, β-thalassemia, Bloom syndrome, Canavan disease, CF, familial dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

Many of the genes included in large carrier screening panels do not meet the prevalence criterion in all ethnic groups.[18] However, self-reports of ethnicity may not be consistent with genetic ancestry in substantial proportion of individuals, particularly in countries with intermixed ethnicity such as the United States.[19-21] A study by Guo and Gregg (2019) found that screening for the 40 genes that met the criterion of at least 1% prevalence in any ethnic group identified nearly all of the 2.52% of couples who would have been identified as at-risk with a 415-gene panel,[22] while Stevens (2017) found that over half of the genes included in carrier screening panels from different laboratories did not meet the prevalence criterion.[18]

Evidence on larger carrier screening panels (generally >100 disorders) includes case series,[23-26] and modeling studies[18, 27, 28] that estimated the incremental number of potentially affected fetuses if panel screening replaced a risk-based approach. Carrier rates with these panels ranged from 19% to 36% in individuals and from 0.2% to 1.2% of couples. Generally, as the size of the panel increases (risk-based to different sizes of expanded panels), the percentage

of patients who are identified as carriers for any recessive disease also increases. With a 218-disorder panel, about one in three individuals were identified as a carrier of a recessive single-gene disorder. Not all publications specified whether the disorders identified met the ACOG criteria; Peyser (2019) commented that some diseases may have late-onset as well as variable phenotypes.[25]

Ben-Shachar (2019) considered all 176 conditions in a commercially-available panel to meet ACOG criteria, except for the criterion of a carrier rate exceeding 1 in 100.[29] Examination of the genes included in the panel suggests potential variability in penetrance and expressivity. In another analysis, medical geneticists evaluated disease severity associated with the 176 genes in the panel.[30] After evaluation of published literature and mapping according to ACOG severity criteria, the investigators concluded that 65 of the genes (36.9%) were associated with profound symptoms (shortened lifespan in infancy/childhood/adolescence and intellectual disability), 65 genes (36.9%) were associated with severe symptoms (shortened lifespan in infancy, childhood, or adolescence, or intellectual disability; or at least one of the following: shortened lifespan in premature adulthood, impaired mobility, internal physical manifestation with three or more traits: shortened lifespan in premature adulthood, impaired mobility, internal physical manifestation, sensory impairment, immunodeficiency/cancer, mental illness, or dysmorphic features), and 42 genes were associated with moderate symptoms. Moderate severity was classified as shortened lifespan in premature adulthood, impaired mobility, or internal physical manifestation; or at least one of the following: sensory impairment, immunodeficiency/cancer, mental illness, or dysmorphic features. It is unclear if these would meet the ACOG criteria of a well-defined phenotype, a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life.

Haque (2016) modeled the potential impact that expanded carrier screening adoption might have had for a cohort of individuals undergoing testing between January 2012 and July 2015.[27] Data were derived from 346,790 individuals undergoing routine carrier screenin. Tests were performed using genotyping (n=308,668) and NGS (n=38,122). The severity of the 94 conditions included in the panel was considered profound according to literature review and algorithm devised by Lazarin (2014).[31] The incremental increase in the rate of potentially affected fetuses identified with carrier panel testing varied according to self-reported ethnicity. Out of 100,000 screened, the model predicted that the screening would identify 392 (95% confidence interval [CI] 366 to 420) affected fetuses compared to 175 (95% CI 164 to 186) with guideline-directed screening in Ashkenazi Jews – a difference of 217. Among African Americans, the incremental increase was 47 in 100,000 (364 vs. 317) and for those of Northern European descent, 104 in 100,000 (159 vs. 55). The authors concluded that expanded screening "may increase the detection of carrier status for a variety of potentially serious genetic conditions compared with current recommendations from professional societies. Prospective studies comparing current standard-of-care carrier screening with expanded carrier screening in at-risk populations are warranted before expanded screening is adopted."

A subsequent report by this group (Beauchamp [2018]) compared the detection rate of an large carrier sequencing panel (Counsyl) with a targeted family screen.[28] The panel was designed for maximizing per-disease sensitivity for diseases categorized as severe or profound. Specificity of variant classification was maximized by comparison of variant classification with at least two other labs. In the model, the targeted panel detected

approximately half the maximal disease risk while the expanded panel was projected to determine 92% of the total risk, with 183 affected conceptions per 100,000 U.S. births.

Although the results of these studies are consistent with larger screening panels being able to identify more fetuses potentially affected by conditions than guideline-directed targeted screening, there are caveats to consider, as discussed in the accompanying editorial and subsequent correspondence on the Haque study.[32, 33] Specifically:

- There may be limited genotype-phenotype data for the additional disorders included.
- The severity of some conditions is variable and accurately informing reproductive decisions potentially problematic (short-chain acyl CoA dehydrogenase deficiency provided as an example).
- A disorder such as phenylketonuria is treatable and detected by newborn screening yet included in the panel.
- It was also noted that fragile X syndrome screening in the absence of a family history (i.e., risk-based) is not recommended by professional guidelines. Widespread screening could have unintended consequences, including unnecessary invasive prenatal testing, labeling of newborns, and for some effectively screening for diseases of adult-onset (e.g., premature ovarian failure and tremor-ataxia dementia syndrome among males), which is contrary to accepted ethical convention.

Assessing the pathogenicity of sequence variants for rare disorders can be challenging, even when guidelines are followed, because laboratories may not provide the same interpretations. For example, Amendola (2016) compared interpretations of nine variants (pathogenic to benign associated with Mendelian disorders) among nine diagnostic laboratories and 90 variants in three of them.[34] They found good concordance between the laboratory's methods for determining pathogenicity and the ACMG-AMP criteria (Krippendorff's α=0.91; concordance 79%). However, across laboratories, there was only 34% concordance of either classification system, and for 22%, there were differences could have affected medical management.

Strom (2011) reported on an example of inclusion of a “nonclassical” CF variant (p.L997F) in a carrier screening panel.[35] In a database of approximately 2,500 CF sequencing analyses, four compound heterozygous patients carrying a pathogenic CF allele and the p.L997F variant were identified. Of these, three were asymptomatic at ages between 28 and 60 months The remaining patient was 10 years old with atypical CF. Another compound heterozygous patient having an allele with the p.L997F variant and another deletion had classical CF. The authors concluded that including the variant in a screening panel could lead to “poorly informed reproductive decisions based on incorrect assumptions.”

As noted by Henneman (2016) "There is no general agreement on classification of genetic disorders based on the severity of disease.[1]

Clinical Utility

In addition to clinical validity—a well-defined predictable risk that the offspring will be affected by severe phenotype—to offer greater clinical utility than recommended risk-based approaches, carrier screening panels must:

1. Correctly identify more carrier couples of those conditions than recommended risk-based screening (higher clinical sensitivity while maintaining specificity [no change in false positives]);
2. Inform reproductive decisions more effectively than recommended risk-based carrier screening.

Several surveys studies evaluated patients' perspectives and reproductive behaviors concerning carrier screening panels (see Table 1). Populations among the studies differed, with some studies including only women known to be carriers and some studies included all pregnant woman, regardless of carrier status. Due to the heterogeneity of the populations and outcomes, combining and summarizing results would not be appropriate.

Table 1. Relevant Clinical Utility Studies

Study	Participants	Number	Outcomes	Results
Ghiossi (2018)[36]	Couples in which both partners carry genes for the same recessive disease who had received ECS	537 eligible couples 64 (12%) completed survey	Action (defined as IVF with PDG or prenatal diagnosis) No action	60% reported taking action following ECS results 40% reported taking no action following results
Propst (2018)[37]	Pregnant women undergoing prenatal counseling prior to an aneuploidy screening	80 women: • 40 elected ECS • 40 declined ECS	Reasons for declining or electing ECS Reproductive planning	Reasons for declining: • Not at risk (77%) • Small chance that both in couple are carriers (60%) • Results would not change reproductive planning (37%) • Too anxious if carrier test was positive (27%) Reasons for electing: • Want to know risk (90%) • Want all information available about genetic risk (72%) • Want to make informed reproductive decisions (61%) • Want to prepare for special needs child (33%)

Study	Participants	Number	Outcomes	Results
Johansen Taber (2018)[38]	Women in couples where both partners carry genes for the same recessive condition, who had received ECS 54% were for IVF	1,701 eligible couples 391 women completed survey	Reproductive planning	77% of patients screened prior to pregnancy planned or pursued actions to avoid having affected offspring 37% of patients screened during pregnancy pursued prenatal diagnostic testing Reasons for declining prenatal testing were: • Fear of miscarriage • Belief that termination would not be pursued for a positive diagnosis • Perception that risk of an affected pregnancy was low

ECS: expanded carrier screening; IVF: in vitro fertilization; PGD: preimplantation genetic diagnosis

SUMMARY OF EVIDENCE

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive risk-based carrier screening, the evidence includes studies supporting analytic validity, clinical validity, and clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination.

For individuals who are either at increased risk or population risk for having offspring with an inherited recessive genetic disorder who receive large carrier screening panel testing, the evidence includes studies supporting clinical validity and clinical utility. Relevant outcomes are test validity and changes in reproductive decision making. Studies have found that larger panels can identify more carriers and more potentially affected fetuses. Many of the genes in large panels do not meet the ACOG consensus-driven criteria of at least 1% carrier rate for all ethnic groups. However, pan-ethnic testing can address the discrepancies between self-reported ethnicity and genetic ancestry in an ethnically mixed population. As panels become larger the likelihood of being identified as a carrier of a rare genetic disorder increases, leading to an at-risk couple rate of nearly 2% for having an offspring with a recessive or X-linked disorder. Many, though notably not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability. With adequate genetic counseling panel screening can inform reproductive choices, and observational studies have shown that a majority of couples would consider intervention that depends on the severity of the condition. Carrier screening for severe recessive and X-linked genetic disorders with a 1% carrier rate in specific populations can have a significant clinical impact.

However, the evidence to support the clinical validity of carrier screening beyond risk-based recommendations is limited and accompanied by some concerns regarding interlaboratory agreement of variant pathogenicity assessment, the validity of disease severity classifications

for rare disorders, and uncertainty that the offspring will be affected by a severe phenotype for all the disorders included in a panel.

PRACTICE GUIDELINE SUMMARY

RISK-BASED CONDITION-SPECIFIC SCREENING RECOMMENDATIONS

The American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) have issued numerous guidelines on conditions discussed herein. Table 2 provides the recommendations by indication for risk-based screening.

Table 2. ACOG and ACMG Recommendations for Risk-Based Screening

Society	Recommendation	Year
Cystic fibrosis[a]		
ACOG	"Cystic fibrosis carrier screening should be offered to all women considering pregnancy or are pregnant."[39]	2017
ACMG	Current ACMG guidelines use a 23-variant panel and were developed after assessing the initial experiences on implementation of cystic fibrosis screening into clinical practice. Using the 23-varian panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.[40]	2013
Spinal muscular atrophy[b]		
ACOG	"Screening for spinal muscular atrophy should be offered to all women considering pregnancy or are pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, SMN1 deletion testing should be recommended for the low-risk partner."[39]	2017
ACMG	Because spinal muscular atrophy is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity.[41]	2013
Tay-Sachs disease		
ACOG	"Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be screened"[39]	2017
Hemoglobinopathies (sickle cell disease, α- and β-thalassemia)		
ACOG	"A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to women before pregnancy. A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed."[39]	2017
Fragile X syndrome		
ACOG	"Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation."[39]	2017

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists.
[a] Carrier rates: Ashkenazi Jews 1/24, non-Hispanic white 1/25, Hispanic white 1/58, African American 1/61, Asian American 1/94.
[b] General population carrier rate: 1/40 to 1/60.

Ashkenazi Jewish Populations

Individuals of Ashkenazi Jewish descent have high carrier rates for multiple conditions—cumulatively between one in four and one in five when all disorders are considered.[42] Recommendations for carrier screening for Ashkenazi Jewish individuals by ACOG[39] and ACMG[42] are summarized in Table 3. According to ACMG, if only one member of the couple is Jewish, ideally, that individual should be tested first. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be screened for that particular disorder. One Jewish grandparent is sufficient to offer testing.

Table 3. ACMG (2008, 2013) and ACOG (2017) Carrier Screening Recommendations for Individuals of Ashkenazi Jewish Descent[39, 42]

Condition	Incidence (Lifetime)	Carrier Rate	ACMG (2008, 2013)	ACOG (2017)
Tay-Sachs disease	1/3000	1/30	R	R
Canavan disease	1/6400	1/40	R	R
Cystic fibrosis	1/2500-3000	1/29	R	R
Familial dysautonomia	1/3600	1/32	R	R
Fanconi anemia (group C)	1/32,000	1/89	R	C
Niemann-Pick disease type A	1/32,000	1/90	R	C
Bloom syndrome	1/40,000	1/100	R	C
Mucolipidosis IV	1/62,500	1/127	R	C
Gaucher disease	1/900	1/15	R	C
Familial hyperinsulinism		1/52		C
Glycogen storage disease type I		1/71		C
Joubert syndrome		1/92		C
Maple syrup urine disease		1/81		C
Usher syndrome		≤ 1/40		C

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynecologists; C: should be considered; R: recommended.

EXPANDED CARRIER SCREENING RECOMMENDATIONS

American College of Obstetricians and Gynecologists

In 2017, ACOG made the following recommendations on carrier screening strategies:[17]

> "Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician-gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening."

> "Expanded carrier screening does not replace previous risk-based screening recommendations."

Based on “consensus,” characteristics of included disorders should meet the following criteria:

- carrier frequency ≥1/100
- “well-defined phenotype”
- “detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life”
- not be primarily associated with a disease of adult onset.

ACOG also noted that expanded panels may not offer the most sensitive detection method for some conditions such as Tay-Sachs disease (i.e., they will miss carrier state in up to 10% of low-risk populations) or hemoglobinopathies.

ACOG also provided a detailed example of a carrier screening panel that includes testing for 22 conditions: α-thalassemia, β-thalassemia, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease.

In 2015, a joint statement on expanded carrier screening panels was issued by ACOG, ACMG, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine.[2] The statement was not intended to replace current screening guidelines but to demonstrate an approach for health care providers and laboratories seeking to or currently offering these panels. Some points considered included the following:

- “Expanded carrier screening panels include most of the conditions recommended in current guidelines. However, molecular methods used in expanded carrier screening are not as accurate as methods recommended in current guidelines for the following conditions:
    a. Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.
    b. Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the three common Ashkenazi mutations. Currently, hexosaminidase A enzyme analysis on blood is the best method to identify carriers in all ethnicities.”
- “Patients should be aware that newborn screening is mandated by all states and can identify some genetic conditions in the newborn. However, newborn screening may include a different panel of conditions than ECS. Newborn screening does not usually detect children who are carriers for the conditions being screened so will not necessarily identify carrier parents at increased risk.”
- “Expanded carrier screening can be performed by genotyping or by DNA sequencing. Genotyping searches for known pathogenic and likely pathogenic variants. Sequencing analyzes the entire coding region of the gene and identifies alterations from the normal sequence. Although genotyping includes only selected variants, sequencing has the potential to identify not only benign, but also likely benign variants. Sequencing also can identify variants of uncertain significance….

- ECS panels should only include “genes and variants” with “a well-understood relationship with a phenotype…. When the carrier frequency and detection rate are both known, residual risk estimation should be provided in laboratory reports.”
- Conditions with unclear value on preconception and prenatal screening panels include α_1-antitrypsin, methylene tetrahydrofolate reductase, and hereditary hemochromatosis.

The statement also included a set of recommendations for screened conditions[2]:

1. “The condition being screened for should be a health problem that encompasses one or more of the following:
   a. Cognitive disability.
   b. Need for surgical or medical intervention.
   c. Effect on quality of life.
   d. Conditions for which a prenatal diagnosis may result in:
      i. Prenatal intervention to improve perinatal outcome and immediate care of the neonate.
      ii. Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care.
      iii. Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth.”

American College of Medical Genetics and Genomics

In 2021, the ACMG issued a position statement on screening for autosomal recessive and X-linked conditions during pregnancy and preconception.[43] This position statement replaces the 2013 ACMG position statement on prenatal and preconception expanded carrier testing,[44] and incorporates ACOG Committee Opinion 691 recommendations.[39]

The ACMG consensus group made the following recommendations:

- Replacing the term "expanded carrier screening" with "carrier screening" as no precise definition for "expanded" exists
- Establishing a tier-based system of carrier screening, to enhance communication and precision while advancing equity in carrier screening (see Table 4 below)
- Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion
- Offering Tier 3 carrier screening to all pregnant patients and those planning a pregnancy
- Male partners of pregnant women and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their female partner
- Consider offering Tier 4 screening when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when family or personal medical history warrants.

The ACMG does not recommend:

- Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups

- Routine offering of Tier 4 panels.

Table 4. American College of Medical Genetics and Genomics Tiered Approach to Carrier Screening

Tier	Screening Recommendations
1	Cystic fibrosis + spinal muscular atrophy + risk-based screening
2	≥1/100 carrier frequency + Tier 1
3	≥1/200 carrier frequency + Tier 2 (includes X-linked conditions)
4	<1/200 carrier frequency + Tier 3 (genes and conditions will vary by lab)

X-linked genes considered appropriate for carrier screening in Tier 3 include: *ABCD1, AFF2, ARX, DMD, F8, F9, FMR1, GLA, L1CAM, MID1, NR0B1, OTC, PLP1, RPGR, RS1, and SLC6A8.* Tables in the ACMG position statement provide additional details regarding appropriate autosomal recessive conditions for screening and their associated carrier frequencies.

The ACMG recommends the following components regarding laboratory reporting of carrier screening panels:

- The content of carrier screen panels and corresponding ACMG tier must be described
- The testing approach and detectable variant types should be clearly stated
- Not reporting residual risk estimates
- Only reporting pathogenic and likely pathogenic variants
- Interpretation should consider genes and variants with multiple disease associations
- Reporting of a variant of uncertain significance (VUS) only in the partners of identified carriers and only with consent of the patient.

National Society of Genetic Counselors

The National Society of Genetic Counselors published a guideline in 2023 that included a conditional recommendation that “the option of expanded carrier screening as an alternative to ethnicity-based carrier screening for all individuals considering reproduction and for all pregnant reproductive pairs.”[45] There were no specific criteria related to the inclusion of specific conditions in such screening.

SUMMARY

Reproductive carrier screening is performed to identify people at risk of having children with inherited single-gene disorders. Carriers are usually not at risk of developing the disease but can pass disease-causing gene variants to their offspring. There is enough research to show that targeted, risk-based carrier screening can help patients make informed reproductive decisions and improve health outcomes. Many clinical guidelines based on research recommend carrier screening for certain disorders in patients at risk. Therefore, carrier screening may be considered medically necessary for patients that meet the policy criteria.

There is enough research to show that targeted carrier testing is unlikely to improve health outcomes and inform reproductive decision making in individuals that are not at increased risk of being carriers for a disorder. Therefore, targeted carrier screening is considered not medically necessary for patients that do not meet the policy criteria.

There is enough evidence to show that non-targeted carrier screening panels can inform reproductive decisions and improve health outcomes when the genes in these panels meet certain criteria. This includes testing that is limited to disorders with an estimated carrier frequency of at least 1 in 200, for which the natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity, when the genetic test has adequate clinical validity to guide clinical decision making. Therefore, non-targeted carrier screening panels may be considered medically necessary when the policy criteria are met.

There is not enough research to show that carrier screening for certain genes or disorders can provide information that can improve reproductive decision making and overall health outcomes for patients and their children. While large carrier screening panels can analyze many genes simultaneously, the results they may provide may include information on genetic variants that are of unclear clinical significance, or which would not be helpful for patients making reproductive decisions. These results may potentially cause harm by leading to additional unnecessary interventions and anxiety. Therefore, non-targeted carrier screening panels that do not meet the policy criteria are considered investigational.

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CODES

NOTE: If CPT tier 1 or tier 2 molecular pathology codes are available for the specific test, they should be used. If the test has not been codified by CPT, the unlisted molecular pathology code 81479 would be used.

Codes	Number	Description
		SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
	0400U	Obstetrics (expanded carrier screening), 145 genes by next generation sequencing, fragment analysis and multiplex ligation dependent probe amplification, DNA, reported as carrier positive or negative
	81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
	81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
	81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
	81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
	81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81221	;known familial variants
	81222	;duplication/deletion variants
	81223	;full gene sequence
	81224	;intron 8 poly-T analysis (eg, male infertility)
	81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
	81243	FMR1 (Fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

Codes	Number	Description
	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
	81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
	81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	;known familial variants
	81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
	81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
	81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
	81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
	81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
	81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
	81400	MOLECULAR PATHOLOGY PROCEDURE LEVEL 1
	81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2
	81402	MOLECULAR PATHOLOGY PROCEDURE LEVEL 3
	81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4
	81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5
	81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6
	81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7
	81407	MOLECULAR PATHOLOGY PROCEDURE LEVEL 8
	81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9
	81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
	81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A,

Codes	Number	Description
		MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
	81431	;duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
	81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
	81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
	81479	Unlisted molecular pathology procedure
HCPCS	S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
	S3845	Genetic testing for alpha-thalassemia
	S3846	Genetic testing for hemoglobin E beta-thalassemia
	S3849	Genetic testing for Niemann-Pick disease
	S3850	Genetic testing for sickle cell anemia
	S3853	Genetic testing for myotonic muscular dystrophy

APPENDIX I: GLOSSARY OF TERMS

APPENDIX 1. DEFINITIONS

Carrier Screening

Carrier genetic screening is performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children.

A carrier of a genetic disorder has one abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative variant are typically unaffected. When associated with an autosomal dominant disorder, the individual has one normal and one mutated copy of the gene and may be affected by the disorder, may be unaffected but at high risk of developing the disorder later in life, or the carrier may remain unaffected because of the sex-limited nature of the disorder. Homozygous-affected offspring (those who inherit the variant from both parents) manifest the disorder.

Compound Heterozygous

The presence of two different mutant alleles at a particular gene locus, one on each chromosome of a pair.

Expressivity/Expression

The degree to which a penetrant gene is expressed within an individual.

Genetic Testing

Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or noninherited (somatic) genetic variants related to disease or health.

Homozygous

Having the same alleles at a particular gene locus on homologous chromosomes (chromosome pairs).

Penetrance

The proportion of individuals with a variant that causes a disorder who exhibit clinical symptoms of that disorder.

Residual Risk

The risk that an individual is a carrier of a disease, but testing for carrier status of the disease is negative (e.g., if the individual carries a pathogenic variant not included in the test assay).

Date of Origin: *September 2018*

Regence

Medical Policy Manual Genetic Testing, Policy No. 83

Expanded Molecular Testing of Cancers to Select Targeted Therapies

Effective: April 1, 2025

Next Review: April 2025
Last Review: March 2025

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 growing number of cancer therapies target specific genetic variants in tumors. Expanded molecular panel tests are used to test tumor tissue for a large number of gene variants, and they are generally not tailored to a specific type of cancer. Tumor profiling with such panels is proposed to aid in treatment selection and to help patients find appropriate clinical trials for experimental therapy.

MEDICAL POLICY CRITERIA

Note: This policy does not address targeted variant testing, gene expression testing, testing for hematologic disorders (e.g., leukemia or lymphoma), or testing of circulating, cell-free tumor DNA (i.e., liquid biopsy) or circulating tumor cells (see Cross References section).

I. Tumor tissue testing to select targeted cancer treatment using molecular panels, including but not limited to broad tumor profiling panels, may be considered **medically necessary** when all of the following criteria are met:

A. The individual has advanced or metastatic (stage III or IV) solid tumor (non-hematologic) cancer; and

B. The test includes one or more genes for which an FDA-approved therapy is available for the cancer indication (see Policy Guidelines); and

C. The individual has not decided to forgo targeted cancer treatment.

II. Tumor tissue testing using broad profiling panels for selecting targeted cancer treatment is considered **investigational** for all other indications or purposes.

III. Whole genome sequencing, whole exome sequencing, and whole transcriptome sequencing of tumor tissue are considered **investigational.**

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

POLICY GUIDELINES

Providers should be aware of the possibility of false positive and false negative results from tumor profiling tests. False positives may lead to a patient receiving an ineffective therapy with the risk of drug-related adverse events. Tests that include normal germline tissue testing for comparison may have a lower incidence of false positives compared with tumor-only tests. It is highly recommended that providers review the test's performance characteristics and discuss this information with patients prior to requesting.

EXAMPLES OF EXPANDED TUMOR PANEL TESTS

Expanded tumor panel tests that may be considered medically necessary when policy criteria are met include but are not limited to:

- Altera™
- FoundationOne® CDx
- GeneTrails® Comprehensive Solid Tumor Panel
- Guardant360 TissueNext™
- HopeSeq Solid Tumors Comprehensive
- Illumina TruSeq™
- Ion AmpliSeq™
- MSK-IMPACT™
- NeoTYPE® Lung Tumor Profile
- NeoTYPE® Precision Profile for Solid Tumors
- OnkoMatch™
- Oncomine Comprehensive Assay
- Oncotype MAP
- Symgene™ NGS Cancer Panel
- Tempus xT
- UW OncoPlex Cancer Gene Panel

EXAMPLES OF WHOLE GENOME, WHOLE EXOME, AND WHOLE TRANSCRIPTOME SEQUENCING TESTS:

- Tempus xE

- Tempus xR
- Caris Molecular Profiling tests, including the Intelligence Profile Panel and MI Tumor Seek

CANCER INDICATIONS AND GENES WITH TARGETED CANCER TREATMENTS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Note: This is not an exhaustive list of all genes with FDA-approved targeted treatments. Please consult the FDA website and/or National Cancer Institute website for more current or specific information.

Cancer Indications with Targeted Treatments			
Indication	**Type**	**Genes**	**Medication**
Any solid tumor	Advanced or metastatic	*BRAF* *NTRK(1/2/3)* *RET*	Tafinlar, Mekinist, Retevmo, Rozlytrek, Vitrakvi
Breast cancer	HER2-negative	*BRCA(1/2)*	Lynparza, Talzenna
	HR-positive, HER2-negative, advanced or metastatic	*AKT1* *ESR1* *PIK3CA* *PTEN*	Truqap, Orserdu, Piqray
	HER2-positive	*ERBB2 (HER2)*	Herceptin, Kadcyla, Perjeta
Cholangiocarcinoma	Advanced or metastatic	*FGFR2* *IDH1*	Pemazyre, Tibsovo
Colorectal cancer	Metastatic	*BRAF* *KRAS* *NRAS*	Braftovi, Erbitux, Fruzaqla, Tukysa, Vectibix
Gastrointestinal stromal tumor (GIST)	Resected, unresectable, or metastatic	*KIT (c-KIT, CD117)* *PDGFRA*	Ayvakit, Gleevec
Melanoma, cutaneous	Resected, unresectable, or metastatic	*BRAF*	Braftovi, Cotellic, Mekinist, Opdivo, Tafinlar, Tecentriq, Zelboraf
Melanoma, uveal	Unresectable, or metastatic	*HLA*	Kimmtrak
Non-small cell lung cancer (NSCLC)	Advanced or metastatic	*ALK* *BRAF* *EGFR* *ERBB2 (HER2)* *KRAS*	Alcensa, Cyramza, Enhertu, Exkivity, Gavreto, Gilotrif, Iressa, Keytruda, Krazati, Lorbrena, Lumakras, Mekinist, Opdivo, Rozlytrek, Rybrevant, Tafinlar, Tagrisso, Tarceva,

Cancer Indications with Targeted Treatments			
Indication	**Type**	**Genes**	**Medication**
		ROS1	Tecentriq, Vizimpro, Xalkori, Zykadia
	Resected	*EGFR*	Tagrisso
Ovarian cancer (including fallopian tube and primary peritoneal cancer)	Advanced or recurrent	*BRCA(1/2)*	Lynparza, Rubraca, Zejula
Pancreatic cancer	Metastatic	*BRCA(1/2)*	Lynparza
Prostate cancer	Metastatic, castration-resistant	*BRCA(1/2)*	Lynparza, Rubraca
Thyroid cancer	Advanced or metastatic	*RET*	Gavreto
	Anaplastic and advanced or metastatic	*BRAF*	Mekinist, Tafinlar
Urothelial carcinoma	Advanced or metastatic	*FGFR(2/3)*	Balversa

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
   - o Date of sample collection (tumor tissue)
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided, if any

CROSS REFERENCES

1. KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer, Genetic Testing, Policy No. 13

2. Gene Expression-Based Assays for Cancers of Unknown Primary, Genetic Testing, Policy No. 15
3. PathFinderTG® Molecular Testing, Genetic Testing, Policy No. 16
4. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
5. BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy, Genetic Testing, Policy No. 41
6. Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
7. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
8. Analysis of Proteomic and Metabolomic Patterns for Early Detection or Assessing Risk of Cancer, Laboratory, Policy No. 41
9. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46
10. Laboratory and Genetic Testing for Use of 5-Fluorouracil (5-FU) in Patients with Cancer, Laboratory, Policy No. 64
11. Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance, Laboratory, Policy No. 72

BACKGROUND

TRADITIONAL THERAPEUTIC APPROACHES TO CANCER

Tumor location, grade, stage, and the patient's underlying physical condition have traditionally been used in clinical oncology to determine the therapeutic approach to a specific cancer, which could include surgical resection, ionizing radiation, systemic chemotherapy, or combinations thereof. Currently, some 100 different types are broadly categorized according to the tissue, organ, or body compartment in which they arise. Most treatment approaches in clinical care were developed and evaluated in studies that recruited subjects and categorized results based on this traditional classification scheme.

This traditional approach to cancer treatment does not reflect the wide diversity of cancer at the molecular level. While treatment by organ type, stage, and grade may demonstrate statistically significant therapeutic efficacy overall, only a subgroup of patients may derive clinically significant benefit. It is unusual for a cancer treatment to be effective for all patients treated in a traditional clinical trial. Spear et al analyzed the efficacy of major drugs used to treat several important diseases.[1] They reported heterogeneity of therapeutic responses, noting a low rate of 25% for cancer chemotherapeutics, with response rates for most drugs falling in the range of 50% to 75%. The low rate for cancer treatments is indicative of the need for better identification of characteristics associated with treatment response and better targeting of treatment to have higher rates of therapeutic responses.

TARGETED CANCER THERAPY

Much of the variability in clinical response may result from genetic variations. Within each broad type of cancer, there may be a large amount of variability in the genetic underpinnings of the cancer. Targeted cancer treatment refers to the identification of genetic abnormalities present in the cancer of a particular patient, and the use of drugs that target the specific genetic abnormality. The use of genetic markers allows cancers to be further classified by "pathways" defined at the molecular level. An expanding number of genetic markers have been identified. Dienstmann (2013) categorized these findings into three classes:[2] (1) genetic markers that have a direct impact on care for the specific cancer of interest, (2) genetic markers that may be biologically important but are not currently actionable, and (3) genetic markers of uncertain importance.

A smaller number of individual genetic markers fall into the first category (i.e., have established utility for a specific cancer type). The utility of these markers has been demonstrated by randomized controlled trials that select patients with the marker and report significant improvements in outcomes with targeted therapy compared with standard therapy. Testing for individual variants with established utility is not covered in this evidence review. In some cases, limited panels may be offered that are specific to one type of cancer (e.g., a panel of several markers for non-small-cell lung cancer). This review also does not address the use of cancer-specific panels that include a few variants. Rather, this review addresses expanded panels that test for many potential variants that do not necessarily have established efficacy for the specific cancer in question.

When advanced cancers are tested with expanded molecular panels, most patients are found to have at least one potentially pathogenic variant.[3-5] The number of variants varies widely by types of cancers, different variants included in testing, and different testing methods among the available studies. In a 2015 study, 439 patients with diverse cancers were tested with a 236-gene panel.[5] A total of 1,813 molecular alterations were identified, and almost all patients (420/439 [96%]) had at least one molecular alteration. The median number of alterations per patient was three, and 85% of patients (372/439) had two or more alterations. The most common alterations were in the genes *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%).

Some evidence is available on the generalizability of targeted treatment based on a specific variant among cancers that originate from different organs.[2, 6, 7] There are several examples of variant-directed treatment that was effective in one type of cancer but ineffective in another. For example, targeted therapy for epidermal growth factor receptor (*EGFR*) variants has been successful in non-small cell lung cancer (NSCLC) but not in trials of other cancer types. Treatment with tyrosine kinase inhibitors based on variant testing has been effective for renal cell carcinoma but has not demonstrated effectiveness for other cancer types tested. “Basket” studies, in which tumors of various histologic types that share a common genetic variant are treated with a targeted agent, also have been performed. One such study was published by Hyman (2015).[8] In this study, 122 patients with *BRAF* V600 variants in nonmelanoma cancers were treated with vemurafenib. The authors reported that there appeared to be antitumor activity for some but not all cancers, with the most promising results seen for NSCLC, Erdheim-Chester disease, and Langerhans cell histiocytosis.

EXPANDED CANCER MOLECULAR PANELS

Table 1 provides a select list of some commercially available expanded cancer molecular panels.

Table 1. Commercially Available Molecular Panels for Solid and Hematologic Tumor Tissue Testing

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
FoundationOne® CDx test (Foundation Medicine, Cambridge, MA)	Solid	324 cancer-related genes and select rearrangements in 36 genes	NGS
OnkoSight™ Solid Tumor Panel (GenPath Diagnostics, Elmwood Park, NJ)	Solid	31 genes	NGS

Test (Manufacturer)	Tumor Type	No. of Genes Tested	Technology
GeneTrails® Comprehensive Solid Tumor Panel (Knight Diagnostic Labs, Portland, OR)	Solid	225 genes	NGS
SmartGenomics™ (PathGroup, Nashville, TN)	Solid and hematologic	160 genes and 126 gene fusions	NGS, cytogenomic array, other technologies
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™; Memorial Sloan Kettering Cancer Center, New York, NY)	Solid	341 cancer-associated genes	NGS
TruSight Tumor 170 (Illumina, San Diego, CA)	Solid	170 solid tumor-related genes	NGS
Oncomine™ Comprehensive Assay v3 (Thermo Fisher Scientific, Waltham, MA)	Solid	161 genes	NGS
Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific, Waltham, MA)	Solid	409 genes	NGS

FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[9] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The evaluation of a genetic test focuses on three main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). This evidence review focuses on clinical validity and utility.

EXPANDED MOLECULAR PANEL TESTING FOR CANCER

The evidence on the clinical validity of expanded panels is incomplete. Because of the large number of variants contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole. While some variants have a strong association with one or a small number of specific malignancies, none has demonstrated high clinical validity across a wide variety of cancers. Some studies have reported that, after filtering variants by comparison with matched normal tissue and cancer variants databases, most identified variants are found to be false positives. Thus, it is likely that clinical validity will need to be determined for each variant and each type of cancer individually.

The most direct way to demonstrate clinical utility is through controlled trials that compare a strategy of cancer variant testing followed by targeted treatment with a standard treatment strategy without variant testing. Randomized trials are necessary to control for selection bias in treatment decisions, because clinicians may select candidates for variant testing based on clinical, demographic, and other factors. Outcomes of these trials would be the morbidity and mortality associated with cancer and cancer treatment. Overall survival (OS) is most important; cancer-related survival and/or progression-free survival (PFS) may be acceptable surrogates. A quality-of-life measurement may also be important if study designs allow for treatments with different toxicities in the experimental and control groups.

Systematic Reviews

Schwaederle (2015) published a meta-analysis of studies comparing personalized treatment with nonpersonalized treatment.[10] Their definition of personalized treatment was driven by a biomarker, which could be genetic or nongenetic. Therefore, this analysis not only included studies of matched versus unmatched treatment based on genetic markers, but also included studies that personalized treatment based on nongenetic markers. A total of 111 arms of identified trials received personalized treatment, and they were compared with 529 arms that received nonpersonalized treatment. On random-effects meta-analysis, the personalized treatment group had a higher response rate (31% vs 10.5%, $p<0.001$), and a longer PFS (5.9 months vs 2.7 months, $p<0.001$) compared with the nonpersonalized treatment group. Another meta-analysis (2015) by this group compared outcomes from 44 Food and Drug Administration-regulated drug trials that used a personalized treatment approach to 68 trials that used a nonpersonalized approach to cancer treatment.[11] Response rates were significantly higher in the personalized treatment trials (48%) than in the nonpersonalized approach (23%; $p<0.001$). PFS was 8.3 months in the personalized treatment trials compared with 5.5 months in the nonpersonalized approach ($p<0.001$). For trials that used a personalized treatment strategy, OS was significantly longer (19.3 months) than in trials that did not (13.5 months, $p=0.01$). Personalized treatment in these studies was based on various biomarkers, both genetic and nongenetic.

Randomized Controlled Trials

SHIVA was a randomized controlled trial of treatment directed by cancer variant testing vs standard care, with the first results published in 2015 (see Table 2).[12, 13] In this study, 195 patients with a variety of advanced cancers refractory to standard treatment were enrolled from eight academic centers in France. Variant testing included comprehensive analysis of three molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, RAF/MEK pathway) performed by targeted next-generation sequencing, analysis of copy number variations, and hormone expression by immunohistochemistry. Based on the pattern of abnormalities found, nine different regimens of established cancer treatments were assigned

to the experimental treatment arm. The primary outcome was PFS analyzed by intention to treat. Baseline clinical characteristics and tumor types were similar between groups.

Table 2. Treatment Algorithm for Experimental Arm, From the SHIVA Trial[12]

Molecular Abnormalities	Molecularly Targeted Agent
KIT, *ABL*, *RET*	Imatinib
AKT, mTORC1/2, *PTEN*, *PI3K*	Everolimus
BRAF V600E	Vemurafenib
PDGFRA, *PDGFRB*, *FLT-3*	Sorafenib
EGFR	Erlotinib
HER2	Lapatinib and trastuzumab
SRC, *EPHA2*, *LCK*, *YES*	Dasatinib
Estrogen receptor, progesterone receptor	Tamoxifen (or letrozole if contraindications)
Androgen receptor	Abiraterone

Ninety-nine patients were randomized to the targeted treatment group, and 96 to standard care. Baseline clinical characteristics and tumor types were similar between groups. Molecular alterations affecting the hormonal pathway were found in 82 (42%) of 195 patients; alterations affecting the PI3K/AKT/mTOR pathway were found in 89 (46%) of 195 patients; and alterations affecting the RAF/MED pathway were found in 24 (12%) of 195 patients. After a median follow-up of 11.3 months, the median PFS was 2.3 months (95% confidence interval [CI] 1.7 to 3.8 months) in the targeted treatment group vs 2.0 months (95% CI 1.7 to 2.7 months) in the standard care group (hazard ratio, 0.88; 95% CI 0.65 to 1.19, p=0.41). Objective responses were reported for four (4.1%) of 98 assessable patients in the targeted treatment group vs three (3.4%) of 89 assessable patients in the standard care group. In subgroup analysis by molecular pathway, there were no significant differences in PFS between groups.

A 2017 crossover analysis of the SHIVA trial evaluated the PFS ratio from patients who failed standard of care therapy and crossed over from molecularly targeted agents (MTA) therapy to treatment at physician's choice (TPC) or vice versa.[14] The PFS ratio was defined as the PFS on MTA (PFSMTA) to PFS on TPC (PFSTPC) in patients who crossed over. Of the 95 patients who crossed over, 70 patients crossed over from the TPC to MTA arm while 25 patients crossed over from MTA to TPC arm. In the TPC to MTA crossover arm, 26 (37%) of patients and 15 (61%) of patients in the MTA to TPC arm had a PFSMTA/PFSTPC ratio greater than 1.3. The post hoc analysis of the SHIVA trial has limitations because it only evaluated a subset of patients from the original clinical trial but used each patient as his/her control by using the PFS ratio. The analysis would suggest that patients may have benefited from the treatment algorithm evaluated in the SHIVA trial.

Nonrandomized Controlled Trials

Numerous nonrandomized studies have been published that use some type of control.[15-19] Some of these studies had a prospective, interventional design. For example, Wheler (2016) reported a prospective comparative trial of patients who had failed standard treatment and had been referred to their tertiary center for admission into phase 1 trials.[18] Comprehensive molecular profiling (FoundationOne® tumor panel) was performed on 339 patients, of whom 122 went onto a phase 1 therapy that was matched to their genetic profile; based on physician evaluation of additional information, 66 patients went onto a phase 1 trial not matched to their genetic profile. There was a significant benefit for time to treatment failure and a trend for an increased percentage of patients with stable disease and median OS in patients matched to their genetic profile. When exploratory analysis divided patients into groups that had high

matching results or low matching results (number of molecular matches per patient divided by the number of molecular alterations per patient), the percentage of patients with stable disease and the median time to failure were significantly better in the high-match group. Median OS did not differ significantly between groups. Notably, those patients had failed multiple prior therapies (median four) and had a number (median five, range 1 to 14) of gene alterations in the tumors. For comparison, response rates in phase 1 trials with treatment-resistant tumors are typically 5% to 10%.

Another type of study compares patients matched to targeted treatment with patients not matched. In this type of study, all patients undergo comprehensive genetic testing, but only a subset is matched to targeted therapy. Patients who are not matched continue to receive standard care. An individual study of this type is Tsimberidou (2012).[19] In it, patients with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. Of 1,144 patients, 460 had a molecular aberration based on a panel of tests, 211 of whom were given “matched” treatment and 141 given nonmatched treatment. The principal analysis presented was of a subgroup of the 460 patients who had only one molecular aberration (n=379). Patients were enrolled in one of 51 phase 1 clinical trials of experimental agents. In the list of trials in which patients were enrolled, it appears that many of the investigational agents were inhibitors of specific kinases, and thus a patient with a particular aberration of that kinase would probably be considered a match for that agent.[19] Among the 175 patients treated with matched therapy, the overall response rate was 27%. Among the 116 patients treated with nonmatched therapy, the response rate was 5% ($p<0.001$ for the difference in response rates). The median time to failure was 5.2 months for patients on matched therapy and 2.2 months for those on nonmatched therapy ($p<0.001$). At a median 15-month follow-up, survival was 13.4 months vs 9.0 months ($p=0.017$) in favor of matched therapy.

There are significant limitations inherent in using these and other types of nonrandomized trials to assess the clinical utility of molecular profiling, which are detailed in a review by Freidlin (2019).[20] Comparisons of patients that receive therapy based on molecular profiling to those that receive do not receive profiling-selected therapy are confounded by the fact that these patient groups are likely to differ in a number of ways other than type of therapy selection. As stated in the review, “the very mechanism by which some patients are separated into the two groups is likely to introduce bias. For example, patients who were treated with MP therapy were selected into that group based on their willingness to accept additional (possibly invasive) MP testing; their willingness to wait for results to come back (and the tumor board to issue a recommendation, if there was one); and their willingness to accept a potentially more aggressive, prolonged, and/or logistically challenging treatment course.”[20] Additionally, patients with certain molecular variants may have a better prognosis regardless of type of treatment, and certain treatments (which may be more commonly prescribed in the profiled patients) may be more efficacious regardless of molecular status. Other common, nonrandomized study designs, such as comparisons of PFS between a selected, targeted therapy and a previously failed therapy, or “basket” trials have similar issues that limit interpretation.

Whole Genome, Whole Exome, and Whole Transcriptome Testing of Cancers to Identify Targeted Therapies

No systematic reviews, randomized controlled trials, or nonrandomized controlled trials were identified that evaluated the use of whole genome, whole exome, or whole transcriptome sequencing of cancer tissue to guide treatment options.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network guidelines for many cancer types include recommendations for molecular profiling. Some examples of indications for which the guidelines recommend broad molecular profiling for advanced or metastatic disease include:

- Breast cancer[21]
- Colon cancer[22]
- Non-small-cell lung cancer[23]
- Chondrosarcoma[24]
- Ovarian cancer[25]
- Biliary tract cancer[26]
- Pancreatic adenocarcinoma[27]
- Rectal cancer[28]

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion based on informal consensus in the absence of a formal systematic review on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.[29] The opinion notes the following:

- PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:
    - When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
    - When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions (strength of recommendation: strong).
- PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).
- PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).
- PCO 2.1. Mismatch repair deficiency status (dMMR) should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-H status in individual tumor types when making this decision (strength of recommendation: strong).
- PCO 2.2. When tumor mutational burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

- PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

SUMMARY

There is limited evidence that molecular profiling of tumor tissue can improve health outcomes for patients with any type of cancer. However, for certain patients with advanced or metastatic cancer, this type of testing may help to identify targeted treatments or clinical trials for which a patient may be eligible. In addition, current clinical guidelines recommend broad molecular profiling for certain patients with advanced cancers. Therefore, tumor testing using molecular panels, including expanded tumor profiling panels, may be considered medically necessary for patients with advanced or metastatic disease who meet the policy criteria.

There is not enough evidence that tumor profiling with expanded panels can improve health outcomes for patients that do not have advanced or metastatic (stage III or IV) cancers, when the testing is not associated with an FDA-approved targeted treatment, or when an individual has already decided not to pursue targeted therapy. Therefore, expanded tumor tissue panel testing is considered investigational for patients that do not meet the policy criteria.

There is not enough evidence that tumor profiling with whole genome, whole exome, or whole transcriptome sequencing can improve health outcomes for patients with cancer compared to more targeted testing. Clinical guidelines based on evidence do not currently recommend these types of tumor testing. Therefore, whole genome, whole exome, or whole transcriptome testing is considered investigational.

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CODES

Codes	Number	Description
		Targeted genomic sequence analysis panel, nonsmall cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/or absence of variants and associated
	0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)

Codes	Number	Description
		nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
	0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffinembedded tumor tissue
	0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
	0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
	0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
	0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
	0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
	0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by nextgeneration sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden
	0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
	0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s)
	0473U	Oncology (solid tumor), nextgeneration sequencing (NGS) of DNA from formalin-fixed paraffinembedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden

Codes	Number	Description
		Oncology (colorectal), nextgeneration sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with
	0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffinembedded (FFPE) tissue, nextgeneration sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection
	0523U	Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single-nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change
	0538U	Oncology (solid tumor), next-generation targeted sequencing analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant
	0543U	Oncology (solid tumor), next-generation sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for single-nucleotide variants, multi-nucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
	81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
	81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)

Codes	Number	Description
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81400	Molecular pathology procedure, Level 1
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81408	Molecular pathology procedure, Level 9
	81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or DNE and RNA analysis
	81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed, DNA analysis or combined DNA and RNA analysis
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
	81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
	81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *April 2019*

Regence

Medical Policy Manual Genetic Testing, Policy No. 84

Genetic Testing for Neurofibromatosis Type 1 or 2

Effective: December 1, 2024

Next Review: September 2025
Last Review: October 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

Neurofibromatoses (NF) are autosomal dominant genetic disorders associated with tumors of the peripheral and central nervous systems. The potential benefit of genetic testing for NF is to confirm the diagnosis in an individual with suspected NF who does not fulfill clinical diagnostic criteria or to determine future risk of NF in asymptomatic at-risk relatives.

MEDICAL POLICY CRITERIA

I. *NF1, NF2, and SPRED1* genetic testing for neurofibromatosis may be considered **medically necessary** when any of the following criteria are met:
   A. The diagnosis is clinically suspected due to signs and symptoms of the disease, but a clinical diagnosis has not been made; or
   B. In at-risk relatives with no signs of disease, when a first-, second-, or third-degree relative has been diagnosed with neurofibromatosis.

II. Genetic testing for neurofibromatosis type 1 or 2 is considered **not medically necessary** if a clinical diagnosis of the disorder has already been made.

III. Genetic testing for neurofibromatosis type 1 or 2 for all other indications 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

REQUIRED DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing
6. Medical records related to this genetic test
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BACKGROUND

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis Type 1 (NF1) is one of the most common dominantly inherited genetic disorders, with an incidence at birth of 1 in 3,000 individuals.

Clinical Characteristics

The clinical manifestations of NF1 show extreme variability, between unrelated individuals, among affected individuals within a single family, and within a single person at different times in life.

NF1 is characterized by multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. Segmental NF1 is limited to one area of the body. Many individuals with NF1 only develop cutaneous manifestations of the disease and Lisch nodules.

Cutaneous Manifestations

Café-au-lait macules occur in nearly all affected individuals, and intertriginous freckling occurs in almost 90%. Café-au-lait macules are common in the general population, but when more than six are present, NF1 should be suspected. Café-au-lait spots are often present at birth and increase in number during the first few years of life.

Neurofibromas

Neurofibromas are benign tumors of Schwann cells that affect virtually any nerve in the body and develop in most people with NF1. They are divided into cutaneous and plexiform types. Cutaneous neurofibromas, which develop in almost all people with NF1, are discrete, soft, sessile, or pedunculated tumors. Discrete cutaneous and subcutaneous neurofibromas are rare before late childhood. They may vary from a few to hundreds or thousands, and the rate of development may vary greatly from year to year. Cutaneous neurofibromas do not carry a risk of malignant transformation but may be a major cosmetic problem in adults.

Plexiform neurofibromas, which occur in about half of individuals with NF1, are more diffuse growths that may be locally invasive. They can be superficial or deep and, therefore, the extent cannot be determined by clinical examination alone; magnetic resonance imaging (MRI) is the method of choice for imaging plexiform neurofibromas.[1] Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1. They tend to develop and grow in childhood and adolescence and stabilize throughout adulthood. Plexiform neurofibromas can compress the spinal cord or airway and can transform into malignant peripheral nerve sheath tumors. Malignant peripheral nerve sheath tumors occur in approximately 10% of affected individuals.[1]

Central Nervous System Tumors

Optic gliomas, which can lead to blindness, develop in the first six years of life. Symptomatic optic gliomas usually present before six years of age with loss of visual acuity or proptosis, but they may not become symptomatic until later in childhood or adulthood.

While optic pathway gliomas are particularly associated with NF1, other central nervous system tumors occur at higher frequency in NF1, including astrocytomas and brainstem gliomas.

Other Findings

Other findings in NF1 include:

- Intellectual disability occurs at a frequency about twice that in the general population, and features of autism spectrum disorder occur in up to 30% of children with NF1.
- Musculoskeletal features include dysplasia of the long bones, most often the tibia and fibula, which is almost always unilateral. Generalized osteopenia is more common in people with NF1 and osteoporosis is more common and occurs at a younger age than in the general population.[1]
- Cardiovascular involvement includes the common occurrence of hypertension. Vasculopathies may involve major arteries or arteries of the heart or brain and can have serious or fatal consequences. Cardiac issues include valvar pulmonic stenosis, and congenital heart defects and hypertrophic cardiomyopathy may be especially frequent in individuals with *NF1* whole gene deletions.[1] Adults may develop pulmonary hypertension, often in association with parenchymal lung disease.
- Lisch nodules are innocuous hamartomas of the iris.

Diagnosis

Although the clinical manifestations of NF1 are extremely variable and some are age-dependent, the diagnosis can usually be made on clinical findings, and genetic testing is rarely needed.[1]

Clinical diagnostic criteria were developed by the National Institutes of Health (NIH) but were revised in 2021 by an international consensus guideline committee to account for phenotypic and genotypic features of NF1 and mosaic NF1.[2]

The diagnostic criteria for NF1 are met when an individual who does not have a parent diagnosed with NF1 and has two or more of the following features:[2]

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Freckling in the axillary or inguinal regions
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Optic pathway glioma
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging.
- A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone

A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cellsThe diagnostic criteria for NF1 are also met if the individual is a child of a parent who meets the diagnostic criteria specified in above merits a diagnosis of NF1 if one or more of the criteria above are present.

The diagnostic criteria for mosaic NF1 are met when an individual has any of the following features present:

- A pathogenic heterozygous NF1 variant with a variant allele fraction of significantly less than 50% in apparently normal tissue such as white blood cells AND one other NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for NF1)
- An identical pathogenic heterozygous NF1 variant in two anatomically independent affected tissues (in the absence of a pathogenic NF1 variant in unaffected tissue)
- A clearly segmental distribution of café-au-lait macules or cutaneous neurofibromas AND
    - Another NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for NF1) OR
    - Child fulfilling diagnostic criteria for NF1
- Only one NF1 diagnostic criterion from the following list
    - Freckling in the axillary and inguinal region
    - Optic pathway glioma
    - Two or more Lisch nodules or two or more choroidal abnormalities
    - Distinctive osseous lesion typical for NF1
    - Two or more neurofibromas or more plexiform neurofibroma AND a child fulfilling the criteria for NF1

Approximately half of the children with NF1 and no known family history of NF1 met previous diagnostic criteria for the clinical diagnosis by age one year. Almost all do by eight years of age because many features of NF1 increase in frequency with age. Children who have inherited NF1 from an affected parent can usually be diagnosed within the first year of life because the diagnosis requires one diagnostic clinical feature in addition to a family history of the disease.

This feature is usually multiple café-au-lait spots, present in infancy in more than 95% of individuals with NF1.[1]

Young children with multiple café-au-lait spots and no other features of NF1 who do not have a parent with signs of NF1 should be suspected of having NF1 and should be followed clinically as if they do.[3] A definitive diagnosis of NF1 can be made in most children by four years of age using the diagnostic criteria.[1]

Genetics

NF1 is caused by dominant loss-of-function variants in the *NF1* gene, which is a tumor suppressor gene located at chromosome 17q11.2 that encodes neurofibromin, a negative regulator of RAS activity. About half of affected individuals have it as a result of a de novo NF1 variant. Penetrance is virtually complete after childhood, however expressivity is highly variable.

The variants responsible for NF1 are very heterogeneous and include nonsense and missense single nucleotide changes, single base insertions or deletions, splicing variants (≈30% of cases), whole gene deletions (≈5% of cases), intragenic copy number variants, and other structural rearrangements. Several thousand pathogenic *NF1* variants have been identified; however, none is frequent.[1]

Management

Patient management guidelines for NF1 have been developed by the American Academy of Pediatrics, the National Society of Genetic Counselors, and other expert groups.[1, 4]

After an initial diagnosis of NF1, the extent of the disease should be established, with personal medical history and physical examination and particular attention to features of NF1, ophthalmologic evaluation including slit lamp examination of the irides, developmental assessment in children, and other studies as indicated on the basis of clinically apparent signs or symptoms.[1]

Surveillance recommendations for an individual with NF1 focus on regular annual visits for skin examination for new peripheral neurofibromas, signs of plexiform neurofibroma or progression of existing lesions, checks for hypertension, other studies (e.g., MRI) as indicated based on clinically apparent signs or symptoms, and monitoring of abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist. In children, recommendations include annual ophthalmologic examination in early childhood (less frequently in older children and adults) and regular developmental assessment.

Long-term care goals for individuals with NF1 are early detection and treatment of symptomatic complications.

It is recommended that radiotherapy is avoided because radiotherapy in individuals with NF1 may be associated with a high risk of developing a malignant peripheral nerve sheath tumor within the field of treatment.

LEGIUS SYNDROME

Clinical Characteristics

A few clinical syndromes may overlap clinically with NF1. In most cases, including Proteus syndrome, Noonan syndrome, McCune-Albright syndrome, and LEOPARD syndrome, patients will be missing key features or will have features of the other disorder. However, the Legius syndrome is a rare autosomal-dominant disorder characterized by multiple café-au-lait macules, intertriginous freckling, macrocephaly, lipomas, and potential attention-deficit/hyperactivity disorder. Misdiagnosis of Legius syndrome as NF1 might result in overtreatment and psychological burden on families about potential serious NF-related complications.

Diagnosis

The diagnostic criteria for Legius syndrome are met when an individual does not have a parent diagnosed with Legius syndrome if the following criteria are present:[2]

- Six or more café-au-lait macules bilaterally distributed and no other NF1-related diagnostic criteria except for axillary or inguinal freckling
- A heterozygous pathogenic variant in *SPRED1* with a variant allele fraction of 50$ in apparently normal tissue such as white blood cells

The diagnostic criteria for Legius syndrome are also met when the individual is a child of a parent who meets the diagnostic criteria specified above merits a diagnosis of Legius syndrome if one or more of the criteria above are present

The diagnostic criteria for mosaic Legius syndrome are met when an individual has any of the following features present:

- A heterozygous pathogenic *SPRED1* variant with a variant allele fraction of significantly less than 50% in apparently normal tissue such as white blood cells AND six or more café-au-lait macules
- An identical pathogenic heterozygous *SPRED1* variant in two independent affected tissues (in the absence of pathogenic *SPRED1* variant in unaffected tissue)
- A clearly segmental distribution of café-au-lait macules AND a child fulfilling the criteria for Legius syndrome

Genetics

Legius syndrome is associated with pathogenic loss-of-function variants in the *SPRED1* gene on chromosome 15, which is the only known gene associated with Legius syndrome.

Management

Legius syndrome typically follows a benign course and management generally focuses on treatment of manifestations and prevention of secondary complications.[5] Treatment of manifestations includes behavioral modification and/or pharmacologic therapy for those with attention-deficit/hyperactivity disorder; physical, speech, and occupational therapy for those with identified developmental delays; and individualized education plans for those with learning disorders.

NEUROFIBROMATOSIS TYPE 2

NF2 is also known as neurofibromatosis type 2 or NF2-related schwannomatosis, bilateral acoustic neurofibromatosis or central neurofibromatosis [6]. It is estimated that NF2occurs in 1 in 33,000 individuals.

Clinical Characteristics

NF2- is characterized by development of multiple benign nerve sheath tumors called schwannomas, particularly affecting the vestibular nerve [7]. Individuals with NF2 typically present with bilateral vestibular schwannomas and associated symptoms include tinnitus, hearing loss, and balance dysfunction.[8] The average age of onset is 18 to 24 years, and almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, ependymomas, meningiomas, and, rarely, astrocytomas. The most common ocular finding, which may be the first sign of NF2, is posterior subcapsular lens opacities; they rarely progress to visually significant cataracts.

Most patients with NF2 present with hearing loss, which is usually unilateral at onset. Hearing loss may be accompanied or preceded by tinnitus. Occasionally, features such as dizziness or imbalance are the first symptom.[9] A significant proportion of cases (20% to 30%) present with an intracranial meningioma, spinal, or cutaneous tumor. The presentation in pediatric populations may differ from adult populations, in that, in children, vestibular schwannomas may account for only 15% to 30% of initial symptoms.[9]

Diagnosis

The diagnostic criteria for NF2 were recently updated by an International Expert Consensus Panel[6]. This update incorporates advances in understanding genotypic and phenotypic features of NF2-related schwannomatosis, as well as other ways to differentiate between NF2 and schwannomatosis. NF2 does not require genetic testing if clinical criteria are met.

The diagnosis of NF2is usually based on clinical findings, with diagnosis depending on presence of one of the following diagnostic criteria:

- Bilateral vestibular schwannomas
- An identical NF2 pathogenic variant in at least 2 anatomically distinct NF2 related tumors including schwannoma, meningioma, and/or ependymoma. (Note: If the variant allele fraction in unaffected tissues is clearly <50%, the diagnosis would be mosaic NF2-related schwannomatosis.
- Either 2 Major Criteria below OR 1 Major Criteria AND 2 minor criteria
  - Major Criteria:
    - Unilateral vestibular schwannoma
    - First-degree non-sibling relative with NF2-related schwannomatosis
    - Two or more meningiomas
    - Germline NF2 pathogenic variant (Note: If the variant allele fraction is clearly <50, the diagnosis would be mosaic NF2-related schwannomatosis.
  - Minor Criteria:
    - Single meningioma
    - >1 type of tumor ependymoma, meningioma or schwannoma (each distinct tumor counts as one minor criterion)
    - Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person <40 years

Genetics

NF2 is inherited in an autosomal-dominant manner; approximately 50% of individuals have an affected parent, and the other 50% have NF2 as a result of a de novo variant.[8]

Between 25% and 33% of individuals with NF2 caused by a de novo variant have somatic mosaicism. Variant detection rates are lower in simplex cases and in an individual in the first generation of a family to have NF2 because they are more likely to have somatic mosaicism. Somatic mosaicism can make clinical recognition of NF2 difficult and results in lower variant detection rates. Clinical recognition of NF2 in these patients may be more difficult because these individuals may not have bilateral vestibular schwannomas. Variant detection rates may also be lower because molecular genetic test results may be normal in unaffected tissue (e.g., lymphocytes), and molecular testing of tumor tissue may be necessary to establish the presence of somatic mosaicism.[1]

Evaluation of At-Risk Relatives

Early identification of relatives who have inherited the family-specific *NF2* variant allows for appropriate screening using MRI for neuroimaging and audiologic evaluation, which result in earlier detection and improved outcomes.[8] Identification of at-risk relatives who do not have the family-specific *NF2* variant eliminates the need for surveillance.

SCHWANNOMATOSIS

Schwannomatosis (also referred to as gene-schwannomatosis)[6] is a rare condition defined as multiple schwannomas without vestibular schwannomas that are diagnostic of NF2.[8] Broadly, schwannomatosis encompasses four subcategories including *SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, and schwannomatosis-NOS (not otherwise specified)[6]. Individuals with schwannomatosis may develop intracranial, spinal nerve root, or peripheral nerve tumors. Familial cases are inherited in an autosomal-dominant manner, with highly variable expressivity and incomplete penetrance. Clinically, schwannomatosis is distinct from NF1 and NF2, although some individuals eventually fulfill diagnostic criteria for NF2. *SMARCB1* or *LZTR1* variants account for approximately 70-80% of familial schwannomatosis but only approximately 30% of sporadic cases[10].

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for NF are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[11] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used

terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The evaluation of a genetic test focuses on three main principles:

1. Analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent);
2. Clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and
3. Clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

This evidence review focuses on the clinical validity and utility of genetic testing for neurofibromatosis.

CLINICAL VALIDITY

Neurofibromatosis Type 1

Detecting variants in the *NF1* gene is challenging because of the gene’s large size, the lack of variant hotspots, and the wide variety of possible lesions.

A multistep variant detection protocol has identified more than 95% of *NF1* pathogenic variants in individuals who fulfill NIH diagnostic criteria.[1] The protocol involves sequencing of both messenger RNA (complementary DNA [cDNA]) and genomic DNA, and testing for whole *NF1* deletions (e.g., by multiplex ligation-dependent probe amplification [MLPA]) because whole gene deletions cannot be detected by sequencing. Due to the wide variety and rarity of individual pathogenic variants in NF1, sequencing of cDNA increases the detection rate of variants from approximately 61% with genomic DNA sequence analysis alone[12] to greater than 95% with sequencing for both cDNA and genomic DNA and testing for whole gene deletions.

Table 1 summarizes several studies conducted on various populations, using various testing techniques to detect NF1 and SPRED variants. Below is a detailed description of two of the studies with high variant detection rates.

Sabbagh (2013) reported on a comprehensive analysis of constitutional *NF1* variants in unrelated, well-phenotyped index cases with typical clinical features of NF1 who enrolled in a French clinical research program.[13] The 565 families in this study (n=1,697 individuals) were enrolled between 2002 and 2005; 1,083 fulfilled NIH diagnostic criteria for NF1. A comprehensive *NF1* variant screening (sequencing of both cDNA and genomic DNA, as well as large deletion testing by MLPA) was performed in 565 individuals, one from each family, who had a sporadic variant or who represented the familial index case. A *NF1* variant was identified in 546, for a variant detection rate of 97%. A total of 507 alterations were identified at the cDNA and genomic DNA levels. Among these 507 alterations, 487 were identified using only the genomic DNA sequencing approach, and 505 were identified using the single cDNA sequencing approach. MLPA detected 12 deletions or duplications that would not have been detected by sequencing. No variant was detected in 19 (3.4%) patients, two of whom had a

SPRED1 variant, which is frequently confused with NF; the remainder might have been due to an unknown variant of the *NF1* locus.

Valero (2011) developed a method for detecting *NF1* variants by combining an RNA-based cDNA-polymerase chain reaction variant detection method and denaturing high-performance liquid chromatography with MLPA.[14] Their protocol was validated in a cohort of 56 patients with NF1 (46 sporadic cases, 10 familial cases) who fulfilled NIH diagnostic criteria. A variant was identified in 53 cases (95% sensitivity), involving 47 different variants, of which 23 were novel. After validation, the authors implemented the protocol as a routine test and subsequently reported the spectrum of *NF1* variants identified in 93 patients from a cohort of 105. The spectrum included a wide variety of variants (nonsense, small deletions or insertions and duplications, splice defects, complete gene deletions, missense, single exon deletions and duplications, and a multi-exon deletion), confirming the heterogeneity of the *NF1* gene variants that can cause NF1.

Table 1. Diagnostic Performance of Genetic Testing for Suspected NF1

Study	N	Population	Test Description	Detection Results
Spurlock (2009)[15]	85	Patients with NF1-like phenotypes (mild), with negative *NF1* testing	PCR sequencing of *SPRED1*	6 *SPRED* variants
Valero (2011)[14]	56	46 sporadic cases, 10 familial cases fulfilling NIH diagnostic criteria	Method combining RNA-based cDNA-PCR variant detection and DHPLC with MLPA	95% (53/56) patients had *NF1* variant
Sabbagh (2013)[13]	565	Unrelated, well-phenotyped index cases with typical clinical features of NF1	*NF1* variant screening (sequencing of both cDNA and genomic DNA, as well as large deletion testing by MLPA)	97% (546/565) patients had *NF1* variant
Zhu (2016)[16]	32	NF1 patients (plus 120 population match controls)	PCR sequencing of *NF1* gene, followed by MLPA	93.8% (30/32) patients had *NF1* variant
Zhang (2015)[17]	109	Patients with NF1-like phenotypes	Sanger sequencing, MLPA, and cDNA of *NF1,* in sequence; followed by Sanger sequencing and MLPA of *SPRED1* if all others negative (n=14)	*NF1* variant in: • 89% (89/100) of NF1 probands 93% (70/75) of patients met NIH criteria for NF1
Bianchessi (2015)[18]	293	Patients meeting NIH NF1 criteria	MLPA, aCGH, DHPLC, and Sanger sequencing, in sequence, of *NF1*	70% had *NF1* variant
	150	Patients with NF1-like symptoms without meeting NIH criteria	MLPA, aCGH, DHPLC, and Sanger sequencing, in sequence, of *NF1*	22% had *NF1* variant
	61	Patients meeting NIH criteria	MLPA followed by RNA sequencing of *NF1*	87% had *NF1* variant
	9	Patients with NF1-like symptoms without meeting NIH criteria	MLPA followed by RNA sequencing of *NF1*	33.3% had *NF1* variant

Study	N	Population	Test Description	Detection Results
Cali (2017)[19]	79	Patients in Italy with suspected or clinically diagnosed NF1	NGS using Ion Torrent PGM Platform followed by MLPA and calculation of mosaicism percentage using Sanger sequencing	73 variants in 79 NF1 patients
Giugliano (2019)[20]	281	Child patients referred and evaluated using NIH criteria	*NF1* and *SPRED1* analyzed at cDNA level, MLPA, PCR sequencing, validated by Sanger sequencing	85.1% (239/281) causative variant: 73.3% *NF1*, 2.8% *SPRED1*, 8.9% different gene
Angelova-Toshkina (2022)[21]	75	Children with suspected or clinically diagnosed NF1	Retrospective chart review comparing 1988 NIH diagnostic criteria and revised 2021 diagnostic criteria. Genetic testing methods were not described.	59% met 1988 NIH criteria and 75% met revised 2021 criteria. Additional patients met revised criteria due to a pathogenic NF1 variant being found.

aCGH: array comparative genomic hybridization; cDNA: complementary DNA; DHPLC: denaturing high-pressure liquid chromatography; MLPA: multiplex ligation-dependent probe amplification; NF1: neurofibromatosis type 1; NGS: next-generation sequencing; NIH: National Institutes of Health; PCR: polymerase chain reaction.

Genotype-Phenotype Correlations

NF1 is characterized by extreme clinical variability between unrelated individuals, among affected individuals within a single family, and even within a single person with NF1 at different times in life. Two clear correlations have been observed between certain NF1 alleles and consistent clinical phenotypes[1]:

1. A deletion of the entire *NF1* gene is associated with large numbers and early appearance of cutaneous neurofibromas, more frequent and severe cognitive abnormalities, somatic overgrowth, large hands and feet, and dysmorphic facial features.[1, 22, 23]
2. A three-base pair in-frame deletion of exon 17 is associated with typical pigmentary features of NF1, but no cutaneous or surface plexiform neurofibromas.[24]

Also, missense variants of *NF1* p.Arg1809 have been associated with typical NF1 findings of multiple café-au-lait macules and axillary freckling but the reduced frequency of NF1-associated benign or malignant tumors.[25, 26] In a cohort of 136 patients, 26.2% of patients had features of Noonan syndrome (i.e., short stature, pulmonic stenosis) present in excess.

In the Sabbagh (2013) study described above, authors evaluated genotype-phenotype correlations for a subset of patients.[13] This subset, which included 439 patients harboring a truncating (n=368), in-frame splicing (n=36), or missense (n=35) *NF1* variant, was evaluated to assess the contribution of intragenic NF1 variants (vs large gene deletions) to the variable expressivity of NF1. Their findings suggested a tendency for truncating variants to be associated with a greater incidence of Lisch nodules and a larger number of café-au-lait spots compared with missense variants.

However, other studies reported no associations between variant type and phenotype.[16, 27, 28]

Legius Syndrome

Pasmant (2009) described a cohort of 61 index cases meeting the NIH clinical diagnosis of NF1 but without a *NF1* variant detectable who were screened for germline loss-of-function variants in the *SPRED1* gene, located on 15q13.2.[29] *SPRED1* variants were detected in 5% of patients with NF1 features, which were characterized by café-au-lait macules and axillary and groin freckling but not neurofibromas and Lisch nodules. The authors characterized a new syndrome (Legius syndrome) based on the presence of a heterozygous *SPRED1* variant.

Messiaen (2009) described a separate cohort of 22 NF1 variant-negative probands who met NIH clinical criteria for NF1 with a *SPRED1* loss-of-function variant and participated in genotype-phenotype testing with their families.[30] Forty patients were found to be *SPRED1* variant-positive, 20 (50%, 95% confidence interval [CI] 34% to 66%) met NIH clinical criteria for NF1, although none had cutaneous or plexiform neurofibromas, typical NF osseous lesions, or symptomatic optic pathway gliomas. The authors also reported on an anonymous cohort of 1,318 samples received at a university genomics laboratory for NF1 genetic testing from 2003 to 2007 with a phenotypic checklist of NF-related symptoms filled out by the referring physician. In the anonymous cohort, 26 pathogenic *SPRED1* variants in 33 probands were identified. Of 1,086 patients fulfilling NIH criteria for a clinical diagnosis of NF1, a *SPRED1* variant was identified in 21 (1.9%, 95% CI 1.2% to 2.9%).

Neurofibromatosis Type 2

At least 200 different *NF2* variants have been described, most of which are point mutations. Large deletions of *NF2* represent 10% to 15% of *NF2* variants. When variant scanning is combined with deletion and duplication analysis of single exons, the variant detection rate approaches 72% in simplex cases and exceeds 92% for familial cases.[8] Wallace et al (2004) conducted *NF2* variant scanning in 271 patient samples (245 lymphocyte DNA, 26 schwannoma DNA).[31] The overall *NF2* variant detection rate was 88% among familial cases and 59% among sporadic cases. Evans et al (2007) analyzed a database of 460 families with *NF2* and 704 affected individuals for mosaicism and transmission risks to offspring.[32] The authors identified a variant in 84 (91%) of 92 second-generation families, with a sensitivity of greater than 90%. Other studies have reported lower variant detection rates, which likely reflects the inclusion of more mildly affected individuals with somatic mosaicism.[8]

Genotype-Phenotype Correlations

Intrafamilial variability is much lower than interfamilial variability, and the phenotypic expression and natural history of the disease are similar within families with multiple members with NF2.[33]

Frameshift or nonsense variants cause truncated protein expression, which has been associated with more severe manifestations of NF2.[33] Missense or in-frame deletions have been associated with milder manifestations of the disease. Large deletions of *NF2* have been associated with a mild phenotype.

Selvanathan (2010) reported on genotype-phenotype correlations in 268 patients with an *NF2* variant.[34] Variants that resulted in a truncated protein were associated with statistically significant younger age at diagnosis, higher prevalence and proportion of meningiomas, spinal tumors and tumors of cranial nerves other than VIII, vestibular schwannomas at a younger

age, and more cutaneous tumors. Certain variants, particularly those in exons 14 and 15, were associated with milder disease and fewer meningiomas.

Section Summary

Studies conducted among multiple cohorts of patients meeting diagnostic criteria for NF1 reported a high sensitivity of multistep variant testing protocol in identifying pathogenic *NF1* variants. On the other hand, studies conducted among familial and sporadic NF2 cases reported a variant detection rate exceeding 90% for familial cases and more than 70% in simplex cases.

CLINICAL UTILITY

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Individuals with Suspected NF

In many cases of suspected NF1, the diagnosis can be made clinically based on diagnostic criteria, which are both highly sensitive and specific, except in young children. However, there are suspected cases in children and adults that do not meet the diagnostic criteria. Given the well-established clinical management criteria, these patients benefit from genetic testing to confirm the diagnosis and to direct clinical management according to accepted guideline recommendations. Grossen (2022) has reported in their systematic review cases of pediatric NF that have been diagnosed by genetic testing.[35] Finding from 15 papers were included that identified 16 clinics that treated more than 2000 patients worldwide.

For NF2, affected individuals may have little in the way of external manifestations, and the onset of symptoms may be due to tumors other than vestibular schwannomas, particularly in children. Early identification of patients with NF2 can lead to earlier intervention and improved outcomes, and direct clinical management according to accepted guideline recommendations.

Section Summary

Currently, there is no direct evidence from studies demonstrating that genetic testing for NF1 and NF2 results in improved patient outcomes (e.g., survival or quality of life) among suspected cases. Suspected cases of NF1 or NF2 among children and adults who do not meet the diagnostic criteria might benefit from genetic testing to confirm the diagnosis and receive treatment, which might result in improved outcomes.

At-Risk Relatives

Similar to the case for suspected NF1, a clinical diagnosis can usually be made in an at-risk relative of a proband because one of the diagnostic criteria for diagnosis is having a first-degree relative with NF1 and, therefore, only one other clinical sign is necessary to confirm the diagnosis. Cases with at-risk relatives who do not fulfill the diagnostic criteria may benefit from genetic testing to direct clinical management according to accepted guideline recommendations.

Testing for NF2 may be useful to identify at-risk relatives of patients with an established

diagnosis of NF2, allowing for appropriate surveillance, earlier detection, and treatment of disease manifestations, and avoiding unnecessary surveillance in an individual who does not have the family-specific variant. Unlike NF1, the age of symptom onset for NF2 is relatively uniform within families. Therefore, it is usually not necessary to offer testing or surveillance to asymptomatic parents of an index case. However, testing of at-risk asymptomatic individuals younger than 18 years of age may help avoid unnecessary procedures in a child who has not inherited the variant.[8]

Section Summary

Currently, there is no direct evidence from studies demonstrating that genetic testing for NF1 and NF2 result in improved outcomes (e.g., survival or quality of life) among asymptomatic individuals with a close relative(s) with an NF diagnosis. However, genetic testing of at-risk asymptomatic individuals not fulfilling clinical diagnostic criteria might benefit through diagnosis, clinical management if needed and in avoiding unnecessary procedures in case of individuals who have not inherited the variant.

SUMMARY OF EVIDENCE

For individuals who have suspected NF who receive genetic testing for NF, the evidence includes clinical validation studies of a multistep diagnostic protocol and genotype-phenotype correlation studies. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. A multistep variant testing protocol identifies more than 95% of pathogenic variants in *NF1*; for NF2, the variant detection rate approaches more than 70% in simplex cases and exceeds 90% for familial cases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic, with a close relative(s) with an NF diagnosis, who receive genetic testing for NF, there is no direct evidence. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. For individuals with a known pathogenic variant in the family, testing of at-risk relatives will confirm or exclude the variant with high certainty. While direct evidence on the clinical utility of genetic testing for NF is lacking, a definitive diagnosis resulting from genetic testing can direct patient care according to established clinical management guidelines, including referrals to the proper specialists, treatment of manifestations, and surveillance. Testing of at-risk relatives will lead to initiation or avoidance of management and/or surveillance. Early surveillance may be particularly important for patients with NF2 because early identification of internal lesions by imaging is expected to improve outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics (2019) published diagnostic and health supervision guidelines for children with neurofibromatosis type 1.[36] The guidance makes the following statements related to genetic testing:

> *NF1* genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with

cafe-au-lait macules, NF1 genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue.

Knowledge of the *NF1* [pathogenic sequence variant] can enable testing of other family members and prenatal diagnostic testing.

The guidance includes the following summary regarding genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity.

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network's consensus guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.1.2025) addressed the association between NF1 and risk of breast and other cancers.[37] According to the guidelines, there is evidence that individuals with a pathogenic variant in *NF1* have an increased risk of breast cancer, malignant peripheral nerve sheath tumors, and gastrointestinal stromal tumors (GIST). The guidelines recommend annual screening mammogram beginning at age 30 years in people with *NF1* variants. Additionally, it is recommended to consider screening breast MRI with and without contrast between the ages of 30-50 years, with the caveat that there is no increased breast cancer risk after age 50 years, and neurofibromas may lead to false-positive breast MRI. The guidelines also recommend a referral to a NF1 specialist.

SUMMARY

There is enough research to show that genetic testing for neurofibromatosis (NF) can be useful for confirming the diagnosis in an individual with suspected NF who does not fulfill clinical diagnostic criteria. There are specific surveillance recommendations for individuals with NF, and clinical guidelines recommend genetic testing when there are signs of the NF type 1, but they are not enough to make a clinical diagnosis. Therefore, *NF1*, *NF2*, and *SPRED1* genetic testing for neurofibromatosis may be considered medically necessary when the diagnosis is suspected due to signs of the disease, but a clinical diagnosis has not been made. If a clinical diagnosis has already been made, genetic testing results are not necessary for patient management. Therefore, genetic testing for NF type 1 or 2 is considered not medically necessary for patients that already have a clinical diagnosis of the disorder.

There is enough research to show that testing for NF may be useful to identify asymptomatic at-risk relatives of patients with an established diagnosis of NF, allowing for appropriate surveillance, earlier detection, and treatment of disease manifestations, and avoiding unnecessary surveillance in an individual who does not have a family-specific variant.

Therefore, *NF1, NF2, and SPRED1* genetic testing for neurofibromatosis in at-risk relatives, with no signs of disease, may be considered medically necessary.

There is not enough research to show that genetic testing for neurofibromatosis improves health outcomes for patients who do not meet the policy criteria. Therefore, genetic testing for neurofibromatosis for other indications is considered investigational.

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CODES

Codes	Number	Description
CPT	81405	Molecular pathology procedure, Level 6 – which includes *NF2* (neurofibromin 2 [merlin]) (eg, neurofibromatosis, type 2), duplication/deletion analysis and *SPRED1* (sprouty-related, EVH1 domain containing 1) (eg, Legius syndrome), full gene sequence
	81406	Molecular pathology procedure, Level 7 – which includes *NF2* (neurofibromin 2 [merlin]) (eg, neurofibromatosis, type 2), full gene sequence.
	81408	Molecular pathology procedure, Level 9 – which includes I (neurofibromin 1) (eg, neurofibromatosis, type 1), full gene sequence.
HCPCS	None	

Date of Origin: *September 2019*

Regence

Medical Policy Manual Genetic Testing, Policy No. 88

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

Effective: December 1, 2024

Next Review: March 2025
Last Review: August 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

Measurable residual disease (MRD), also known as minimal residual disease, refers to residual clonal cells in blood or bone marrow following treatment for hematologic malignancies such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). MRD is typically assessed by flow cytometry or polymerase chain reaction but can also be assessed using the clonoSEQ® test, which uses next-generation sequencing (NGS).

MEDICAL POLICY CRITERIA

Notes: ClonoSEQ® testing generally includes two components: an initial clonoSEQ® ID test followed by clonoSEQ® MRD testing. These are reviewed together as clonoSEQ® testing.

I. ClonoSEQ® B-cell testing to detect measurable residual disease (MRD) may be considered **medically necessary** for individuals with any of the following:

   A. B-cell acute lymphoblastic leukemia (B-ALL)

   B. Chronic lymphocytic leukemia (CLL)

C. Multiple myeloma

II. ClonoSEQ® T-cell testing and ClonoSEQ® testing for all other indications, including but not limited to diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma, is considered **investigational**.

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

POLICY GUIDELINES

B-ALL and B-cell lymphoblastic lymphoma are generally considered clinically indistinct, and B-ALL is intended to encompass both entities in this 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.

- Name of the test and performing laboratory
- Relevant billing codes
- Brief description of how the test results will guide clinical decisions that would not otherwise be made in the absence of testing
- Medical records related to this test:
  - Diagnosis
  - History and physical exam
  - Date of blood draw for test
  - Conventional testing and outcomes

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59

BACKGROUND

HEMATOLOGIC DISEASE

There are three main types of hematologic malignancies: lymphomas, leukemias, and myelomas. Lymphoma begins in lymph cells of the immune system, which originate in the bone marrow and collect in lymph nodes and other tissues. Leukemia is caused by the overproduction of abnormal white blood cells in the bone marrow, which leads to a decrease in the production of red blood cells and plasma cells. The most common forms of leukemia are acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Multiple myeloma (MM), also called plasma myeloma, is a malignancy of plasma cells in the bone marrow. The present evidence review will address B-cell ALL (B-ALL), CLL, MM, diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). As B-ALL and B-cell lymphoblastic lymphoma are generally considered clinically indistinct, reference to B-cell ALL is intended to encompass both entities.

B-cell Acute Lymphoblastic Leukemia

B-ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years and 20% of acute leukemias in adults. Remission of disease is now typically achieved with pediatric chemotherapy regimens in 98% of children with ALL, with up to 85% long-term survival rates. The prognosis after the first relapse is related to the length of the original remission. For example, the leukemia-free survival rate is 40% to 50% for children whose first remission was longer than three years compared with 10% to 15% for those who relapse less than three years after treatment. Between 60% and 80% of adults with ALL can be expected to achieve a complete response after induction chemotherapy; however, only 35% to 40% can be expected to survive two years. “Poor prognosis” genetic abnormalities such as the Philadelphia chromosome (translocation of chromosomes 9 and 22) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis count of greater than 30,000/µL (B-cell lineage) or greater than 100,000/µL (T-cell lineage) at presentation.

Induction therapy aims to reduce the leukemic cell population below the cytological detection limit (about 10^{10} cells or one malignant cell for every 20 to 100 normal cells), but it is believed that remaining leukemic cells that are below the level of clinical and conventional morphologic detection lead to relapse if no further treatment were given. Consolidation and intensification therapy is intended to eradicate this residual disease. The type of post-remission therapy (chemotherapy or autologous or allogeneic hematopoietic cell transplantation [HCT]) depends on the expected rate of relapse and patient characteristics such as age and comorbidities. Bone marrow is examined every three to six months for a minimum of two years to determine clinical relapse. If a patient is in complete response for seven to eight years, they are considered cured. Most children and up to one-half of adults will have prolonged disease-free survival, but up to 20% of adults will have a resistant disease, and a majority of adults and some children will eventually relapse and die of leukemia.

Chronic Lymphocytic Leukemia

CLL is the most common leukemia in Western countries, representing approximately 25% to 30% of all leukemias. CLL is characterized by progressive accumulation of functionally incompetent monoclonal B lymphocytes. It occurs primarily in older adults, but occurrence in younger adults is not unusual. The incidence of CLL increases with age with a median age at diagnosis of 70 years. Malignant cells in CLL and the non-Hodgkin lymphoma small lymphocytic lymphoma have identical pathologic and immunophenotypic features. The term CLL is used when the disease manifests primarily in the blood, whereas the term small lymphocytic lymphoma is used for primarily nodal manifestation.

Not all patients with CLL will require treatment at the time of diagnosis. Median survival for patients with asymptomatic CLL is 10 years, and some patients with early stage CLL may be asymptomatic without treatment for decades. Importantly, randomized trials evaluating immediate versus delayed treatment strategies have found no improvement in long-term survival with early treatment, survival in some patients will not be different from the normal population, and with the exception of HCT, there is currently no cure for CLL. Therefore, the standard of care for patients with early stage asymptomatic CLL is observation rather than immediate treatment.

Treatment is indicated for patients with disease-related complications, termed "active disease"

by the International Workshop on Chronic Lymphocytic Leukemia.[1] Criteria for active disease include one or more of the following: progressive marrow failure, splenomegaly, lymphadenopathy, progressive lymphocytosis, autoimmune anemia and/or thrombocytopenia, extranodal involvement (e.g., skin, kidney, lung, spine), and constitutional symptoms such as weight loss, fatigue, fever, and night sweats. The goal of therapy is to ameliorate symptoms and improve progression-free survival (PFS) and overall survival (OS). The choice of therapy is based on patient and tumor characteristics and goals of therapy. Most patients will have an initial complete or partial response to treatment but will eventually relapse. Relapse may be asymptomatic but is monitored closely for progression to active disease.

Multiple Myeloma

MM represents approximately 17% of all hematologic cancers, largely occurring in patients over 60 years of age. It is characterized by the proliferation of plasma cells in the bone marrow producing a monoclonal immunoglobulin. The clonal plasma cells frequently result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures; additional complications can include hypercalcemia, renal insufficiency, anemia, and infections.

MM is treatable but is typically incurable, with treatment reserved for patients with symptomatic disease (usually progressive). Without effective therapy, symptomatic patients die within a median of six months. Asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage. In some patients, an asymptomatic but more advanced premalignant stage is referred to as smoldering MM. Patients with smoldering MM may remain stable for prolonged periods, with an overall risk of disease progression from smoldering to symptomatic MM of 10% per year for the first five years, approximately 3% per year for the next five years, and 1% for the next 10 years.

Prognosis and treatment for MM depend on risk stratification based on underlying genetic variants, age, performance status, comorbidities, stage, and response to therapy. Patients are assessed to determine eligibility for HCT because HCT has been shown to prolong both event-free and OS compared with chemotherapy alone. The response to treatment is usually determined by a morphologic evaluation and visual quantitation of the percentage of plasma cells in the bone marrow. Most patients with MM will have an initial response to treatment, but will ultimately progress with serial relapse, and will be treated with most available agents at some point during their disease course. Other patients will not respond to initial treatment (refractory disease).

Response to treatment is categorized into clinical response, MRD response, and imaging response. A complete (clinical) response is defined by the International Myeloma Working Group and the National Comprehensive Cancer Network.[2, 3] MRD response is defined as a complete response plus the absence of clonal plasma cells by next-generation flow cytometry (NGF) or next-generation sequencing (NGS) at a minimum sensitivity of 1 in 10^{-5} nucleated cells in bone marrow, and there is a category of “imaging plus MRD-negative” in which patients are determined to have a complete response, be MRD negative in the bone marrow, and have also achieved positron emission tomography (PET)/computed tomography (CT)-negativity. "Sustained MRD negativity” is achieved when both imaging and MRD are negative in assessments that are a minimum of one year apart. It is not known whether patients with sustained MRD negative status can be considered cured. MRD measured by NGS is currently used as a surrogate outcome measure in clinical trials, and there are ongoing trials to test the

effectiveness of using NGS-MRD to guide therapy.[4]

Large Diffuse B-Cell Lymphoma

Lymphoma refers to any cancer that starts in the lymph system and includes 2 broad categories of disease, Hodgkin lymphoma and non-Hodgkin lymphoma.[5] There are multiple forms of non-Hodgkin lymphoma with B-cell malignancies comprising 85% of cases.[6] Of the B-cell lymphomas, DLBCL accounts for approximately one-third of cases. DLBCL occurs most commonly in older patients with the mean age of diagnosis of approximately 60 years of age. Although aggressive, DLBCL generally responds well to treatment, and 75% of patients have no signs of disease after initial treatment. Historically, PET and CT imaging have been used to assess lymphoma tumor burden and disease response; however, techniques such as flow cytometry, polymerase chain reaction (PCR)-based methods, and NGS-based techniques are being increasingly used.[7]

Mantle Cell Lymphoma

A small percentage of B-cell lymphomas (about 5%) are categorized as MCL.[6] Similar to DLBCL, it occurs most commonly in patients over 60 years of age and tends to be an aggressive lymphoma; however, the response to treatment has traditionally been poor. Most patients present with advanced stage disease, and treatment is dependent on stage and eligibility for HSCT. Historically, PET and CT imaging have been used to assess lymphoma tumor burden and disease response; however, techniques such as flow cytometry, PCR-based methods, and NGS-based techniques are being increasingly used.[7]

MEASURABLE RESIDUAL DISEASE

Relapse is believed to be due to residual clonal cells that remain following "complete response” after induction therapy but are below the limits of detection using conventional morphologic assessment. Residual clonal cells that can be detected in the bone marrow or blood are referred to as measurable residual disease (MRD), also known as minimal residual disease. MRD assessment is typically performed by flow cytometry or PCR with primers for common variants. Flow cytometry or next generation flow cytometry evaluates blasts based on the expression of characteristic antigens, while PCR assesses specific chimeric fusion gene transcripts, gene variants, and overexpressed genes. PCR is sensitive for specific targets, but clonal evolution may occur between diagnosis, treatment, remission, and relapse that can affect the detection of MRD. NGS has 10- to 100-fold greater sensitivity for detecting clonal cells, depending on the amount of DNA in the sample (see Table 1) and does not require patient-specific primers. For both PCR and NGS a baseline sample at the time of high disease load is needed to identify tumor-specific sequences. MRD with NGS is frequently used as a surrogate measure of treatment efficacy in drug development.

It is proposed that by using a highly sensitive and sequential MRD surveillance strategy, one could expect better outcomes when therapy is guided by molecular markers rather than hematologic relapse. However, some patients may have hematologic relapse despite no MRD, while others do not relapse despite residual mutation-bearing cells. Age-related clonal hematopoiesis, characterized by somatic variants in leukemia-associated genes with no associated hematologic disease, further complicates the assessment of MRD. One available test, clonoSEQ®, uses both PCR and NGS to detect clonal DNA in blood and bone marrow. ClonoSEQ® Clonality (ID) PCR assessment is performed when there is a high disease load (e.g., initial diagnosis or relapse) to identify dominant or “trackable” sequences associated with

the malignant clone. NGS is then used to monitor the presence and level of the associated sequences in follow-up samples. As shown in Table 1, NGS can detect clonal cells with greater sensitivity than either flow cytometry or PCR, although next-generation flow techniques have reached a detection limit of 1 in 10^{-5} cells, which is equal to PCR and approaches the limit of detection of NGS (see Table 1).

Table 1. Sensitivity of Methods for Detecting Measurable Residual Disease

Technique	Sensitivity	Detection limit of blasts per 100,000 Nucleated Cells
Microscopy (complete response)		50,000
Multiparameter flow cytometry	10^{-4}	10
Next-generation flow cytometry	10^{-5}	1.0
Polymerase chain reaction	10^{-5}	1.0
Quantitative next-generation sequencing	10^{-5}	1.0
Next-generation sequencing	10^{-6}	0.1

REGULATORY STATUS

The clonoSEQ® Minimal Residual Disease Test is offered by Adaptive Biotechnologies. clonoSEQ® was previously marketed as clonoSIGHT™ (Sequenta), which was acquired by Adaptive Biotechnologies in 2015. clonoSIGHT™ was a commercialized version of the LymphoSIGHT platform by Sequenta for clinical use in MRD detection in lymphoid cancers. In September 2018, clonoSEQ® B-cell testing received marketing clearance from the U.S. Food and Drug Administration (FDA) through the de novo classification process to detect MRD in patients with B-ALL or MM. In 2020, clonoSEQ® B-cell testing received marketing clearance from the FDA to detect MRD in patients with CLL.

EVIDENCE SUMMARY

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Review of the literature focused on identifying evidence related to clinical validity and clinical utility, particularly whether the tests can be used to improve treatment planning compared with the standard of care, and whether their use results in improved health outcomes. For the evaluation of the clinical validity of the clonoSEQ® test, studies that met the following eligibility criteria were considered:

- Included a suitable reference standard (PFS or OS)
- Evaluated outcomes at different levels of MRD
- Comparative trials that evaluated health outcomes when therapy was guided by NGS

assessment of MRD.

CLONOSEQ® TO DETECT MEASURABLE RESIDUAL DISEASE IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Clinical Validity

Table 2 describes studies that have evaluated prognosis based on MRD levels detected by FC and clonoSEQ®. Overall, higher levels of MRD are associated with a worse prognosis. In an analysis of samples from two multicenter studies, Pulsipher (2022) compared FC at a threshold of 10^{-4} with clonoSEQ® at thresholds of 10^{-4}, 10^{-5}, 10^{-6}, and any detectable level (approximately 10^{-7}) in pediatric and young adult patients with B-ALL who received tisagenlecleucel.[8] In 95 patients with both NGS and FC results, 18% of samples were MRD-positive with FC compared with 22%, 29%, 33%, and 41% with NGS at cutoff values of 10^{-4}, 10^{-5}, 10^{-6}, and any detectable level, respectively. No samples were positive by FC and negative by NGS. Relapse before 12 months occurred without MRD detection in 50% of patients by FC, 31% by clonoSEQ® at 10^{-6}, and 0% of those with clonoSEQ® below the 10^{-6} level. Limitations of the study included limited follow-up and inclusion of only patients treated with tisagenlecleucel. Additional limitations are noted in Table 3.

Liang (2023) reported results of a study of the prognostic performance of the clonoSEQ® assay in 111 adult participants with B-ALL or T-cell ALL (T-ALL) who underwent allogeneic HCT at Stanford University or Oregon Health & Science University between 2014 and 2021.[9] Participants were followed for leukemia relapse and/or death for up to two years after HCT. Relapse was defined as morphologic or clinical. The MRD samples came from either peripheral blood or bone marrow. The median age of the patients was 44 years (range, 19 to 70 years), 62 (56%) were male, and 95 (86%) had B-ALL. Pre-HCT MRD was significantly associated with relapse in multivariable analysis, however detectable post-HCT MRD was the strongest predictor (HR 4.60, 95% CI 3.01 to 7.02).

Table 2. Characteristics of Prognostic Studies Assessing ClonoSEQ® for MRD in B-ALL

Study	Study Population	Design[a]	Reference Standard	Threshold for PIT	Follow-up
Liang (2023)[9]	Blood and bone marrow samples from adults with B-ALL (86%) or T-cell ALL undergoing HCT	Retrospective from banked samples; assessed by NGS	Relapse	B-ALL: a detectable IgH clonotype T-ALL: a detectable TCRβ or TCRγ clonotype Stratified as undetectable (0), low (<10–4), high (≥10–4 to ≤10–3), or very high (>10–3)	Up to two years
Pulsipher (2022)[8]	Blood and bone marrow samples from 143 patients in tisagenlecleucel trials	Retrospective from banked samples with comparison of FC and clonoSEQ®	Relapse	FC at 10^{-4}; NGS at 10^{-4} or less	38.4 months

B-ALL: B-cell acute lymphoblastic leukemia; FC: flow cytometry; MRD: measurable residual disease; PIT: positive index test, T-ALL: B-cell acute lymphoblastic leukemia.

Table 3. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Complete-ness[e]	Statistical[f]
Liang (2023)[9]	2. Selection based on availability of samples from prior studies	1. Blinding was not described				
Pulsipher (2022)[8]	2. Selection based on availability of samples from prior studies	1. Blinding was not described	2. FC analysis was part of the original trials; NGS was performed on frozen samples post hoc			

NGS: next-generation sequencing.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinical Utility

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing. Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). No trials were identified that compared outcomes when treatment was guided by clonoSEQ®.

Section Summary: ClonoSEQ® to Detect Measurable Residual Disease in B-Cell Acute Lymphoblastic Leukemia

Evidence on the clinical validity of clonoSEQ® to risk-stratify patients include two retrospective studies in adults. Comparison with FC showed comparable results when the same threshold (10^{-4}) was used for both NGS and FC, and OS in pediatric patients with MRD positivity was significantly lower than in pediatric patients who were MRD negative. However, NGS at the limit of detection was found to have lower specificity.

CLONOSEQ® TO DETECT MEASURABLE RESIDUAL DISEASE IN CHRONIC LYMPHOCYTIC LEUKEMIA

Clinical Validity

Study characteristics and results are described in Tables 4 and 5. Study limitations are described in Tables 6 and 7.

Material submitted for U.S. Food and Drug Administration (FDA) approval included data analyzed from two studies that assessed MRD with clonoSEQ® using available blood samples from two clinical trials (NCT02242942 and NCT00759798).[10] The primary endpoint of the first study was to evaluate whether MRD at a threshold of 10^{-5} at three months after treatment could predict PFS. Secondary objectives were to assess different cutoff values and repeated measurements. Patients with MRD greater than 10^{-5} had a 6.64-fold higher event risk compared to MRD negative patients (95% confidence interval [CI] 3.65 to 12.1). The primary distinction was at a cutoff of 10^{-4}, where only 16.5% of patients with MRD in blood greater than 10^{-4} were progression free at four years follow-up, compared to 44%, 49%, and 47% with MRD less than 10^{-6}, 10^{-5}, and 10^{-4}, respectively.

The second study was published by Thompson (2019), who analyzed MRD with clonoSEQ® in stored samples of bone marrow (n=57), blood (n=29) and plasma (n=32) from 62 patients who had previously tested negative for MRD by FC (n=63) in a phase 2 clinical trial.[11] MRD rates by NGS varied according to sample type with fewer patients with undetectable MRD in bone marrow (25%) than blood (55%) or plasma (75%). MRD at the end of treatment was predictive of PFS. Patients with undetectable MRD did not progress by the end of the study (mean 82 months, range 28 to 112 months) compared with PFS of 67 months (bone marrow) or 74 months (blood). The percent of patients who were progression free with MRD less than 10^{-6}, 10^{-5}, and 10^{-4} was 85%, 75%, and 67.5%, respectively. The authors note that "At this time, no additional treatment is offered to eradicate low-level MRD ($<10^{-4}$) after first-line treatment of CLL, given the generally favorable prognosis for such patients."

Munir (2023) reported results of the prognostic performance of clonoSEQ® in participants from the GLOW study.[12] GLOW (n=211) was a phase 3 trial comparing fixed-duration ibrutinib+venetoclax to chlorambucil+obinutuzumab in participants with previously untreated CLL who were older and/or had comorbidities. MRD was assessed by clonoSEQ® from samples collected every three to four months from peripheral blood and at 9 and 18 months from bone marrow. Detectable MRD defined as having ≥1 CLL cell per 10,000 leukocytes. Median follow-up was 34 months. PFS at 12 months after the end of treatment with ibrutinib+venetoclax was high regardless of MRD status at the end of treatment: 96% versus 93% in patients with undetectable MRD versus detectable MRD.

Table 4. Characteristics of Prognostic Studies Assessing ClonoSEQ® for MRD in CLL

Study	Study Population	Design[a]	Reference Standard	Threshold for PIT	Follow-up (range)
clonoSEQ® Technical Summary	Patients treated for CLL with blood samples at 3 months after treatment (n=337)	Analysis of prospectively collected blood samples from a phase 3 trial (NCT02242942)	PFS	NGS at 10^{-6}, 10^{-5}, 10^{-4} in blood	4 years
Thompson (2019)[11]	Patients with CLL treated with up to 6 courses of FCR and MRD negative by FC (n=62)	Analysis of prospectively collected samples from a phase 2 trial (NCT00759798)	PFS	NGS at 10^{-6}, 10^{-5}, 10^{-4} in blood, plasma, or bone marrow	82 months (28-112)
Munir	Patients with CLL	Analysis of	PFS	NGS at 10^{-4}	1 year

Study	Study Population	Design[a]	Reference Standard	Threshold for PIT	Follow-up (range)
(2023)[12]	treated with ibrutinib+venetoclax (I+V)	prospectively collected samples from the phase 3 GLOW trial (NCT03462719)			

CLL: chronic lymphocytic leukemia; FC: flow cytometry; FCR: fludarabine, cyclophosphamide, and rituximab; MRD: measurable residual disease; PIT: positive index test; PFS: progression-free survival.

Table 5. Results of Prognostic Studies Assessing ClonoSEQ® for MRD in CLL

Study	N	Tissue Source	Progression Free at End of Study n/N (%)					
			EOT MRD $<10^{-6}$	EOT MRD $>10^{-6}$	EOT MRD $<10^{-5}$	EOT MRD $>10^{-5}$	EOT MRD $<10^{-4}$	EOT MRD $>10^{-4}$
clonoSEQ® Technical Summary			33/75 (44.0%)		50/106 (47.2%)		24/49 (49.0%)	17/103 (16.5%)
Thompson (2019)[11]	53	Bone marrow	11/13 (84.6%)	21/40 (52.5%)	18/24 (75.0%)	14/29 (48.3%)	27/40 (67.5%)	5/13 (38.4%)
	29	Blood	7/8 (87.5%)	8/13 (61.5%)				
Munir (2023)[12]	211 (106 I+V)	Bone marrow					I+V: 96% C+O: 83%	I+V: 93% C+O: 59%

C+O: chlorambucil+obinutuzumab; EOT: end of treatment; I+V: ibrutinib+venetoclax; MRD: measurable residual disease; NGS: next-generation sequencing; PFS: progression free survival

Limitations in study relevance, and study design and conduct are shown in Tables 6 and 7.

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
clonoSEQ® Technical Summary			3. Did not compare results to FC		
Thompson (2019)[11]					1. Mean follow-up was 82 months (range of 28 to 118 months) which is insufficient to determine PFS in CLL
Munir (2023)[12]			3. Did not compare results to FC		1. Follow-up of 1 year

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CLL: chronic lymphocytic leukemia; FC. flow cytometry; PFS: progression-free survival.
[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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
clonoSEQ® Technical Summary		1. Blinding was not described		2. Details from the technical summary are limited and did not discuss the minimal difference of the different thresholds.		
Thompson (2019)[11]	2. Selection based on availability of tissue samples from prior studies	1. Blinding was not described				
Munir[12] (2023)		1. Blinding was not described				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinical Utility

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Section Summary: ClonoSEQ® to Detect Measurable Residual Disease in Chronic Lymphocytic Leukemia

The evidence on clonoSEQ® for detection of MRD includes two studies that were submitted to the FDA. These studies evaluated the association between the level of MRD detected by NGS in the bone marrow or blood and PFS in samples of blood or bone marrow from completed phase 2 and 3 trials. Both studies submitted to the FDA demonstrated an association between the level of MRD and PFS with lower risk of progression in patients who exhibit MRD negativity below 10^{-4} compared to patients who have detectable residual disease. Evidence is sufficient to support the clinical utility of using clonoSEQ® to measure MRD for prognosis based on test results at a sensitivity of 10^{-4}. Analysis of samples from the GLOW study suggests that for participants treated with ibrutinib+venetoclax, PFS was high regardless of MRD status using threshold of 10^{-4} at the end of treatment.

CLONOSEQ® TO DETECT MEASURABLE RESIDUAL DISEASE IN MULTIPLE MYELOMA

Table 8. Definitions of Complete Response and MRD from the International Myeloma Working Group[2]

Standard Response criteria	
Complete response	"Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates"
MRD Response Criteria (requires a complete response)	
Sequencing MRD-negative	Absence of clonal plasma cells with a minimum sensitivity of 1 in 10^{-5} nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus imaging criteria

MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing

Clinical Validity

Three published retrospective studies were identified that evaluated the association between MRD by clonoSEQ® and disease progression in patients with MM (see Tables 9 and 10). Two of the studies assessed MRD levels from patients who had participated in earlier MM treatment trials.

In a study by Perrot (2018), a threshold of 10^{-6} was used to evaluate the association between MRD and PFS, finding that the dichotomous division into MRD positive and MRD negative (no detectable MRD at the limit of detection) was highly predictive of PFS with an HR for MRD negative/MRD positive of 0.19 (p<.001).[13] The median PFS was 29 months in patients who were positive for MRD and was not reached among patients with no detectable MRD.

Martinez-Lopez (2020) reported a retrospective analysis of patients (n=234) treated at their center for newly diagnosed or relapsed MM who had been evaluated for MRD by clonoSEQ®.[14] MRD assessment by clonoSEQ® was performed after a complete response, but there was no consistent time after treatment; most were performed within one year. Successful identification of at least one trackable sequence in the pretreatment sample was obtained in 234 out of 251 (93%) patients. Sensitivity was assessed at 10^{-4}, 10^{-5}, and 10^{-6}. Out of all patients, 91 (39%) had MRD less than 10^{-6} and 129 (55%) had MRD less than 10^{-5}. For both newly diagnosed MM and relapsed MM patients, MRD less than 10^{-5} or less than 10^{-6} was associated with prolonged survival. In patients who had repeat testing, rising MRD levels preceded clinical relapse by a median of 13 months (range 1 to 28 months). Patients who

reached a molecular response at 10^{-5} had similar outcomes to those who achieved MRD negativity at 10^{-6}.

Cavo (2022) analyzed pooled data from four phase 3 studies in patients with relapsed or refractory MM who were ineligible for transplant.[15] MRD was assessed at a sensitivity of 10^{-5}. Patients who achieved a complete response or better and were MRD negative had improved PFS and an 80% reduction in the risk of disease progression or death compared with those who failed to reach complete response or were MRD positive (HR 0.20, p<0.0001).

Oliva (2023) reported results of analyses of MRD status from samples available from the FORTE trial.[16] The FORTE trial was a phase 2, multicenter RCT including participants with newly diagnosed, transplant-eligible multiple myeloma randomized between 2015 and 2021 to one of three induction-intensification-consolidation strategies. Multiparameter FC status was assessed in patients with at least a very good partial response first at premaintenance and then every six months during maintenance treatment until progressive disease. The cut-off for FC MRD positivity was set at ≥20 clonal plasma cells out of the total of nucleated cells, with a sensitivity of $\geq 10^{-5}$. NGS was performed in a subset of participants with at least a suspected complete response at pre-maintenance and monitored every 6 months during maintenance treatment until progressive disease using the clonoSEQ® assay with sensitivities at 10^{-5} and 10^{-6}. There were 2,020 samples available for analysis of FC MRD status and 728 samples available for the analysis of the correlation between FC and NGS in the “suspected complete response population”. Median follow-up was 62 months. The hazard ratios for PFS in FC-MRD and NGS-MRD-negative vs. -positive patients were 0.29 (95% CI 0.20 to 0.40) and 0.27 (95% CI 0.18 to 0.39), respectively.

The major limitations of these studies are described in Tables 11 and 12.

Table 9. Characteristics of Studies Assessing ClonoSEQ® for MRD in MM

Study	Study Population	Design	Reference Standard	Threshold
Perrot (2018)[13]	Patients with myeloma enrolled in the IFM 2009 clinical trial[a]	Retrospective	PFS and OS	MRD at 10^{-6}
Martinez-Lopez (2020)[14]	Patients with MM who had been treated at their clinic between 2005 and 2018 (n=234)	Retrospective	PFS	MRD at 10^{-5}
Cavo (2022)[15]	Patients with bone marrow samples from POLLUX, CASTOR, ALCYONE, and MAIA trials[b]	Retrospective	PFS	MRD at 10^{-5}
Oliva (2023)	Patients with bone marrow samples from FORTE trial	Retrospective	PFS	MRD at 10^{-5} and 10^{-6}

MRD: measurable residual disease; NGS: next-generation sequencing; OS: overall survival; PFS: progression-free survival; TTP: time to progression.

[a] IFM 2009 was phase 3 trial from the Intergroupe Francophone du Myelome, conducted between 2010 and 2012, which evaluated the role of autologous cell transplantation in patients with newly diagnosed myeloma.

[b] POLLUX, CASTOR, ALCYONE, and MAIA were daratumumab-based studies in patients with newly diagnosed MM.

Table 10. Results of Prognostic Studies Assessing ClonoSEQ® for MRD in MM

Study	N	MRD Threshold	TTP, months (95% CI)	
Perrot (2018)[13]	509	10^{-6}	MRD negative/MRD positive	

Study	N	MRD Threshold	TTP, months (95% CI)	
Hazard Ratio for Progression Free Survival (95% CI)			0.19 (0.13 to 0.26)	
p-Value			<0.001	
Martinez-Lopez (2020)[14]			**PFS, months (95% CI)**	**3-year survival (95% CI)**
Newly Diagnosed		$<10^{-6}$		90% (81% to 98.78%)
		$<10^{-5}$	87	85.9% (78.2% to 94.5%)
		$>10^{-5}$	32	46.8% (33.9% to 64.7%)
HR (95% CI)			3.54 (1.94 to 6.45)	
p-Value			<0.001	
Relapsed	27/75 (36%)	$<10^{-6}$	not reached	
	35/75 (47%)	$<10^{-5}$	42	
		$>10^{-5}$	17	
HR (95% CI)			2.45 (1.25 to 4.82)	
p-Value			.01	
Cavo (2022)[15]			**48-month PFS, %**	
	2,510	10^{-5}		
Complete response or better and MRD negative			70.4	
Less than very good partial response or MRD positive			23.9	
Oliva (2023)[16]			**48-month PFS, %**	**48-month OS, %**
MRD positive			46%	78%
MRD negative			83%	94%
HR (95% CI)			0.27 (0.18 to 0.39)	0.31 (0.17 to 0.54)
p-value			<0.01	<0.01

CI: confidence interval; HR: hazard ratio; MRD: measurable residual disease; PFS; progression free survival; OS: overall survival; TTP: time to progression.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Perrot (2018)[13]	4. The study included patients from the IFM 2009 trial who had at least a very good partial response but did not report separately on patients with a complete response				
Martinez-			3. No		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lopez (2020)[14]			comparison to other tests for MRD		
Cavo (2022)[15]			3. No comparison to other tests for MRD		
Oliva (2023)[16]	4. MFC status was assessed in patients with at least a very good partial response and NGS was assessed in patients with at least a suspected complete response				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Perrot (2018)[13]	2. Selection based on availability of tissue samples in the original study	1. Blinding not described				1. Post-hoc exploratory analysis, not adjusted for multiple comparisons
Martinez-Lopez (2020)[14]	2. Retrospective assessment of clinical data	1. Blinding not described	2. There was no uniform timing of the test.			
Cavo (2022)[15]			2. MRD assessed at different time points in individual studies.			
Oliva	2.	1.				

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
(2023)[16]	Retrospective assessment of clinical data	Blinding not described				

MRD: measurable residual disease
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Kriegsmann (2020) found moderate concordance between NGS and NGF in a study of 113 patients with MM (Table 13).[17] Concordance between methods was obtained in 68% of patients while discordant results were found in 28 patients (11.2% in each direction). Cohen's kappa coefficient for interrater agreement between the MRD status of the two methods was 0.536 (n=113, p<0.001). A threshold of 10^{-5} was chosen as the best-fit MRD cut-off for evaluation as it met the international guidelines and resulted in a tolerable proportion of nonassessable cases in both methods (1.6%, n=2 in NGS and 8.0%, n=10 in NGF).

Table 13. Concordance Between NGS and NGF in Study by Kriegsmann (2020)

		Flow Cytometry		
		+	–	*Total*
NGS	**+**	42	14	56
	–	14	43	57
	Total	56	57	

NGF: next generation flow cytometry; NGS: next-generation sequencing.

Clinical Utility

No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Costa (2023) reported results of the MASTER multicenter (five centers), single-arm, phase 2 study conducted in the US between 2018 and 2020.[18] MASTER was the first study to use prospective adaptation of treatment duration based on MRD status but MRD status was used to guide therapy in all participants with sufficient unique clonogenic sequences. There is no comparison to management without MRD status. Instead, MASTER demonstrates the feasibility of using MRD to guide therapy. MASTER included 123 adults with newly diagnosed multiple myeloma, life expectancy >12 months, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and no previous treatment except up to one cycle of therapy containing bortezomib, cyclophosphamide, and dexamethasone. 70 (57%) of the participants were men; 94 (76%) of participants were non-Hispanic White, 25 (20%) were non-Hispanic Black. The median age was 61 years (IQR, 55 to 68). 53 (43%) had no high-risk chromosome abnormalities (HRCA), 46 (37%) had one HRCA, and 24 (20%) had two or more HRCAs. The median follow-up duration was 42 months (IQR, 35 to 46). MRD status was assessed by

clonoSEQ® using a detection threshold of 10^{-5} to adjudicate response-adapted therapy. Five participants had an absence of sufficiently unique clonogenic sequences to enable tracking by the clonoSEQ® assay. There were 84 participants who reached MRD negativity after or during two consecutive treatment phases, who then stopped treatment and began observation with MRD surveillance. Twenty participants who did not reach two consecutive MRD-negative results received maintenance lenalidomide. Ten participants discontinued treatment early: three died, five had disease progression, and two chose to discontinue. Of the 84 participants who transitioned to MRD surveillance, 36-month PFS was 88% (95% CI 77 to 96) for those with no HRCAs, 85% (95% CI 73 to 96) for those with one HRCA, and 60% (95% CI 35 to 82) for those with two or more HRCAs. Of the 84 participants, 23 (27%) resumed therapy due to MRD resurgence or disease progression not preceded by MRD resurgence.

Section Summary: ClonoSEQ® to Detect Measurable Residual Disease in Multiple Myeloma

The evidence on clonoSEQ® for detection of MRD includes three published retrospective studies in patients with MM. These studies evaluated the association between the level of MRD detected by NGS in the bone marrow and the TTP or PFS from the completed phase 3 trials or from a clinical population. All of the studies demonstrated an association between the level of MRD and PFS with longer TTP in patients who exhibit MRD negativity below 10^{-5} or 10^{-6} compared to patients who have detectable residual disease. There was also high concordance between NGS and FC. Patients who were discordant for the two tests had outcomes that were intermediate between patients who were positive for both tests and those who were negative for both tests.

In exploratory analysis of the largest study, the median PFS was 29 months in patients who were positive for MRD and was not reached among patients with no detectable clones, suggesting that assessment of MRD might have utility in guiding therapy. About one-quarter of MRD negative patients progressed within 36 months in these trials, raising questions about whether clonoSEQ® could be used to guide therapy. It is unknown whether progression is due to very low levels of residual disease or to new clonal rearrangements in MM. Direct evidence from RCTs is needed to evaluate whether patient outcomes are improved by changes in postinduction care (e.g., continuing or discontinuing therapy, avoiding unnecessary adverse events) following clonoSEQ® assessment of residual disease. Trials that test the effectiveness of MRD to guide therapy in MM are ongoing.

CLONOSEQ® TO DETECT MEASURABLE RESIDUAL DISEASE IN DIFFUSE LARGE B-CELL LYMPHOMA

Clinical Validity

There are two studies assessing the prognostic value of clonoSEQ® for MRD specifically in patients with DLBCL. One prospective, single-center, observational study by Chase (2021) attempted to correlate MRD with prognosis in patients with newly diagnosed DLBCL receiving conventional treatment; however, attrition limited outcome assessment.[19] Only three patients had early clinical relapse, and no conclusions can be drawn.

In a phase 2, single-center, prospective trial in patients with DLBCL undergoing HSCT, Kambhampati (2021) assessed 15 patients for MRD with NGS.[20] Of the 14 patients with available MRD samples after salvage therapy, 11 were MRD negative and three were MRD positive. MRD tests were predictive of survival in these patients (see Tables 14 and 15).

Limitations of the study included the lack of comparator MRD test and the MRD testing threshold was not described.

Table 14. Characteristics of Studies Assessing ClonoSEQ® for MRD in DLBCL

Study	Study Population	Design	Reference Standard	Threshold
Kambhampati (2021)[20]	Patients with relapsed/refractory DLBCL undergoing HSCT enrolled in a phase 2 trial	Single-center, prospective	PFS/OS	NR

DLBCL: diffuse large B-cell lymphoma; HSCT: hematopoietic stem cell transplant; NR: not reported: OS: overall survival; PFS: progression-free survival.

Table 15. Results of Prognostic Studies Assessing ClonoSEQ® for MRD in DLBCL

Study	N	Median OS, mo	Median PFS, mo
Kambhampati (2021)[20]	27 (14 with MRD samples after salvage therapy)		
MRD negative		Not reached	Not reached
MRD positive		3.5	1.3

MRD: measurable residual disease; OS: overall survival; PFS: progression-free survival.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Indirect evidence on clinical utility rests on clinical validity. Further studies will be needed to determine whether treatment can be guided by this test.

Section Summary: ClonoSEQ® to Detect Measurable Residual Disease in Diffuse Large B-Cell Lymphoma

The evidence on NGS for detection of MRD in DLBCL includes an analysis from a single-center, prospective trial that did not include comparison to another MRD measure. Although both PFS and OS correlated with MRD positivity, the trial is limited by its small sample-size and inclusion of only patients eligible for HSCT from a single center.

CLONOSEQ® TO DETECT MEASURABLE RESIDUAL DISEASE IN MANTLE CELL LYMPHOMA

Clinical Validity

Characteristics and results of trials evaluating NGS for MRD in MCL are summarized in Tables 16 and 17, and limitations of these trials are summarized in Tables 18 and 19. Smith (2019) conducted a retrospective review of samples from patients enrolled in the ECOG1411 trial which evaluated MCL patients treated with bendamustine-rituximab induction followed by rituximab (with or without lenalidomide) consolidation and evaluated MRD by both FC and NGS.[21] Concordance between tests was high both after cycle 3 and end of induction. MRD status correlated with PFS. For patients who were MRD negative after cycle 3 by either method, PFS was 58.9 months. For those who were MRD positive by NGS, PFS was 26.9

months and PFS was 29.9 months for those who were positive by FC. The authors concluded both NGS and FC were feasible to assess MRD.

Lakhotia (2022) conducted an exploratory review of circulating tumor DNA analyzed by NGS from a trial of bortezomib induction in 53 MCL patients found patients who had undetectable MRD after two induction cycles had longer PRS and OS than those with MRD.[22] As this was an exploratory analysis, key details are not included, and no firm conclusions can be drawn.

Table 16. Characteristics of Studies Assessing ClonoSEQ® for MRD in patients with MCL

Study	Study Population	Design	Reference Standard	Threshold	Test Version
Smith (2019)[21]	Patients with MCL enrolled in ECOG1411	Retrospective	PFS	MRD at 10^{-4}	"Research version" of clonoSEQ®
Lakhotia (2022)[22]	Patients with MCL enrolled in a trial of bortezomib induction treatment	Retrospective	PFS	NR	Not specified; however, test supplied by Adaptive Biotechnologies

ECOG: Eastern Cooperative Oncology Group; MCL: mantle cell lymphoma; MRD: measurable residual disease; NR: not reported; PFS: progression free survival.

Table 17. Results of Prognostic Studies Assessing ClonoSEQ® for MRD in patients with MCL

Study	N	MRD Threshold	MRD Negative, (%)[a]	PFS	OS
Smith (2019)[21]	214	MRD at 10^{-4}			
FC			95 (peripheral blood)		
NGS			91 (peripheral blood)/90 (bone marrow)		
MRD negative (by NGS)				58.9 mo	
MRD positive (by NGS)				26.9 mo	
Lakhotia (2022)[22]	53				
MRD negative[b]				2.7 yr	13.8 yrs
MRD positive[b]				1.8 yr	7.4 yrs

FC: flow cytometry; MRD: measurable residual disease; NGS: next-generation sequencing; OS: overall survival; PFS: progression free survival.
[a] Results reported at end of induction.
[b] After 2 cycles of induction.

Table 18. Study Relevance Limitations

Study	Populationa	Interventionb	Comparatorc	Outcomesd	Duration of Follow-Upe
Smith (2019)[21]		2. Unclear if "research version" of clonoSEQ®			1. Data reported from mid-induction or end of

Study	Populationa	Interventionb	Comparatorc	Outcomesd	Duration of Follow-Upe
		used in study is same as commercially available test.			induction
Lakhotia (2022)[22]		1,2			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 19. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Smith (2019)[21]		1. Blinding not described				
Lakhotia (2022)[22]	2. Selection based on availability of tissue samples in the original study	1. Blinding not described				1. Post-hoc exploratory analysis

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs assessing the clinical utility of MRD by NGS to guide therapy were identified.

Indirect evidence on clinical utility rests on clinical validity. High concordance has been shown between NGS and FC at a threshold of 10^{-4}, indicating that NGS may be considered an alternative to FC at this threshold. Further studies are needed to determine whether treatment can be guided by this test.

Section Summary: ClonoSEQ® to Detect Measurable Residual Disease in Mantle Cell Lymphoma

The evidence on clonoSEQ® for detection of MRD in patients with MCL includes a retrospective study and an exploratory analysis of patients enrolled in treatment clinical trials. When compared with FC, NGS had strong correlation, and MRD positivity with either method was associated with worse PFS. However, the relevance of these findings to the commercial version of clonoSEQ® is unclear as a "research version" was used in the study. An exploratory analysis in patients with MCL enrolled in a treatment trial found improved survival in patients who were MRD negative after two cycles of induction. However, interpretation was limited by imprecision and unspecified NGS testing level.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL MYELOMA WORKING GROUP

The International Myeloma Working Group developed consensus criteria for response and minimal residual disease (MRD) assessment in multiple myeloma (Table 20).[2]

Table 20. IMWG Criteria

Standard Response Criteria	
Complete response	"Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates"
Stringent complete response	"Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)"
MRD Response Criteria (requires a complete response)	
Sequencing MRD-negative	Absence of clonal plasma cells by NGS using the LymphoSIGHT platform (or validated equivalent) with a minimum sensitivity of 1 in 10^5 nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus imaging criteria
MRD Response Criteria (requires a complete response)	
Sustained MRD-negative	MRD negativity by NGF or NGS, and by imaging, at a minimum of 1 year apart.

FLC: free light chain; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing.

INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA

The 2018 guidelines from the International Workshop on Chronic Lymphocytic Leukemia (CLL) have the following recommendations regarding the assessment of MRD:[1]

"The complete eradication of the leukemia is a desired end point. Use of sensitive multicolor flow cytometry, PCR [polymerase chain reaction], or next generation sequencing can detect MRD in many patients who achieved a complete clinical response. Prospective clinical trials

have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become well standardized. Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of 1 CLL cell in 10,000 leukocytes. Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81). As such, patients will be defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with,1 CLL cell per 10,000 leukocytes."

THE NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network has published guidelines of relevance to this review (see Table 21).

Table 21. Recommendations on Assessing Measurable Residual Disease

Guideline	Version	Recommendation
Acute lymphoblastic leukemia[23]	2.2024	MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping. The most frequently used methods for MRD quantification include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays specifically designed to detect abnormal MRD immunophenotypes at low frequency, real-time quantitative PCR (RQ-PCR) assays (eg, clonally rearranged Ig, TCR genes), and RT-qPCR assays (eg, BCR::ABL1). High-sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1×10^{-4} (0.01%) bone marrow mononuclear cells (MNCs). NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of $1\times10^{--6}$ (0.0001%) MNCs.
Chronic lymphocytic leukemia/small lymphocytic lymphoma[24]	3.2024	Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of fixed duration treatment is an important predictor of efficacy. MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.
Multiple myeloma[3]	3.2023	Consider baseline clone identification and storage of aspirate sample for future MRD testing by NGS. Bone marrow aspirate and biopsy with FISH, SNP array, NGS, or multi-parameter flow cytometry as clinically indicated. Consider MRD testing as indicated for prognostication after shared decision with the patient.
B-cell lymphomas[25]	2.2023	MRD surveillance is not included in the current guidelines.

ALL: acute lymphoblastic leukemia, FC: flow cytometry; FISH: fluorescence in situ hybridization; MRD: measurable residual disease; NGS: next-generation sequencing; PCR: polymerase chain reaction; SNP: single nucleotide polymorphism.

SUMMARY

There is enough evidence to show that clonoSEQ® B-cell testing for measurable residual disease (MRD) can improve health outcomes for individuals with B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM) who are being monitored following treatment. Clinical practice guidelines recommend MRD assessment, including the use of NGS testing for these indications. Therefore, clonoSEQ® B-cell testing for measurable residual disease (MRD) may be considered medically necessary for individuals with B-ALL, CLL, or MM.

There is not enough research to show that clonoSEQ® B-cell testing can improve health outcomes for individuals with diffuse large B-cell lymphoma (DLBCL) who are being monitored for residual disease following treatment. In addition, the test has not been approved by the FDA for this condition. Therefore, clonoSEQ® testing is considered investigational for patients with DLBCL.

There is not enough research to show that clonoSEQ® B-cell testing can improve health outcomes for individuals with mantle cell lymphoma (MCL) who are being monitored for residual disease following treatment. Overall, the literature is limited, and guidelines for testing to detect MRD in patients with MCL are lacking. In addition, the test has not been approved by the FDA for this condition. Therefore, clonoSEQ® testing is considered investigational for patients with MCL.

There is not enough research to show that clonoSEQ® T-cell testing or testing for individuals with hematologic malignancies other than B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), or multiple myeloma can improve health outcomes. Only the clonoSEQ® B-cell testing has been approved by the FDA, and only for B-ALL, CLL and multiple myeloma. Therefore, clonoSEQ® T-cell testing and clonoSEQ® for all other indications is considered investigational.

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CODES

Codes	Number	Description
CPT	0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate
HCPCS	None	

Date of Origin: *March 2023*

Facility Guidelines

We follow specific guidelines for billing and payment for facilities that are outlined in this section.

To the extent the terms of this *Administrative Manual* are inconsistent with the terms of the participating agreement, the terms of the agreement prevail.

For purposes of clarification, payment for inpatient services (whether priced as a diagnosis-related group, per diem or other methodology) shall be based on the reimbursement schedule in effect as of the relevant member's date of admission irrespective of contract amendments that take effect during the term of that member's inpatient admission. Any amendments to compensation amount shall be applied to services rendered to members admitted after such amendment's effective date.

Pre-authorization, eligibility and benefits
Please verify the patient's eligibility and benefits. Services in this section may require pre-authorization for medical necessity. Pre-authorization requirements can be found in the Pre-authorization section of our website.

Audits
We may audit any claim for appropriate coding, payment per contract and payment per medical and reimbursement policy. We will request any combination of invoice, medical records or itemized bill to support audit. All documentation requested must be provided within the time frame specified in the audit letter.

Medical policies
We maintain our own medical policies for most services and procedures while following MCG for inpatient and tertiary services. This includes services and care received in inpatient hospitals, skilled nursing facilities, long-term acute care hospitals and facilities, inpatient rehabilitation centers, residential treatment facilities, partial hospitalization and intensive outpatient behavioral health services.

Hospital guidelines

An **outpatient facility** is that portion of a hospital which provides the following to sick or injured persons who do not require hospitalization.

- Rehabilitation services
- Diagnostic, therapeutic (both surgical and no-surgical) services
- May perform laboratory tests that are billed by the hospital
- May provide services in an emergency room or outpatient clinic
- May offer ambulatory surgical procedures and/or medical supplies

Site of service (outpatient to ASC)
Some services require pre-authorization for the site of service. Pre-authorization requirements are published in the Pre-authorization section of our provider website, **regence.com**. Providers can check whether services require pre-authorization and then request pre-authorization using Availity's Electronic Authorization application at **availity.com**.

For additional site of service information, see our commercial and Medicare Advantage *Surgical Site of Service – Hospital Outpatient* (Utilization Management #19) medical policies on our provider website, **regence.com**: Policies & Guidelines>Medical Policy.

Inpatient hospital

An **inpatient hospital** is a facility, other than psychiatric, which primarily provides diagnostic, therapeutic (both surgical and non-surgical) and rehabilitation services by or under the supervision of physicians, to patients admitted for a variety of medical conditions.

Inpatient hospital claims are submitted electronically or on an ANSI 837I (Institutional) format and exclude all professional components and air ambulance. Inpatient hospital claims must include the appropriate room and board revenue codes. Professional components, including pathology, radiology, anesthesia, emergency, etc., should be submitted electronically on an ANSI 837P (Professional) format.

Billing inpatient versus outpatient stays

We use MCG at **mcg.com** to determine appropriate level of care, and we use American Society of Addiction Medicine (ASAM) guidelines for substance use disorder treatment. Inpatient hospital claims must include the appropriate room and board revenue codes. The total units billed on the room and board revenue codes should match the length of stay as calculated as discharge date less admission date plus one.

Observation

Hospital observation is intended to allow a physician an opportunity to monitor and observe a patient and make a decision about on-going care. We reimburse for up to 48 hours of observation, if clinically appropriate, per the outpatient reimbursement terms. Observation stays beyond 48 hours may be rebilled by the provider as an inpatient stay and will process per inpatient guidelines. If the member meets the inpatient level-of-care standard, the provider will be reimbursed for inpatient care for the entire length of stay. Applicable pre-authorization and notification requirements will apply.

If inpatient level of care is not met, reimbursement will be made for up to 48 hours per outpatient reimbursement terms. Covered charges, generally billed under revenue code 0762 will be for the number of hours a patient is in observation, up to 48 hours. Charges for any twenty-four (24) hour period of observation cannot exceed the hospital/providers usual semi-private room rate.

Revenue code 0760 is not accepted for use to identify observation room charges.

We use MCG to determine appropriate level of care. In addition, we follow Centers for Medicare & Medicaid Services (CMS) guidelines regarding proper documentation of observation stays, including the *Medicare Outpatient Observation Notice* (MOON), form *CMS-10611* for Medicare members receiving outpatient observation care for more than 24 hours. All hospitals, including critical access hospitals, are required to provide this notice. You can find the notice and accompanying instructions at **cms.gov/Medicare/Medicare-General-Information/BNI/**.

Hospital-based physician services

To the extent your hospital and/or provider agreement does not address hospital-based physician services, the following guidelines will apply:

- Professional fees for covered services rendered to members by hospital-based physicians during a covered inpatient hospital stay, are not included in the hospital maximum allowable.
- Professional services should be submitted in an electronic ANSI 837P (Professional) format

Pre-admission services
Pre-admission services are considered:

- Outpatient hospital services rendered two calendar days prior to an inpatient admission
- Diagnostic services (including clinical diagnostic laboratory tests) provided to a patient by the hospital and/or provider, or by an entity wholly owned or wholly operated by the hospital and/or provider (or by another entity under arrangements with the hospital and/or provider), within two days prior to and including the date of the patient's admission are deemed to be inpatient hospital services and included in the inpatient payment.

Hospital readmission review (group and Individual plans)
All hospital readmissions for the same, similar or related condition that occur within 72 hours of the original discharge from hospital/facility or as defined in the hospital provider contract are considered a continuation of initial treatment.

The two diagnosis-related group (DRG) hospital claims (identified using the assigned provider identifier) will be consolidated into one, combining all necessary codes, billed charges and the length of stay. The maximum allowable for covered services will be recalculated per the reimbursement terms of the hospital/facility contract so that reimbursement is for a single, per case reimbursement.

This policy applies but is not limited to the following:

- Emergent readmissions
- Clinically related readmissions

This policy does not apply to the following:

- Transplants
- Medical treatment for cancer
- Psychiatric and substance abuse
- Readmission for unrelated condition
- Transfer from one inpatient stay at an acute care hospital to an inpatient stay at another acute care hospital
- Patient discharged from the hospital against medical advice
- Readmission for the medical treatment of rehabilitation care
- Readmission for cancer chemotherapy or transfusion for chronic anemia

For additional information view the *Inpatient Hospital Readmissions* (Administrative #111) reimbursement policy on our provider website: Policies & Guidelines>Reimbursement Policy.

Hospital readmission review (Medicare Advantage plans)

Our policy aligns with CMS and includes readmission to the same hospital (using the assigned provider identifier) within 30 days of the initial admission. Hospital stays are subject to clinical review to determine if the readmission is related to or similar to the initial admission. Readmissions occurring:

- On the same day (or within 24 hours) will be processed as a single claim
- Within 2-30 days will be subject to clinical reviews. If the clinical review indicates that the readmission is for the same or a similar condition, it may be considered a continuation of the initial admission for the purposes of reimbursement.

When we receive DRG claims for both an initial and subsequent hospital stay, we combine the subsequent hospital stay with the initial claim within our system. When this occurs, we will send you a notification reflecting these changes and additional payment, if applicable.

This applies to, but is not limited to:

- Emergent readmissions
- Clinically related readmission
- Planned readmission or leave of absence

This policy does not apply to the following:

- Transplants
- Medical treatment for cancer
- Psychiatric and substance abuse
- Readmission for unrelated condition
- Transfer from one inpatient stay at an acute care hospital to an inpatient stay at another acute care hospital
- Readmission for the medical treatment of rehabilitation care
- Patients discharged from the hospital against medical advice
- Readmission for cancer chemotherapy, transfusion for chronic anemia or similar repetitive treatments

For additional information, view the *Inpatient Hospital Readmissions* (Medicare Administrative #111) reimbursement policy on our provider website: Policies & Guidelines>Reimbursement Policy.

Submission of maternity/newborn claims

Separate claims must be submitted for the mother and newborn services. Claims that reflect both maternity and newborn charges on the same claim form will be returned to the hospital and/or provider for correct billing.

Interim billing

For interim claims paid on a per case basis, payment will be based on the full case allowance on the initial claim received. All remaining interim claims will be denied, pending the final claim.

Once the final claim is received, we will review the total claim and make any necessary adjustment of the initial payment should the final diagnosis change the per case allowance or if there are charge outliers. Please do not bill the patient until the final payment is issued.

Claims that span multiple years

CMS coding guidelines require institutional claims that span from one calendar year to another to be split into separate claims by year. This allows proper processing of all items on the claim. CMS' general guidance is:

FL 6. Statement covers period (from - through)

- These fields cannot exceed eight positions in either "from" or "through" portion, allowing for separations (non-numeric characters) in the third and sixth positions.
- The "from" date must be a valid date that is not later than the "through" date.
- The "through" date must be a valid date that is not later than the current date.

Facility claims (ANSI 837I claims) that span from one calendar year to the next (e.g., December 28, 2022, to January 3, 2023) will be denied automatically if they are submitted on the same claim. The following claim types are exceptions that do not need to be split:

- Home health prospective payment system (PPS) claims
- Outpatient hospital observation or emergency room visits
- Facility inpatient claims

Late charges

Late submissions in general are not accepted. Late charges are defined as Type of Bill (TOB) code 115 and are not reimbursable. The hospital and/or provider must submit a corrected billing of the entire claim with TOB code 117 to receive reimbursement for charges not included when the original bill was submitted.

Hospital corrected billings and/or adjustments

Corrected claims must be submitted using TOB code 117. All claims must contain all pertinent information including all applicable International Classification of Diseases (ICD) diagnosis and procedure codes, present on admission (POA) flags and discharge status. Charges included on previously submitted claims, whether billed as interim or complete claims, must be included on the corrected claim. Itemizations or records may be requested to re-adjudicate the corrected claim.

Grouper use

To determine the DRG for an inpatient stay, we use the grouper version in effect on the date of admission. The grouper used for reimbursement purposes is the DRG grouper version as defined in the Inpatient Reimbursement Schedule found in your hospital and/or provider agreement and shall also be based on the date of admission.

Ungroupable DRGs

MS DRG 998 and 999 are defined as ungroupable DRGs.

Any claim which groups to an ungroupable DRG will be returned to the provider for correction of coding or claim errors.

Member deductible and coinsurance calculation
Member deductible, copayment and coinsurance amounts will be calculated based on the billed charges or maximum allowable, whichever is less.

DRG reimbursement
Inpatient-type institutional services provided to the patient from the admission date to the discharge date (including pre-admit and emergency room work-up) will be covered as part of the DRG payment, case rate and percent.

Inpatient hospital claims that are paid using DRG methodology are billed on an ANSI 837 Institutional format and should not include any professional components or air ambulance charges.

DRG methodology
The following charges and fees are included in the DRG reimbursement:

- Late discharge
- Observational/outpatient
- Diagnostic laboratory services
- Emergency or after-hours admission
- Admission or utilization review paperwork
- Discharge (take home) prescription drugs
- Emergency room, if the patient is admitted
- Medical transportation (excluding air ambulance)
- Room and board, including services and supplies
- Pre-admission services two days prior to admission and one day post-discharge

Medicare post-acute transfer policy
It is important to follow the CMS requirements to report the correct discharge status when transitioning to another hospital, nursing facility, home health, hospice, inpatient rehabilitation facility, long-term care hospital or psychiatric hospital. We will audit and, if applicable, adjust claims based on the appropriate discharge status indicator.

The CMS policy is outlined in the MLN Matters article Fiscal Year (FY) 2006 Inpatient Prospective Payment System (IPPS) and Long Term Care Hospital (LTCH) PPS Changes (MM4046) at **cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R692CP.pdf**.

Facility pre-authorization requirements

Please note facility pre-authorization is required for:

- Rehabilitation

- Detoxification
- Skilled nursing facility (SNF)
- Long-term acute care facility (LTAC)
- Intensive outpatient for mental health and chemical dependency
- Partial hospitalization for mental health and chemical dependency
- Residential treatment for mental health and chemical dependency
- All elective inpatient admissions, including behavioral health (effective May 1, 2019)

Admission and discharge notification requirements

Notification of admission must occur within 24 hours of admission to assist with coordination of care and reduce 30-day readmission. **Note**: On January 1, 2023, all admissions will require notification within 24 hours regardless of the day of week or holiday status. Facilities that submit patient data, including admission and discharge data, via electronic record submission are no longer required to submit notification of inpatient admissions in another format.

Admission notification includes:

- All inpatient hospice admissions
- Chemical dependency detoxification
- All unplanned acute care admissions
- All planned and elective acute care admissions
- All admissions that follow an outpatient surgery
- All admissions that follow outpatient observation
- Intensive outpatient admissions for chemical dependency
- All newborns who are admitted to the neonatal intensive care unit
- All newborns who remain hospitalized after the mother is discharged
- Inpatient admissions or partial hospitalizations for mental health and chemical dependency

Admission and discharge notification, must be made via fax to 1 (800) 453-4341 or by providing us with access to the information via an electronic medical record application. For Medicare lines of business, if the admission notification is not completed, we will review post-payment.

- Admission notification by the facility for non-Medicare lines of business is required even if a pre-authorization was completed by the physician or other health care professional and a pre-authorization approval is on file with us.
- Receipt of an admission notification does not guarantee or authorize payment. Payment of covered services is contingent upon coverage within our individual member's benefit plan, the facility being eligible for payment, any claim processing requirements, and the facility's participation agreement with us.
- Admission notifications must contain the following details:
    - Member/patient's full name, date of birth and member number
    - Facility name and TIN or NPI

    - Actual admission date and anticipated discharge date
    - Admitting/attending physician full name and TIN or NPI
    - Description for admitting diagnosis or valid ICD diagnosis code
- Discharge Notifications must also contain the following information related to patient discharge:
    - Member/patient's full name, date of birth and member number
    - Primary diagnosis
    - Discharge disposition
    - Date of actual discharge,
    - Facility name and TIN or NPI

Notification timeframe reimbursement

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

1. Member presented with an incorrect member card or member number.
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) their medical insurance coverage. Neither family nor other support present can provide coverage information.
4. Compelling evidence the provider or facility attempted to obtain pre-authorization or provide hospital admission notification. The evidence shall support the provider or facility followed our policy and that the required information was entered correctly by the provider office or facility into the appropriate system. **Note**: A copy of the faxed preauthorization request showing the information was entered correctly or a copy of the provider's or facility's fax cover sheet for hospital admission notifications indicating the member health plan information and a fax confirmation from the fax machine showing the fax was successfully sent to the appropriate health plan fax number will be considered compelling evidence
5. A surgery which requires pre-authorization occurs in an urgent/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.

Inpatient concurrent review

All hospital and behavioral health admissions are subject to concurrent review. Upon receipt of the admission notification, we will respond with an acknowledgment fax that includes the date clinical information will be due.

Facilities are required to send us medical records upon request.

Discharge planning for members with long length of stay

Our care management team provides discharge planning support for members with long length of stays. We engage high-risk members in an acute inpatient setting. This care management

process includes assisting the member with discharge planning, transition of care management and performing medical necessity reviews.

We require facilities to provide documentation, such as a treatment plan, when requested for extended length of stays and assist us with discharge and care coordination to reduce readmissions. Providers must provide records when requested and within the required timeframe.

All clinical reviews are based on medical necessity criteria.

We may also conduct post-service reviews for medical necessity when such reviews are not conducted concurrently. Documentation for review via records requests may continue, as needed, for care coordination or upon receipt of the claim(s). If a claim does not meet the guidelines for the inpatient stay, it will be denied. Facilities should rebill Medicare Advantage claims using Type of Bill 0127, following CMS guidelines. Commercial claims can be rebilled with Type of Bill 0127 or 0137, whichever is appropriate. For more information, view the:

- Medicare Benefit Policy Manual (Chapter 6): **cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c06.pdf**
- MLN Matters Number MM8820: **cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R1412OTN.pdf**

Payment implications for failure to pre-authorize services

Failure to secure approval for services subject to pre-authorization requirements will result in an administrative denial, claim non-payment and facility liability. The complete list of payment implications is available in the Pre-authorization section of our provider website.

Other facility guidelines

Level of care

When a member's procedure or service is performed in a place other than the site of service approved by the health plan during the pre-authorization process, the member will not be liable for the charges and they will become a facility write-off.

Preventable adverse events

We follow our *Preventable Adverse Events* (Administrative #106) reimbursement policy. We also encourage the use of the World Health Organization's *Surgical Safety Checklist* at **who.int/teams/integrated-health-services/patient-safety/research/safe-surgery/tool-and-resources**.

Reimbursement of room and board

We follow our *Reimbursement of Facility Room and Board* (Facility #103) reimbursement policy.

Finance charges

We will not pay finance charges assessed against outstanding balances payable by us; nor may our members be billed for such charges. Members may be held liable for finance charges assessed against outstanding balances payable by the member (e.g., deductibles, copayments, coinsurance) commencing once we have made payment or issued a denial.

After-hours services charges

We will not reimburse hospitals for additional charges assessed for emergency room services provided to our members after regular business hours; nor may our members be billed for such charges.

Because hospitals offer emergency services to the public on a 24-hour basis, the hospital's overall operational costs and charge structure should incorporate any additional expenses incurred by the hospital for staffing after regular hour care.

After-hours emergency room charges will not be allowed for radiology, lab or physician callback or for an emergency room surcharge.

Adjustments to processed claims

We pay processed claims which are resubmitted for an adjustment as a result of provider audit activity only when each of the following criteria is met:

- The claims are resubmitted as a result of audit activity which is performed routinely as a quality control function and for which charts are selected randomly.
- Claims are resubmitted uniformly for all patients regardless of third-party payer involvement or of third-party payer.
- Claims which are resubmitted reflect a full debit and credit procedure and not just "lost charges."
- Written documentation that the service was provided is available.
- Resubmitted claims are received within the appropriate timely filing guidelines as defined by your facility Agreement.

Our members may not be billed for amounts denied as a result of this adjustment guideline.

We may further investigate claims for the period in question and further offset or obtain a refund for additional claims in which we have overpaid the provider.

Medical management

Services and supplies that are eligible for reimbursement must be medically necessary, as defined in the medical policies.

Examples of medical management responsibilities may include, but are not limited to, the following:

- Preadmission review to determine whether a scheduled inpatient admission is medically necessary
- Admission review to determine whether an unscheduled inpatient admission or an admission not subject to preadmission review is medically necessary
- Concurrent review to determine whether a continued inpatient admission is medically necessary, including the management of patient care by suggesting alternative sites and methods of care

- Length-of-stay review to assign the number of inpatient days appropriate for an inpatient stay
- Retrospective review to determine whether services and supplies were medically necessary including the assignment of appropriate diagnostic and procedure codes
- Case management to coordinate the care for patients whose medical needs are extensive and usually longer term, when applicable
- Review of the hospital's health care practices and utilization patterns
- Utilization guidelines to determine appropriate rendering of health care services
- Collaboration with us on clinical guidelines/pathways and disease management programs
- Post-payment review for appropriate level of care when concurrent management has not occurred.
- Our on-site reviewers will have access from the provider, and appropriate personnel, to chart documents to assure the above. Concurrent reviewers will have access to charts and patients as needed on the nursing floors. Retrospective and quality reviewers will have access to chart documents in the provider's medical records department. Our reviewers will make best efforts to work with the provider and to audit policies
- Quality improvement activities that support credentialing, re-credentialing, clinical and service studies and other medical management functions

Non-reimbursable revenue codes

Unless otherwise specified in the contract*:

- Clinic charges 0510-0529 are non-reimbursable.
- Revenue code 0761 must be appropriately billed. As directed in the UB-04 Editor, bill revenue code 0761 for actual use of a treatment room in which a specific procedure has been performed or a treatment rendered. Do not bill evaluation & management (E&M) CPT codes with revenue code 0761.
- E&M codes billed with revenue codes that include, but are not limited to, 0280, 0480, 0760, 0762-0769 and 0960-0989 are not reimbursable.

* Some critical access hospitals (CAHs) are excluded from the above terms regarding E&M billings for revenue codes 0510-0529 and 0960-0989.

Freestanding ambulatory surgery centers

Freestanding ambulatory surgery centers (ASC) provide an alternative setting for surgical procedures that would otherwise be performed in a hospital on an outpatient basis.

Facility accreditation

Before reimbursement can be approved, or contracted for facility fees, a freestanding ASC must be credentialed. The freestanding ASC must have:

- A current passing state quality review survey
- A current onsite quality assessment completed by us, or
- A current passing quality review from CMS

CMS or state surveys cannot be more than three years old and may be submitted upon recredentialing.

ASC facility fee services

Unless otherwise specified in the contract, the maximum allowable is intended to include, but not limited to the following:

- Intraocular lenses for insertion during or after cataract surgery
- Administrative functions such as scheduling or cleaning, utilities and rent
- Anesthetic and any materials, disposable or re-useable, needed to administer anesthesia
- Implants, including but not limited to the following: screws, plates, anchors, pins, and wires
- Nursing, technical staff, orderlies and others involved in patient care connected to the procedure, intravenous therapy, and other related services
- Use of facility, including operating room, recovery and/or short stay rooms, prep areas, and use of waiting rooms and lounges created for patients and relatives
- Diagnostic testing such as urinalysis, blood hemoglobin or hematocrit, pre-operative chest x-ray, and therapeutic items and services directly related to the procedure/service
- Drugs (including take home), biologicals (blood), surgical dressings, supplies, splints, casts, appliances, non-custom braces, disposable infusion pain control pump, and equipment related to the provision of care

Services not included in the ASC facility fee

Unless otherwise specified in the contract, these items should be billed separately from the facility fee with appropriate Healthcare Common Procedure Coding System (HCPCS) or CPT coding.

- Ambulance services
- Custom braces (e.g., leg, arm, back and neck)
- Services furnished by an independent laboratory
- Physician or other individually contracted provider services, including anesthesia
- The sale, lease or rental of durable medical equipment to ASC patients for use in their homes
- Prosthetic devices defined as those items that are permanent replacements to existing body parts, including artificial legs, arms and eyes. Invoices are to be submitted upon request. Shipping and handling are not separately reimbursed.

Submitting claims

- ASCs cannot append a modifier 50 when billing bilaterally. ASCs must bill bilateral procedures on two separate lines with an RT and LT modifier.
- When billing multiple procedures, each procedure will need to be billed on a separate line with a unit of 1 in order for the system to calculate correctly.

Notice of Medicare non-coverage (NOMNC)

Our network SNF, home health and hospice (applies to participating MA hospice providers in Oregon, Utah and Clark County, Washington only)-providers with Medicare contracts are

expected to deliver the NOMNC according to CMS guidelines at least two days before the last day of covered SNF, home health or hospice services for Medicare members.

The NOMNC informs our members of the date they no longer meet criteria for SNF, home health or hospice care and describes their appeal rights.

We will request the clinical documentation to support continued SNF and home health care three to five days before the current authorization period ends. Based on our review, we will notify you of our determination as follows:

- If we determine that continued SNF or home health care is appropriate, we will send notification of the new authorized dates.
- If we determine that the patient no longer meets the criteria for SNF and home health coverage, we will prepare the patient-specific NOMNC and send it to you with our determination. **It is your responsibility to deliver the NOMNC to the patient or their authorized representative at least two days prior to the last day of coverage.**

Please follow these steps to ensure that the NOMNC is delivered in compliance with the requirements:

1. The SNF, home health or hospice agency discusses discharge with the patient and family or authorized representative informing them of the last covered day of services and presents the NOMNC provided by Regence.

2. The patient or authorized representative signs page 2 of the NOMNC. If the patient is unable to sign and the SNF, home health or hospice agency is working with an authorized representative who is unable to be present that day, the SNF, home health or hospice agency may issue the NOMNC by telephone. For a telephonic notice to be valid, the documentation on the NOMNC must include all of the following:

    - The name of the staff person initiating the contact
    - The name of the representative contacted by phone
    - The date and time of the telephone contact
    - The telephone number called
    - A notation that full appeal rights were given to the representative

    The date of the telephone conversation is the date of the receipt of the notice. The facility or agency must confirm the telephone contact by sending written notice to the authorized representative on that same date.

3. Please indicate on the NOMNC that the member is a participant in the VBID Hospice Model. This will be helpful for CMS Quality Improvement Organizations (QIOs), if needed.

4. Copies of the completed NOMNC are:

- Given to the patient or the authorized representative who signed the NOMNC
- Placed in the patient's medical record at the SNF, home health or hospice agency
- Faxed to Regence at 1 (855) 240-6498 as soon as possible after the form is signed

NOMNCs can be issued early to accommodate a weekend or to provide a longer transition period. After delivery of the NOMNC, the patient may choose to appeal the decision. They must contact the QIO to request a review no later than noon on the day before services are to end. The QIO appeal decision will generally be completed within 48 hours of the patient's request. Please be prepared to provide documentation to us quickly to assist the QIO review process.

Provider responsibility for failure to deliver a valid NOMNC:
Medicare Advantage providers are responsible for the delivery of the NOMNC. **If a QIO or Regence determines that you did not deliver a valid NOMNC to a beneficiary or that requested records were not returned by a stated deadline, you will be financially liable for continued services until two days after the beneficiary receives valid notice, or until the effective date of the valid notice, whichever is later.** You must supply all information, including medical records, requested for the QIO Appeal to Regence.

The *Notice of Medicare Non-coverage* (NOMNC) Form CMS-10123 form is available on the CMS website at **cms.gov/Medicare/Medicare-General-Information/BNI**.

Hospice

See the *Notice of Medicare Non-coverage* (NOMNC) section above.

Hospice services provide medical, nursing, and emotional care when a cure is no longer possible. Hospice care is provided by a coordinated team of professionals and may include a:

- Nurse
- Physician
- Therapist
- Social worker
- Home health aid
- Bereavement counselor

View pre-authorization requirements for Medicare Advantage members on our provider website: Pre-authorization>Medicare.

Treatment plans
Treatment plans and progress notes may be requested for selected patients. We reserve the right to review past records and claims submissions. We require fully documented treatment plans to include:

- Physician prescription or referral
- Appropriate and legible chart note documentation

- Progress reports and/or notes which support the status of the patient should include:
    - The diagnosis or diagnoses must support the level of care provided.
    - Medical necessity of the care provided must be demonstrated and may be subject to review.
    - For Clark County, Washington: Procedures performed must be within the scope of license as defined by either the Revised Code of Washington, Washington Administrative Code or the governing Quality Assurance Commission.

Submitting claims

- Submit claims electronically on an ANSI 837I claim format and submit it once every month.
- Include all charges for each month on one claim. Do not overlap calendar months or years.

Revenue code	Procedure code	Description
0650	S9126	Routine home care, in home, 1-7 hours (61+ days)
0651	S9126, Q5001	Routine home care, in home, 1-7 hours (1-60 days)
0652	S9125, S9126, Q5001	Continuous home care, 8-24 hours
0655	Q5003-Q5008	Respite care, Inpatient
0656	Q5003-Q5008	General inpatient hospice care
0663	S9125	Respite care, in home

Skilled nursing facilities

See the *Notice of Medicare Non-coverage* (NOMNC) section above.

Skilled nursing facilities (SNF) care for individuals requiring rehabilitative services and/or the daily attention of nurses. SNF care is for patients that no longer need all of the medical support provided by a hospital but need more skilled care than they would have at home or in a nursing home.

SNFs may be referred to as transitional care units, extended care facilities, nursing homes or sub-acute facilities.

Admissions require pre-authorization to determine medical necessity, treatment plan, length of stay, as well as requiring ongoing concurrent reviews. It is the responsibility of the SNF to ensure that a pre-authorization is in place and completed upon admission. View the Pre-authorization section of our provider website.

Medicare Advantage SNFs

The Medicare Advantage SNF program aligns reimbursement with quality for our Medicare Advantage SNFs. The program is based on the CMS Quality of Patient Care Star Ratings in

Medicare Home Health Compare. Medicare Compare is available at **medicare.gov/care-compare**.

Quality ratings and reimbursement will be reviewed annually. Notification to facilities of changes to the percentage of Medicare allowable will be provided by June 1 each year for an October 1 effective date. Reimbursement rates will be based on an agency's Quality of Patient Care Star Ratings for the period ending each April based on the previous calendar year's data. Payment continues to be based on a percentage of the current CMS Home Health Prospective Payment System (PPS) fee schedule, available at **cms.gov/medicare/medicare-fee-for-service-payment/snfpps**.

CMS Star Rating	Regence quality rating	% of CMS allowable
5 Stars	Excellent	85%
4 Stars	Good	80%
2-3 Stars	Adequate	75%*
1 Star	Poor	70%
*If a provider is new and does not have any published Medicare Star data available or inadequate data (e.g., too few to score), Regence will utilize the Quality Rating of Adequate.		

Note: A SNF receives a "Poor" rating based on April Quality of Patient Care Star Ratings for two consecutive periods will receive a 90-day notice terminating their agreement effective September 30 of that year. If terminated, the facility is not eligible to reapply for participation in any of our networks for two years from the end of the network participation date.

Home health

See the *Notice of Medicare Non-coverage* (NOMNC) section above.

Home health encompasses a broad spectrum of both health and social services delivered to the recovering, disabled or chronically ill person in the home environment. These services include:

- Nutritional services
- Medical social services
- Therapy services (e.g., physical, occupational, speech)
- Traditional professional nursing and home care aide services

Generally, home health is appropriate whenever a person needs assistance that cannot be easily or effectively provided only by a family member or friend on an ongoing basis, for a short or long period of time.

Home health care is subject to the following limitations:

- The patient's condition must be serious enough to require hospitalization in the absence of home health care.
- The patient must be homebound, which means that leaving the home could be harmful to him or her or would involve a considerable and taxing effort.

Please verify the patient's eligibility and benefits. Home health services may require pre-authorization for medical necessity; refer to the Pre-authorization section of our provider website.

Billing guidelines

The following services can be performed by any of the following professionals, if they are employees of and billed by an approved home health agency:

- Certified aide
- Speech therapist
- Registered nurse
- Physical therapist
- Nutritionist/dietician
- Master social worker
- Occupational therapist
- Licensed practical nurse

A written treatment plan and the signature of the attending physician must be on file at the home health agency.

A home health agency can submit claims for supplies and home medical equipment that are eligible for reimbursement. The treatment plan should describe in detail the specific services to be provided to the patient.

Claims submission

Claims for home health services must be submitted on an ANSI 837I (Institutional) claim format and include the appropriate HCPCS Code in addition to the appropriate revenue code as indicated below.

Revenue code	Procedure code	Description
551	CPT 99500-99507, 99511, 99512 and 99600	Skilled nursing visit
552	HCPCS S9123	Hourly skilled nursing services
552	HCPCS S9124	Hourly LPN care
571	HCPCS 99509	Home health aide visit
572	HCPCS S9122	Hourly home health aide or CNA care
561	HCPCS S9127	Medical social services per diem
421	HCPCS S9131	Physical therapy per diem
431	HCPCS S9129	Occupational therapy per diem
441	HCPCS S9128	Speech therapy per diem

691	CPT 99509	Palliative care home health aide visit
691	CPT 99510	Palliative care medical social services visit
942	HCPCS S9470	Nutritionist visit

Note: Reimbursement for supplies is included in the payment amounts listed in your Agreement. Supplies shall not be considered eligible for additional reimbursement.

Pre-authorization

Covered Services for home health care are limited to services which are medically appropriate for the individual patient's condition. Review our pre-authorization lists in the Pre-authorization section of our website.

Pre-authorization requests should be submitted five to seven days before the subsequent episode begins. Requests should include the original Outcome and Assessment Information Set (OASIS) and the completed medication reconciliation form, both signed by the physician.

Medicare Advantage home health agencies

The Medicare Advantage home health program aligns reimbursement with quality for our Medicare Advantage home health agencies. The program is based on the CMS Quality of Patient Care Star Ratings in Medicare Home Health Compare. Medicare Home Health Compare is available at **medicare.gov/homehealthcompare/search.html**.

Quality ratings and reimbursement will be reviewed annually. Notification to agencies of changes to the percentage of Medicare allowable will be provided by October 1 each year for a January 1 effective date. Reimbursement rates will be based on an agency's Quality of Patient Care Star Ratings for the period ending each July based on the previous calendar year's data. Payment continues to be based on a percentage of the current CMS Home Health Prospective Payment System (PPS) fee schedule.

If a provider location has a CMS Star Rating that falls between two levels, Regence will round up to the next Star Rating and reimburse at the respective provider quality rating and percentage of CMS allowable. For example, a 4.5 Quality of Patient Care Star Rating will be rounded to 5 Stars, considered as an "Excellent" quality rating and reimbursed at 105% of the CMS allowable.

CMS Star Rating	Regence Quality Rating	% of CMS Allowable
5 Stars	Excellent	105%
4 Stars	Good	85%
2-3 Stars	Adequate	75%*
1 Star	Poor	70%
*If a provider is new and does not have any published Medicare Star data available or inadequate data (e.g., too few to score), Regence will utilize the Quality Rating of		

Adequate.

Note: If a home health agency has a poor quality rating for two consecutive years, we will evaluate continued participation for the agency and may determine that terminating participation is appropriate.

Notification requirements for Medicare Advantage home health agencies

Home health agencies are required to provide written notification to Medicare patients before reducing or terminating an item and/or service and when home health services are ending.

In accordance with Medicare guidelines, home health agencies are responsible for issuing the following beneficiary rights and protections notices to Medicare patients when required:

- *Home Health Change of Care Notice* (HHCCN) Form CMS-10280
- *Advance Beneficiary Notice of Noncoverage* (ABN) Form CMS-R-131
- *Notice of Medicare Non-coverage* (NOMNC) Form CMS-10123 (See instructions under Skilled nursing facilities above)
- *Detailed Explanation of Non-coverage* (DENC) Form CMS-10124

These forms are available on the CMS website at: **cms.gov/Medicare/Medicare-General-Information/BNI**.

Home infusion therapy

Home infusion therapy allows patients to receive vital fluids and medications without the inconvenience or costs of a hospital visit. These services may be provided by any agency that is dually licensed as a pharmacy and a home health agency.

Home infusion therapy services are not allowable for days when a patient is in an inpatient facility.

Infusion services and/or administrative drugs may require pre-authorization. The patient must have a written prescription and plan of care. The provider should always sign changes in infusion therapy, including the dose and frequency of medication.

Wastage policy

Medicine mixed and delivered to the patient but not used must be billed by using the J code with modifier JW and the National Drug Code (NDC) number.

Per diem rate includes

- Lab draws
- Setup and disposal
- Administrative overhead
- Clinical pharmacy services
- Delivery of medication and supplies

- Pharmacy compounding and dispensing fees
- Intravenous solutions, diluents and compounding ingredients
- Equipment (e.g., IV pumps, poles), ancillary medical supplies (e.g., syringes, tubing) and nursing supplies (e.g., catheter care kits, catheter-flushing solutions, dressings)

Nursing services include:

- Pharmacokinetic dosing
- Compounding of medication
- Patient/caregiver educational activities
- Monitoring for potential drug interaction
- Pharmacy assessment and clinical monitoring
- Review and interpretation of patient test results
- Medication profile set-up and drug utilization review
- Comprehensive knowledge of vascular access systems
- Development and implementation of pharmaceutical care plans
- Home visit by a health care professional in a single 24-hour period
- Recommendation of dosage or medication changes based on clinical findings
- Coordination of care with physicians, nurses, the patient and his or her family, other providers and caregivers
- Patient discharge services, including communication with other medical professionals and closing of the medical record
- Sterile procedures including intravenous admixtures, clean room upkeep, vertical and horizontal laminar flow hood certification and all other biomedical procedures necessary for a safe environment

Growth hormones

All growth hormones must be pre-authorized and a contracted growth hormone provider must render all services.

Durable medical equipment and prosthetic devices

Durable medical equipment (DME) can enhance the quality of life for those in need of services by providing durable medical equipment and supplies. Rehabilitation products are a necessity for anyone who has been involved in any minor or serious injury or condition such as a stroke. For those whose injuries are less severe, DME needs may include items such as crutches, canes and walkers.

DME refers to equipment that is:

- Able to withstand repeated use
- Appropriate for use in the home
- Primarily and customarily used to serve a medical purpose
- Not generally useful to a person in the absence of illness or injury

The provider agrees to provide medical equipment, orthotic devices, prosthetic appliances and other medically necessary supplies to Regence's members who submit a physician's prescription to secure such equipment or supplies. Such medical equipment and supplies shall be immediately available in the provider's warehouse. Items not routinely available shall be delivered to the patient as rapidly as possible, not to exceed two calendar days unless delayed by the manufacturer. The provider shall obtain pre-authorization from Regence prior to providing certain medical equipment in accordance with Regence's policies and pre-authorization lists.

The provider also agrees to the following additional responsibilities:

- Accept orders for medical equipment, related products and services on a 24-hour basis.
- Provide free delivery and installation of medical equipment and related products ordered for or furnished to patients.
- If requested by Regence, perform in-service training for Regence's employees on the medical equipment and related products and supplies.
- Maintain an adequate inventory of medical equipment and related products and supplies including economical models that meet the patient's needs and quality standards.
- Provide installation by people properly trained and qualified to do so.
- Ensure that all equipment has been maintained to manufacturer's specifications and standards and that records are available to confirm this.
- Meet or exceed all applicable standards in the Joint Commission Accreditation Manual for Home Care.

The provider agrees that the maintenance, replacement or repair of medical equipment and other items and supplies shall be available as follows:

- If a patient's life is threatened by a sudden equipment malfunction, emergency services are available 24 hours a day, seven days a week.
- If the performance and intended use of the equipment is affected by a sudden malfunction, services for repair or replacement are available 24 hours a day, seven days a week.
- If the performance and intended use of the equipment is not affected by a sudden malfunction, services for assessment, repair or replacement (when applicable) are available within five business days.
- Emergency backup systems for electrical equipment are provided either through a manual means or a self-contained battery integral to the equipment.
- The medical equipment, items and supplies are safe, sanitary and working as intended for use in the patient's home. The provider will complete a written assessment at the time of delivery and ensure that the medical equipment, items or supplies are appropriate for use within the patient's home.

The provider shall provide education appropriate to the medical equipment, items and/or supplies provided and shall document ongoing education of the patient, family members and care givers, including but not limited to the following:

- Written instructions in terms the patient and family can reasonably understand, which includes but is not limited to the care, storage, handling and therapeutic use of the medical equipment, items and supplies
- Written instructions regarding when and how to contact the provider for maintenance and/or repair
- Documentation of the patient's and/or patient's family's receipt and understanding of the above required education and their demonstrated ability to operate the equipment safely and appropriately
- Verbal and written instructions regarding emergency procedures
- Provide at a minimum, a one-year warranty for purchased medical equipment, orthotic devices and prosthetic appliances (this does not supersede or replace any manufacturer's warranty)

The provider shall be responsible for servicing, at no additional charge, all rented medical equipment. The provider shall provide warranty services for purchased medical equipment, orthotic devices and prosthetic appliances limited to the manufacturer's warranty. Repairs and replacements covered by warranties are not eligible for reimbursement. Any maintenance or repair performed on the medical equipment shall not be billed to Regence unless pre-approved by Regence.

Least costly items and services: The provider shall provide or arrange for the provision of the least costly items and services appropriate to the member's needs and safety. Exceptions must be discussed and approved by Regence and the patient prior to delivery of the item or service.

Dispensing codes

Dispensing codes are not eligible for separate reimbursement.

Oxygen equipment rental-only reimbursement

Our DME exhibits specify that life-sustaining oxygen equipment is eligible for reimbursement based on rental periods only. Reimbursement exceeding the rental allowable rate is not provided for equipment purchased by the member.

If the member purchases the equipment, DME providers should obtain a member consent form signed by the member that specifies that neither the DME provider nor the Company is financially responsible in excess of one month's rental allowable amount.

For more information, refer to our reimbursement policy *Durable Medical Equipment Purchase and Rental Limitations* (Administrative #131).

Oxygen and oxygen equipment

The fee schedule amount for oxygen system rentals is a monthly allowance and will include all equipment, oxygen, accessories, supplies, maintenance and repairs. The provider will include the appropriate modifier identifying the amount of oxygen prescribed.

We reserve the right to determine if an item should be rented or purchased on an individual item basis according to the medical recommendations of physicians and the determination of our appropriate employees or agents who may review such recommendations.

Sales tax *(Clark County, Washington only)*
In compliance with Washington state Senate Bill (SB) 6273 at **http://apps.leg.wa.gov/billinfo/summary.aspx?year=2010&bill=6273**, our payment to providers for eligible prescribed durable medical equipment or mobility enhancing equipment claims includes the sales tax or use a tax calculation.

Please note the following billing information:

- A separate line item should appear on claims for the sales tax or tax calculation.
- Use HCPCS S9999 *Sales tax* when submitting claims. The tax should be based on the equipment's allowable amount listed in our fee schedules.

Our payment to the provider will include the tax in the payment. Providers must then remit the tax to the Department of Revenue.

Rental/purchase guidelines
Rental

- Rental is paid up to the purchase price
- Use modifier RR with HCPCS codes to indicate rental
- Repairs required on rented equipment are not separately reimbursable
- One unit of service equals one month's rental, with the exception of HCPCS B4034, B4035, B4036, E0277, E0935, and E2402 where one unit of service equals one day's rental

Purchase

- Use modifier NU if purchasing new HME equipment
- Use modifier UE if purchasing used HME equipment
- The outstanding dollars are paid toward the purchase price

We will only reimburse up to the purchase price regardless of when the decision to purchase is made.

Additional modifiers
When appropriate, use the following modifiers when billing for DME services. If more than one modifier is used, place the modifier in the first position or directly after the procedure and/or HCPCS code.

- Modifier AW *Items furnished in conjunction with surgical dressings*
- Modifier KM *Replacement of facial prosthesis including new impression/modulage*
- Modifier KN *Replacement of facial prosthesis using previous master model*

Shipping and handling
Shipping and handling charges are not eligible for separate reimbursement.

Repairs and modifications
If the purchased equipment is not covered by the manufacturer's warranty, we allow one month's rental fee for loaner equipment while the equipment is being repaired or serviced.

All claims for repairs and servicing are subject to review and approval to ensure charges do not exceed the purchase price.

Replacement
If an item needs to be replaced, the referring physician must submit a new prescription and the supplier must indicate the condition of the present equipment on the prescription. Claims for replacement are subject to our review and approval.

Customization
When it is necessary for a manufacturer, factory or supplier to create an item to fit a specific patient, it is considered a custom item. Custom items must be purchased rather than rented and medical necessity criteria must be met.

Back-up DME
Back up DME items are not eligible for separate reimbursement.

Deluxe products/upgrades
The patient may choose to upgrade from a standard product. We reimburse up to the allowable amount for the standard product.

It is the responsibility of the provider to inform the patient that there are standard products available that meet medical necessity. The patient must sign a waiver indicating that he or she has been informed of his or her responsibility for any outstanding balance prior to ordering the product or before the product is delivered. If the patient does not sign a waiver, the outstanding balance will be a provider write-off. The provider should keep this waiver on file and submit it with their invoice if requested.

Providers should use HCPCS S1001 *Deluxe item, patient aware (list in addition to code for basic item)* when billing for the cost in excess of the standard product. The signed waiver must accompany the bill and be on file if a health care service requests the waiver at a future date.

If a member is requesting a deluxe item that is medically necessary—such as a deluxe hearing aid—that exceeds the cost of the device, please bill as follows:

- Report the appropriate HCPCS code and standard charge for the least expensive device that meets the member’s medical needs and is considered medically necessary on the first line of the claim.
- Report code S1001 *Deluxe item, patient aware (list in addition to code for basic item)* and the balance between the base model considered medically necessary and the deluxe model on the second line of the claim.

- Before providing service, have the member sign a waiver indicating they are aware that the deluxe model is not covered by their insurance and that they will be liable for the difference in cost between the deluxe and standard charges.

Pre-authorization
Pre-authorization may be required. View our pre-authorizations lists, forms and submission information on our provider website.

Orthoses
Custom-made, functional orthotics are covered when they are medically necessary to treat a condition of the foot, ankle or leg. Prefabricated, supportive, accommodative and digital orthotics are not covered on most of our products.

Billing guidelines
- Indicate the units of service
- Use HCPCS codes to bill for the orthoses

Note: Reimbursement for HCPCS orthotic codes include the cost of orthoses, cast impression and materials.

Fitting or adjustment
Adjustment and/or fitting of orthoses and prosthetics is not covered. This service is included in the cost of the device.

Repair and/or replacement
The repair and/or replacement of an orthotic or prosthetic device may be allowed, based on the patient's benefit. Please use the appropriate HCPCS or CPT code when submitting a claim for repair or replacement.

Prosthetic devices
For purposes of this document, the definition of prosthetic devices (other than dental) is: A device which replaces all or part of an internal body organ (including contiguous tissue) or replaces all or part of the function of a permanently inoperative or malfunctioning internal body organ.

A prescription must be on file and the prescribing physician's name must be submitted on the claim. Pre-authorization may be required.

DME documentation requirements for Medicare Advantage Plans
Providers must follow CMS criteria for durable medical equipment (DME) for our Medicare Advantage Plan members. This includes using appropriate Certificates of Medical Necessity (CMN) or other forms.

Criteria, documentation requirements, CMN forms and instructions for completing the forms are available in chapter 4 of the Supplier Manual **med.noridianmedicare.com/web/jddme/education/supplier-manual** from Noridian Heathcare Solutions. Noridian has also made

several documentation checklists at **https://www.noridianmedicare.com/dme/coverage/checklists.html**, available for various DME, to help ensure compliance with the requirements.

We do not require the CMN to be submitted with the DME claim, however, it must be available in the event of an audit or medical necessity review.

Urgent care clinics

Urgent care is a category of walk-in clinics focused on the delivery of ambulatory care in a dedicated medical facility outside of a traditional emergency room. Urgent care centers primarily treat injuries or illnesses requiring immediate care, but not serious enough to require an emergency room visit. Urgent care clinics are distinguished from similar ambulatory health care centers, such as emergency rooms and convenient care clinics, by the scope of conditions treated and available facilities on-site.

Urgent care clinics can only submit professional claims electronically via an ANSI ASC X12N 837P Health Care Claim Transaction using the Place of Service Code 20 (POS -20).

Qualifying criteria for categorization as an urgent care clinic

Availability and capability

- The facility accepts walk-in patients of all ages for a broad spectrum of illness, injury and disease.
    - **Hours**: During weekdays and evenings and at least one weekend day.
    - **Appointments**: Not needed.
- The facility has access to rapid diagnostic testing (including labs and radiology), on-site injectable medications for emergent needs, and transfer or admission arrangements with local hospitals.

Building and equipment

- The facility has at least one exam room and separate waiting area.
- The following equipment is available (and the staff are trained to use this equipment):
    - Automated external defibrillator (AED) or standard defibrillator
    - Oxygen and emergency breathing equipment
    - Drug cart with some emergency medications

Staffing

- A licensed physician (MD/DO) has been designated as the facility's medical director and is responsible for overall clinical quality.
- All medical care is provided under the direction or supervision of a physician who accepts responsibility for that care.
- Any paraprofessionals who assist in providing care (e.g., RN) are appropriately licensed.
- Licensed providers are able to:
    - Perform pulse oximetry, cardiac monitoring, and advanced cardiac life support in an emergency, while 911 is called.
    - Obtain and read an EKG and X-ray.
    - Administer oral, intramuscular, and intravenous medication and fluids.

- Perform minor procedures (e.g., suturing, cyst removal, incision, drainage, splinting)

Licensure and compliance

- The facility is licensed by the state in which it is located if the state requires such licensure.
- The facility complies with applicable federal, state and local laws and regulations.

If your clinic meets the criteria above and is interested in being designated as an Urgent Care Clinic, please update your information through the Self-Service Tool on our provider website: Quick Links>Self-Service Tool. You may also call our Provider Contact Center:

- For Uniform Medical Plan, call 1 (888) 894-3682
- For all other lines of business, call 1 (800) 253-0838

Retail clinics

Retail clinics, sometimes referred to as convenient care clinics, are a category of walk-in clinics focused on the delivery of ambulatory care in a retail setting, such as a supermarket or pharmacy location outside of a traditional dedicated medical facility. Retail clinics provide convenient access to care for preventive health services. Retail clinics also provide care for minor illnesses and injuries for which immediate care is desired but not medically required and that are not serious enough to require an urgent care or emergency room visit. Retail clinics are distinguished from similar ambulatory health care centers, such as urgent care and emergency rooms, by the scope of conditions treated and available services on-site.

Retail Clinics should only submit professional claims electronically via an ANSI ASC X12N 837P Health Care Claim Transaction using the place of service code 17 (POS 17).

Qualifying criteria for categorization as a retail clinic

Availability and capability

- The clinic accepts walk-in patients for minor illness, injury and disease. Age ranges may vary by clinic (e.g., 18 months or older).
  - **Hours**: During weekdays and evenings and at least one weekend day
  - **Appointments**: Not needed
- The clinic has access to Point of Care “CLIA” waived lab testing, the ability to send out for lab services and write prescriptions for medications routinely within the scope of services provided.

Building and equipment

- The clinic has at least one exam room and a separate waiting area.

Staffing

- A licensed physician (MD/DO) provides oversight or supervision of a retail clinic and is responsible for ensuring clinic policy and procedures are in place with a dedicated team of medical professionals.

- An advance practice provider (ARNP, PA) provides treatment of patient in the retail clinic and is responsible for following the policies and procedures while providing the best care within those guidelines.
- Any paraprofessionals who assist in providing care (e.g., medical assistants) are appropriately licensed.
- Licensed providers can:
    - Obtain samples from venipuncture and/or non-venipuncture lab tests
    - Perform point of care testing, such as rapid strep, urinalysis and conjunctivitis testing
    - Administer immunizations including travel vaccinations, following a pre-travel health evaluation
    - Write prescriptions for medications to treat minor illnesses and injuries that fall within the retail clinic scope of service

Licensure and compliance

- The clinic is licensed by the state in which it is located, if the state requires such licensure.
- The clinic complies with applicable federal, state and local laws and regulations.
- Joint Commission Accreditation is preferred.

If your clinic meets the criteria above and is interested in being designated as a retail clinic, please update your information through the Self-Service Tool on our provider website: Quick Links>Self-Service Tool. You may also call our Provider Contact Center:

- For Uniform Medical Plan, call 1 (888) 894-3682
- For all other lines of business, call 1 (800) 253-0838

Behavioral health

Behavioral health facilities must meet the contracting service requirements for each level of service in the delivery of mental health and substance use treatment. Facilities must be licensed for the level(s) of care they provide in the state where services are rendered.

All treatment should be individualized to meet the member's needs.

Mental health and eating disorder treatment expectations and requirements are detailed in our medical policies, which are available on our provider website.

- **Commercial policies**: Policies & Guidelines>Medical Policy>Explore Commercial Policies>Continue to the Medical Policy Manual>Table of Contents>Behavioral Health.
- **Medicare Advantage policies**: Policies & Guidelines>Medical Policy>Explore Medicare Advantage Medical Policy>Continue to the Medicare Advantage Policy Manual>Table of Contents>Behavioral Health.

Substance use disorder treatment expectations and requirements are based on ASAM criteria.

Regence

Regence BlueShield serves select counties in the state of Washington
and is an Independent Licensee of the Blue Cross and Blue Shield Association

NICU/PICU Notification of Admission Form

Initial Review Form

Please complete this form at the time of admission for all new NICU/PICU admits and fax it back to (800) 453-4341

Request authorization:

Bed Type Requested
☐ **PICU** ☐ **NICU**

Level of Care (NICU Only)
☐ **1** ☐ **2** ☐ **3** ☐ **4**

Admit date:	☐ Premature Delivery ☐ Complicated Term Delivery

Member information (Parent/Guardian information)

Member ID #:	
Member Name:	Member DOB:

Child information

Child Name:	Child DOB:

Facility information

Facility name:	
NPI/TID:	
Facility fax #:	Facility phone #:

Utilization Reviewer Information

Name:		
Phone #:	Confidential voicemail ☐ Yes ☐ No	Fax #:

Discharge Planning

Discharge planner name:		
Phone #:	Confidential voicemail ☐ Yes ☐ No	Fax #:

ICD-10 diagnoses

Maternal History including psychosocial issues & pregnancy related medical issues

Patient Treatment History

Risk Assessment / Functional Impairments ☐ Not applicable

Co-occurring medical / physical illness ☐ Not applicable

Weight, Vitals, Gestational Age, Corrected Age

Treatment Plan

Treatment goals:

Medications:

Aftercare plan:

Additional Notes

Regence

Medical Policy Manual Laboratory, Policy No. 46

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

Effective: April 1, 2025

Next Review: August 2025
Last Review: March 2025

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

Liquid biopsy refers to the analysis of circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

MEDICAL POLICY CRITERIA

Notes:

- This policy only addresses testing for solid tumor cancers. For expanded tumor tissue panels, see Genetic Testing, Policy No. 83 in the Cross References section below (expanded panel testing is not covered for many indications).
- This policy does not address plasma-based *PIK3CA* testing for breast cancer.
- This policy does not address blood-based testing for *EGFR* variants in non-small cell lung cancer. See Genetic Testing, Policy No. 56 in the Cross References section below.

I. The use of cell-free tumor DNA testing for targeted treatment selection may be considered **medically necessary** when either of the following are met (see Policy Guidelines):

A. The patient has advanced or metastatic breast cancer that is estrogen receptor (ER)-positive and HER2-negative, OR

B. Both of the following (1. and 2.) are met:

1. There is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor); and

2. The test includes one or more genes for which an FDA-approved targeted therapy is available for the cancer indication (see Policy Guidelines).

II. The use of cell-free DNA testing for targeted treatment selection is considered **investigational** when Criterion I. is not met.

III. The use of cell-free DNA or circulating tumor cell testing is considered **investigational** for all other indications related to solid tumors, including but not limited to measurable residual disease (MRD) testing and cancer screening in asymptomatic individuals.

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

POLICY GUIDELINES

TESTING FOR TARGETED TREATMENT SELECTION

Cell-free tumor DNA tests to guide targeted treatment selection may be limited to a single gene or include sequencing of many, often hundreds of genes. Tests that are commonly used for this purpose include, but are not limited to the following:

- Caris Assure™ (Caris MPI)
- CellMax-LBx (CellMax Life)
- FoundationOne® Liquid CDx (Foundation Medicine)
- Guardant360® CDx
- LiquidHALLMARK® (Lucence)
- Northstar Select™ (BillionToOne)
- OncoBEAM™ (Sysmex)
- PGDx elio plasma complete and resolve (Labcorp)
- Tempus xF (Tempus)

CANCER INDICATIONS AND GENES WITH TARGETED CANCER TREATMENTS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Note: This is not an exhaustive list of all genes with FDA-approved targeted treatments. Please consult the FDA website and/or National Cancer Institute website for more current or specific information.

Cancer Indications with Targeted Treatments			
Indication	**Type**	**Genes**	**Medication**
Any solid tumor	Advanced or metastatic	*BRAF* *NTRK(1/2/3)*	Tafinlar, Mekinist, Rozlytrek, Vitrakvi
Breast cancer	HER2-negative	*BRCA(1/2)*	Lynparza, Talzenna
	HR-positive, HER2-negative, advanced or metastatic	*ESR1* *PIK3CA*	Orserdu, Pigray
	HER2-positive	*ERBB2 (HER2)*	Herceptin, Kadcyla, Perjeta
Cholangiocarcinoma	Advanced or metastatic	*FGFR2* *IDH1*	Pemazyre, Tibsovo
Colorectal cancer	Metastatic	*BRAF* *KRAS* *NRAS*	Braftovi, Erbitux, Tukysa, Vectibix
Gastrointestinal stromal tumor (GIST)	Resected, unresectable, or metastatic	*KIT (c-KIT, CD117)*	Gleevec
Melanoma, cutaneous	Resected, unresectable, or metastatic	*BRAF*	Braftovi, Cotellic, Mekinist, Opdivo, Tafinlar, Tecentriq, Zelboraf
Melanoma, uveal	Unresectable, or metastatic	*HLA*	Kimmtrak
Non-small cell lung cancer (NSCLC)	Advanced or metastatic	*ALK* *BRAF* *EGFR* *ERBB2 (HER2)* *KRAS* *ROS1*	Alcensa, Cyramza, Enhertu, Exkivity, Gavreto, Gilotrif, Iressa, Keytruda, Krazati, Lorbrena, Lumakras, Mekinist, Opdivo, Rozlytrek, Rybrevant, Tafinlar, Tagrisso, Tarceva, Tecentriq, Vizimpro, Xalkori, Zykadia
	Resected	*EGFR*	Tagrisso
Ovarian cancer (including fallopian tube and primary peritoneal cancer)	Advanced or recurrent	*BRCA(1/2)*	Lynparza, Rubraca
Pancreatic cancer	Metastatic	*BRCA(1/2)*	Lynparza

Cancer Indications with Targeted Treatments			
Indication	**Type**	**Genes**	**Medication**
Prostate cancer	Metastatic, castration-resistant	*BRCA(1/2)*	Lynparza, Rubraca
Thyroid cancer	Advanced or metastatic	*RET*	Gavreto
	Anaplastic and advanced or metastatic	*BRAF*	Mekinist, Tafinlar
Urothelial carcinoma	Advanced or metastatic	*FGFR(2/3)*	Balversa

HR: hormone receptor

TESTING FOR OTHER PURPOSES, INCLUDING MEASURABLE RESIDUAL DISEASE (MRD) AND CANCER SCREENING

Some cell-free tumor DNA and circulating tumor cell tests are not intended to identify genetic variants to guide targeted treatment selection, but instead are used to screen for the presence of cancer or for disease recurrence. Tests that are commonly used for this purpose include, but are not limited to the following:

- Avantect Pancreatic Cancer Test and Ovarian Cancer Test (ClearNote Health)
- BTG Early Detection of Pancreatic Cancer (Breakthrough Genomics)
- CellMax-PanCa Monitoring Test (CellMax Life)
- CellMax-Prostate Cancer Test (CellMax Life)
- CELLSEARCH® Circulating Tumor Cell (CTC) tests (Cellsearch)
- Colvera® (Clinical Genomics)
- FirstSight™ (CellMax Life)
- Galleri® (Grail)
- Guardant360® Response (Guardant Health)
- Guardant360® Reveal (Guardant Health)
- HelioLiver™ (Fulgent Therapeutics)
- Northstar Response™ (BillionToOne)
- Signatera™ (Natera)
- Velox™ (IV Diagnostics)

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test and the performing laboratory
2. The exact gene(s) and/or variant(s) being tested
3. Relevant billing codes
4. Brief description of why tumor tissue testing is not possible

5. Name of medication(s) under consideration that requires genetic testing
6. Medical records related to the indication for testing:
    - Cancer type
    - Treatments received

CROSS REFERENCES

1. Gene-Based Tests for Screening, Detection, and Management of Prostate or Bladder Cancer, Genetic Testing, Policy No. 17
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer, Genetic Testing, Policy No. 42
4. Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
6. Analysis of Proteomic and Metabolomic Patterns for Cancer Detection, Risk, Prognosis, or Treatment Selection, Laboratory, Policy No. 41

BACKGROUND

CIRCULATING TUMOR DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs.[1] Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

CIRCULATING TUMOR CELLS

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs.[1] Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

DETECTING CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver

mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.[1]

TARGETED TREATMENTS FOR SOLID TUMORS

There are many targeted treatments available for various solid tumor cancers. A list of some that have been approved by the FDA can be found in at their website listing the tests and associated companion diagnostics.

BLOOD-BASED MULTI-CANCER SCREENING

Cancer is the second leading cause of death in the US following heart disease. Many cancers appear to have a better prognosis if diagnosed early in their natural history. This has led to efforts to detect preclinical cancers in asymptomatic persons through screening. However, screening tests have associated benefits and harms that must be considered when evaluating whether a test should be used in a population.

Cancer screening tests such as 'liquid biopsies' that are minimally invasive and can simultaneously detect multiple types of cancer have been called multicancer early detection (MCED) tests. The primary benefit of screening for cancer is the potential to diagnose cancer at an earlier stage or detect precursor lesions that can be treated with less aggressive or more effective treatment, thereby theoretically improving the length or quality of life. Thus, cancer-specific mortality and quality of life are the primary outcomes of interest for assessing benefit. However, mortality is a demanding outcome that requires long follow-up times and a large number of participants in order to produce reliable and precise estimates.

Longitudinal examination of the population-based, age-standardized stage distribution of all cancers may give early information on the likelihood of a survival benefit. However, it is possible for screening to increase the proportion of early-stage cancers that are detected without reducing the absolute incidence of advanced cancer because of overdiagnosis.

Population-based screening is applied to asymptomatic people without signs of disease. The prevalence of any given cancer is generally low. Therefore, the majority of those screened for a particular cancer are not destined to develop clinically significant cancer that needs treatment and therefore do not benefit from screening. However, all persons screened are at risk of harm from either the screening test or the cascade of events following from a positive screening test.

The majority of harms from cancer screening come from downstream cascading events. The harms may arise from the diagnostic work-up of false positive screens, from diagnosis and treatment of overdiagnosed cancers, and from false negative screens for those cancers where screens are already part of standard care.

The harms from the diagnostic work-up of false positives depends on the false positive rate and on the nature of the work-up. The false positive rate per screening test may be low, but given that many screening strategies include repeated screening tests over many years or a

lifetime, the absolute number of people with complications as a result of a false-positive diagnostic work-up can be considerable. In addition, in the context of a test for multiple cancers, false positives can occur across several diseases.

Additionally, overdiagnosis of cancer that would not have become burdensome during an individual's lifetime leads to unnecessary treatments along with their associated risks.

There is also the potential for false-negative test results to cause harm. For example, for those cancers that already have established screening recommendations as part of standard care (e.g., breast, prostate), the new cancer screening test might alter individuals' adherence to existing recommendations which could lead to missed early diagnoses.

REGULATORY STATUS

The CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and CTCs. In 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in 2007 for monitoring metastatic colorectal cancer, and in 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immunicon for sample preparation (CellTracks® AutoPrep) and analysis (CellSpotter Analyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex. FDA product code: NQI.

Signatera® (Natera) is a laboratory developed test regulated under CLIA. The test has not been cleared or approved by the US Food and Drug Administration (FDA), but has received 3 Breakthrough Device Designations from FDA.

No blood-based multi-cancer screening tests have been approved or cleared by the U.S. Food and Drug Administration (FDA). Several tests, including Galleri® (GRAIL), CanScan™ (Geneseeq), OverC™ Multi-Cancer Detection Blood Test (Burning Rock) have been granted breakthrough device designation by the FDA.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

The context of this literature search focuses on treatment selection, monitoring treatment response, risk prediction, and screening in asymptomatic individuals. Validation studies are limited; therefore, this review is predominately focused on studies that correlate survival and risk of disease progression.

SELECTING TREATMENT IN ADVANCED CANCER

Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of liquid biopsy testing of patients who have

advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In patients able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

CIRCULATING TUMOR DNA

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.[2] The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1,338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections, by indication.

Merker (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC). Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as *BRAF* variants in melanoma[3] and *PIK3CA* and *ESR1* variants in breast cancer were identified.[4, 5]

Since the end date of the searches conducted by Merker (2018), a number of observational studies have been published for various ctDNA tests. For example, two observational studies of the clinical validity of FoundationOne® Liquid (formerly FoundationACT®) in patients with various cancers compared liquid biopsy to tissue biopsy with FoundationOne® comprehensive genomic testing.[6, 7] Additional studies have assessed the validity of other tests, including the Guardant360 test[8, 9] and OncoBEAM™ CRC assay[10-13]. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. Merker (2018) concluded that no such trials have been reported for ctDNA tests.[2]

CIRCULATING TUMOR CELLS

In breast cancer, observations that estrogen receptor–positive tumors can harbor estrogen receptor–negative CTCs,[14, 15] that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 (HER2) status compared with the primary tumor,[16-18] and that the programmed death-ligand 1 is frequently expressed on CTCs in patients with

hormone receptor–positive, *HER2*-negative breast cancer[19] have suggested that trials investigating whether CTCs can be used to select targeted treatment are needed.

The clinical validity of each commercially available CTC test must be established independently. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility.

MONITORING TREATMENT RESPONSE IN CANCER

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of liquid biopsy testing in patients who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes. Standard monitoring methods for assessing treatment response are tissue biopsy or imaging methods.

CIRCULATING TUMOR DNA

Merker (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants.[2] However, authors reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established. Additionally, the authors concluded that there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes. Therefore, no inferences can be made about clinical utility.

CIRCULATING TUMOR CELLS

Two randomized controlled trials have evaluated the clinical utility of using CTC to guide treatment decisions in patients with metastatic breast cancer.

Bidard (2021) reported on a noninferiority trial comparing CTC-driven and clinician-driven first-line therapy choice in patients with metastatic breast cancer.[20] Median PFS was 15.5 months (95% confidence interval [CI] 12.7 to 17.3) in the CTC arm and 13.9 months (95% CI 12.2 to 16.3) in the standard arm. The primary end point was met, with a hazard ratio (HR) of 0.94 (90% CI 0.81 to 1.09).

Smerage (2014) reported on the results of a randomized controlled trial of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after one cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[21] _ENREF_44 Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 (12.5 months, p=0.98). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35

months, 23 months, and 13 months, respectively (p<0.001). This trial showed the prognostic significance of CTCs in patients with metastatic breast cancer receiving first-line chemotherapy, but also that there was no effect on overall survival if patients with persistently increased CTC levels after 21 days of first-line chemotherapy were switched to alternative cytotoxic therapy.

Trials demonstrating that use of CTCs to monitor treatment for the purpose of making treatment changes are needed to demonstrate clinical utility. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

PREDICTING RISK OF RELAPSE

Monitoring for relapse after curative therapy in patients with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in patients who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes. Standard monitoring methods for detecting relapse are imaging methods and clinical examination.

CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Chidambaram (2022) conducted a systematic review and meta-analysis of the clinical utility of circulating tumor DNA testing in esophageal cancer.[22] Four retrospective studies (n=233, range 35 to 97) provided data to assess ctDNA for monitoring for recurrence after treatment. The pooled sensitivity was 48.9% (range 29.4% to 68.8%) and specificity was 95.5% (range 90.6% to 97.9%).

Merker (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse.[2] However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

Rack (2014) published results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System.[23] After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,[24] CRC,[25] bladder cancer,[26, 27] liver cancer,[28] and esophageal cancer.[29]

Merker (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.[2] Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

Signatera®

Colorectal Cancer

Chidharla (2023) published a systematic review and meta-analysis of 23 studies (n=3,568) investigating the use of ctDNA as a biomarker for minimal residual disease in patients with CRC after curative-intent surgery; only three of the included studies used the Signatera® ctDNA assay.[30] Loupakis (2021) evaluated the association of Signatera® on survival outcomes in 112 individuals who had undergone resection for metastatic CRC, and the sensitivity of Signatera testing was compared to digital droplet polymerase chain reaction (PCR) testing, but not to standard methods to identify recurrence, such as CEA and imaging.[31] Henriksen (2022) assessed the added benefit of serial ctDNA analysis; with samples taken at diagnosis, following surgery, during adjuvant therapy, and at follow up.[32] Kotani (2023) analyzed presurgical and postsurgical ctDNA levels in a large (n=1,039) prospective study that included patients with stage II to IV resectable CRC, and found that postsurgical ctDNA positivity at four weeks after surgery was associated with a significantly higher risk of recurrence (HR 10.0, 95% CI 7.7 to 14, p<0.0001), and identified patients who derived a benefit from adjuvant chemotherapy.[33] The results of the meta-analysis demonstrated that ctDNA positivity (including all tests, not just Signatera®) after surgery was associated with a significantly higher risk of recurrence, with a pooled HR of 7.27 for all stages of CRC. Furthermore, post-adjuvant chemotherapy ctDNA positivity was associated with an even higher risk of recurrence (pooled HR 10.59).

Several additional non-randomized studies have evaluated CTC tests for colon cancer recurrence. For example, Reinert (2019) enrolled 125 patients with stage I to III colon cancer in a validation study of the Signatera® assay.[34] Plasma samples were collected before surgery, at 30 days following surgery, and every three months for up to three years. The recurrence rate at three years was 70% in patients with a positive ctDNA test (7 of 10) compared to 11.9% (10 of 84) of those with a negative ctDNA test. In multivariate analyses, ctDNA status was associated with recurrence after adjusting for clinicopathological risk factors including stage, lymphovascular invasion, and microradical resection status.

Fakih (2022) directly compared Signatera® testing to other surveillance strategies in individuals with resected colorectal cancer in a retrospective observational study.[35] This study was unique in that it used NCCN recommended guidelines for surveillance and ctDNA testing was performed at the same interval as standard surveillance with CEA and imaging. Test characteristics for Signatera® were not significantly different from standard imaging techniques. Estimates were imprecise, with wide confidence intervals.

Altogether, five nonrandomized studies, for of which were noncomparative, examined the association of Signatera® testing to prognosis in individuals with CRC. They differed in their study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Three studies evaluated the association between positive ctDNA results and prognosis in CRC. These studies did not provide comparisons of ctDNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. One retrospective study compared Signatera® testing to other surveillance strategies in individuals with resected colorectal cancer. There are no randomized controlled trials, and no studies in which Signatera® testing was used to guide treatment decisions.

Signatera® for Breast Cancer

Two noncomparative studies reported the association of Signatera® testing with survival outcomes in breast cancer. There are no randomized controlled trials, and no studies in which Signatera® testing was used to guide treatment decisions. Coombes (2019) evaluated Signatera® for disease surveillance in 49 individuals who had received surgery and adjuvant therapy for stage I to III breast cancer of various subtypes.[36] In this study, the test detected ctDNA in 16 of 18 individuals who subsequently relapsed, and the presence of ctDNA test was associated with poorer prognosis. Magbanua (2021) evaluated the test as a predictor of response to neoadjuvant chemotherapy in 84 individuals with nonmetastatic breast cancer who were enrolled in the I-SPY2 trial.[37] In this population, ctDNA positivity decreased during the course of neoadjuvant chemotherapy, from 73% before treatment, to 35% at three weeks, to 14% at the inter-regimen time point, and down to 9% after chemotherapy. HRs for recurrence indicate that positive predictive value increased over time. Major limitations of both studies include a lack of comparison to standard methods of monitoring, and heterogeneity in the study populations.

Signatera® for Bladder Cancer

Two nonrandomized studies have reported an association between Signatera® testing and prognosis in bladder cancer.

Christensen (2019) assessed the association of ctDNA with prognosis in 68 individuals with localized advanced bladder cancer.[38] The presence of ctDNA at diagnosis, after chemotherapy but before cystectomy, and after cystectomy were significantly associated with recurrence (HR 29.1, p=0.001; HR 12.0, p<0.001, and HR 129.6, p<0.001, respectively).

Powles (2021) reported the association of a positive Signatera® test with treatment response in 581 individuals who had undergone surgery for urothelial cancer and were enrolled in a trial of atezolizumab versus observation.[39] Study participants who were positive for ctDNA had improved disease-free survival (DFS) and overall survival in the atezolizumab arm versus the observation arm (DFS HR 0.58, 95% CI 0.43 to 0.79, p=0.0024; overall survival HR, 0.59, 95% CI 0.41 to 0.86). No difference in DFS or overall survival between treatment arms was noted for patients who were negative for ctDNA. At two-year follow up, ctDNA status remained prognostic and no relapses were observed in the ctDNA-negative patients at baseline and after neoadjuvant therapy.

Study limitations, including a lack of comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Signatera® for Additional Indications

The evidence for the use of Signatera® to detect relapse in non-small cell lung cancer (NSCLC) following surgery is limited to a subgroup analysis of 24 individuals enrolled in TRACERx, a longitudinal cohort study of tumor sampling and genetic analysis in individuals with NSCLC.[40] Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least two single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days (range 688 to 945 days), one had a positive ctDNA test (10%). Major limitations include no comparison to standard surveillance methods and

imprecise estimates due to the small sample size. Additionally, the commercially available Signatera® has been updated since this publication.

One noncomparative retrospective study reported the association of Signatera® testing measured before and after surgery with relapse and recurrence in 17 individuals with esophageal adenocarcinoma.[41] Patients who were ctDNA-positive before surgery had significantly poorer DFS (p=0.042), with a median DFS of 32.0 months vs. 63.0 months in ctDNA-negative preoperative patients. This study was limited by the very small number sample size, and its retrospective design.

Bratman (2020) evaluated the use of Signatera® to predict treatment response in 106 individuals receiving pembrolizumab for solid tumors, including squamous cell cancer of head and neck, triple negative breast cancer, high-grade serous ovarian cancer, malignant melanoma, and mixed solid tumors.[42] Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted HR 0.49, 95% CI 0.29 to 0.83) and PFS (adjusted HR 0.54; 95% CI, 0.34 to 0.85). Among participants with at least two ctDNA measurements, any rise in ctDNA levels during surveillance above baseline was associated with rapid disease progression and poor survival (median overall survival of 13.7 months), whereas among 12 patients whose ctDNA cleared during treatment, overall survival was 100% at a median follow up of 25.4 months (range 10.8 to 29.5 months) following the first clearance. This single-center study is limited by its small sample size and variability in results across different tumor types. The study did not include a comparison of monitoring with ctDNA to standard methods of monitoring response such as repeat imaging.

Colvera®

Murray (2018) enrolled 172 patients with invasive colorectal cancer with plasma samples collected within 12 months after surgery.[43] In this study, multivariate analysis found that risk of recurrence was increased among patients who had positive Colvera® tests following surgery. Risk of colorectal cancer-related death was also increased among patients who had a positive ctDNA test following surgery, but multivariate analysis could not be performed for this outcome due to the low number of events.

Symonds (2020) examined the association between a positive Colvera® test result and recurrence of colorectal cancer in 144 patients who had no evidence of residual disease after surgical resection and/or neoadjuvant chemotherapy.[44] Blood samples were also tested for carcinoembryonic antigen (CEA), and the association between a positive CEA test and recurrent colorectal cancer was assessed. A positive Colvera® test was an independent predictor of recurrence, while a positive CEA test was not found to be a significant predictor of recurrence after adjusting for other predictors of recurrence (e.g., stage at primary diagnosis). Sensitivity of the Colvera® assay for detecting recurrence was significantly greater than the sensitivity of CEA (66% vs. 31.9%, p=0.001), but specificity was not significantly different (97.9% vs. 96.4%, p=1.00). The positive predictive value was not significantly different for Colvera® and CEA (94.3% vs. 83.3%, p=0.262), but the negative predictive value was significantly greater for Colvera® (84.4% vs. 71.7%, p<0.001).

Musher (2020) conducted an additional prospective cross-sectional observational study in patients undergoing surveillance after definitive therapy for stage II or III colorectal cancer.[45] Samples were collected within six months of planned radiologic surveillance imaging and tested using the Colvera® assay and a CEA assay. A total of 322 patients were included, with 27 experiencing recurrence and 295 not experiencing recurrence. The sensitivities of Colvera®

and CEA for detecting colorectal cancer recurrence using a single time-point blood test were 63% (17/27) and 48.1% (13/27), respectively (p=0.046). The specificities of single time-point Colvera® and CEA were 91.5% and 96.3%, respectively (p=0.012).

While several non-randomized studies have shown an association between Colvera® ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients. Management decisions were not based on test results. There are no controlled studies of management changes made in response to Colvera® test results compared to other risk factors, and no studies showing whether testing improved outcomes.

SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS

It has been proposed that liquid biopsy tests, such as the Galleri® test (Grail), could be used to screen asymptomatic patients for early detection of cancer, which could allow for initiating treatment at an early stage, potentially improving outcomes. The outcome of primary interest is progression-free survival. Diagnosis of cancer that is not present or would not have become clinically important (false-positives and overdiagnosis) would lead to unnecessary treatment and treatment-related morbidity.

GALLERI®

Schrag (2023) reported results of the PATHFINDER prospective study of the Galleri® test. PATHFINDER enrolled 6,662 adults aged 50 years or older without signs or symptoms of cancer from oncology and primary care outpatient clinics at seven U.S. health networks between 2019 and 2020.[46] A total of 6,621 participants had analyzable results and were included in the analysis; 64% of participants were women and 92% were White. The reference standard was a cancer diagnosis established by pathological, laboratory, or radiographic confirmation. Diagnostic assessments were coordinated by, and at the discretion of, the participant's doctor. Participants were followed for 12 months. A cancer signal was detected by the Galleri® test in 92 (1.4%) participants. In two of those participants, diagnostic assessments began before Galleri test results were reported. Thirty-five of the participants with a positive Galleri® test were diagnosed with cancer; 57 of the participants with a positive Galleri® test had no cancer diagnosis. The median time to diagnostic resolution was 79 days (interquartile range [IQR] 37 to 219). A total of 76 of the 90 participants with positive Galleri® test results had laboratory tests, 83 (92%) had at least one imaging test, 44 (53%) had more than one imaging study, and 44 (49%) had at least one procedure. Within 12 months of enrollment, 122 cancers were diagnosed in 121 participants: 35 (29%) detected by Galleri®; 38 (31%) detected through other screening tests; 48 (40%) clinically detected. Overall positive predictive value (PPV) was 35/92 (38%, 95% CI 29 to 48). Negative predictive value (NPV) was 6,235/6,321(99%, 95% CI 98 to 99). Specificity was 6,235/6,290 (99%, 95% CI 99 to 99). Sensitivity was not reported in the publication but is 35/121 (29%, 95% CI 21 to 38) based on the values provided. A correct first or second prediction of tissue of origin was returned for 33 (97%) of 34 true positives.

There are no studies demonstrating clinical utility of the Galleri test. A randomized controlled trial is underway in the United Kingdom, conducted within the National Health Service, to test whether Galleri® can reduce the number of late-stage cancers.[47] The trial has enrolled over 140,000 people from the general population of England ages 50 to 77 years who did not have or were not being investigated for cancer. Participants were randomized to have their blood tested using Galleri® or to the control group who will have their blood stored. Blood is being

collected up to three times annually. Follow-up is underway. The study registration indicates that estimated study completion date is in 2026.

Merker (2018) reported that there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[2]

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[48, 49] Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests as a screening test for cancer; therefore, no inferences can be made about clinical utility through a chain of evidence.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The American Society of Clinical Oncology (ASCO) 2022 guideline update on biomarkers for systemic therapy in metastatic breast cancer (MBC) does not recommend the use of ctDNA as a biomarker to monitor the response to therapy (Type of recommendation: informal consensus-based; Quality of evidence: low; Strength of recommendation: moderate).[50] The guidelines also provide the following recommendations:

- Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for hormone receptor-positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

NATIONAL COMPREHENSIVE CARE NETWORK

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type (see examples below).

The National Comprehensive Care Network (NCCN) Clinical Practice Guidelines for colon cancer (v.4.2024) does not include circulating tumor cells or circulating tumor DNA in the treatment algorithms and states that "Circulating tumor (ctDNA) is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results."[51]

The NCCN guidelines for breast cancer (v.4.2024) state that the "clinical use of circulating tumor cells or ctDNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS. In spite of its prognostic ability, CTC count has failed to show a predictive value."[52]

For NSCLC (v.7.2024), the NCCN guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of a histological tissue diagnosis, and that "ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I–III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing."[53] The guidelines state that limitations of ctDNA testing include:

- Low tumor fraction/ctDNA; some assays include a measure of ctDNA fraction, which can aid in identification of situations in which low ctDNA fraction might suggest compromised sensitivity
- The presence of mutations from sites other than the target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or postchemotherapy marrow clones. KRAS and TP53 can be seen in either of these circumstances
- The inherent ability of the assay to detect fusions or other genomic variation of relevance

NCCN Guidelines on Genetic/Familial High-risk Assessment: Breast, Ovarian, and Pancreatic make the following statement regarding screening with ctDNA tests:[54]

"For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined. The psychological impact of ctDNA testing remains unknown."

SUMMARY

Although there is limited evidence regarding the clinical utility of circulating tumor DNA (ctDNA) testing in patients with cancer, this testing may help to determine eligibility for FDA-approved targeted cancer treatments for advanced or metastatic breast cancer that is estrogen receptor (ER)-positive and HER2-negative, and for other solid tumors when tumor tissue is not available. Therefore, this testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that testing for variants in circulating tumor DNA (ctDNA) to select targeted treatment improves health outcomes when policy criteria are not met. This includes ctDNA testing as an adjunct to, or replacement for tumor tissue testing, when tumor tissue is possible, or testing when there is no FDA-approved targeted treatment

for the indication. Plasma-based ctDNA testing is generally less sensitive than tumor tissue testing and may identify changes that are not associated with the tumor. Therefore, this testing is considered investigational when medical necessity criteria are not met. Note that expanded tumor tissue panels to select targeted treatment are addressed in a separate policy and may not be covered for some indications.

There is not enough research to show that testing for circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) for purposes other than targeted treatment selection can improve overall health outcomes for patients. Various ctDNA and CTC tests have been proposed to detect the presence or recurrence of solid tumor cancers. However, the impact such testing on health outcomes has not been clearly demonstrated in prospective studies. In addition, no clinical practice guidelines based on research recommended routine use of this type of testing in patient management. Therefore, CTC and ctDNA testing that is not for the purpose of selecting a targeted treatment, including but not limited to measurable residual disease (MRD) testing or cancer screening in asymptomatic individuals, is considered investigational.

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CODES

Codes	Number	Description
		Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer,
	0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
	0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
	0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
	0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD
	0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
	0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer
	0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in highrisk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gammacarboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood
	0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
	0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
	0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and

Codes	Number	Description
	0405U	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected
	0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability
	0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected
	0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
	~~0428U~~	~~Oncology (breast), targeted hybrid-capture genomic sequence analysis panel, circulating tumor DNA (ctDNA) analysis of 56 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutation burden~~ (Deleted 01/01/2025)
	0470U	Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma
	0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
	0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction
	0487U	Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidy corrected gene copy number amplifications and losses, gene rearrangements, and microsatellite instability
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanoma associated antigen, CD34 and CD45 protein biomarkers, peripheral blood
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker–expressing cells, peripheral blood

Codes	Number	Description
	0507U	Oncology (ovarian), DNA, whole genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
	0530U	Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation
	0539U	Oncology (solid tumor), cell-free circulating tumor DNA (ctDNA), 152 genes, next-generation sequencing, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required
HCPCS	None	

Date of Origin: *July 2005*

Regence

Medical Policy Manual Laboratory, Policy No. 51

Laboratory Tests for Organ Transplant Rejection

Effective: April 1, 2025

Next Review: May 2025
Last Review: March 2025

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

Laboratory tests have been explored as an alternative or adjunct to biopsy. These laboratory tests are intended to screen for, estimate risk for, detect, and/or to rule out rejection following organ transplantation.

MEDICAL POLICY CRITERIA

I. The use of peripheral blood gene expression profiling tests (e.g., AlloMap) in the management of patients after heart transplant may be considered **medically necessary** when all of the following are met (A. – D.):

A. The patient is at least 15 years old; and

B. The patient is at least 6 months post heart transplant; and

C. There is not documentation of signs and symptoms that are attributed to heart transplant rejection (see Policy Guidelines); and

D. The patient has no history of treatment for heart transplant rejection.

II. The use of peripheral blood gene expression profiling tests in the management of patients before or after organ transplantation is considered **investigational** when Criterion I. is not met or for organs other than the heart.

III. The measurement of volatile organic compounds to assist in the detection of heart transplant rejection is considered **investigational**.

IV. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal, heart, or lung transplantation, including but not limited to the detection of acute transplant rejection or transplant graft dysfunction, is considered **investigational**.

V. The measurement of immune response of recipient lymphocytes to donor lymphocytes in cell culture to assess the likelihood of acute cellular rejection after renal, liver, and/or small bowel transplantation is considered **investigational**.

VI. The use of gene expression profiling tests on biopsy tissue (e.g., Molecular Microscope® Diagnostic System) to estimate transplant rejection risk is considered **investigational**.

VII. The measurement of urinary CXCL10 chemokines to monitor for rejection or determine the need for graft biopsy after renal transplant 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.

1. Name of gene expression profiling test
2. Relevant billing codes
3. Medical records related to this test
    - History and physical exam
    - Date of heart transplant

POLICY GUIDELINES

Heart transplant rejection risk includes signs or symptoms that can be attributed to rejection. These may include orthopnea, shortness of breath, paroxysmal nocturnal dyspnea, syncope, chest pain, palpitations, nausea, loss of appetite, weight gain, edema, arrhythmias, oliguria, and hypotension.

The Clarava and Tutevia™ tests (Verici Dx), and TruGraf™ Kidney are gene expression profiling tests that use peripheral blood samples to assess for rejection after kidney transplant. (Criterion II).

The HeartsBreath™ test measures breathe markers of oxidative stress (Criteria III).

AlloSure is a commercially available, next-generation sequencing (NGS) assay which quantifies the fraction of donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients, relative to total cfDNA, by measuring single nucleotide variants (Criterion IV).

The Prospera test (Natera) is also a dd-cfDNA test for renal transplant rejection (Criterion IV).

CROSS REFERENCES

1. Heart Transplant, Transplant, Policy No. 2

BACKGROUND

HEART TRANSPLANT REJECTION

After heart transplantation, patients are monitored for cellular rejection by endomyocardial biopsies that are typically obtained from the right ventricle. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following six months, and several times (monthly to quarterly) between six months and one-year post transplant. Surveillance biopsies may also be performed after the first postoperative year; e.g., on a quarterly or semi-annual basis. Due to the low rate of rejection after one year, some centers no longer routinely perform endomyocardial biopsies after a year in patients who are clinically stable.

Endomyocardial biopsy is invasive and carries significant risk of adverse effects. Additionally, while endomyocardial biopsy is considered the gold standard for assessing heart transplant rejection, biopsy may be limited by a high degree of interobserver variability in grading of results and the significant morbidity and even mortality that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy, and biopsy cannot be used to identify patients at risk of rejection, limiting the ability to initiate therapy to interrupt the development of rejection. For these reasons, endomyocardial biopsy is considered a flawed gold standard.

Therefore, noninvasive methods of detecting cellular rejection have been explored. It is hypothesized that noninvasive tests will assist in determining appropriate patient management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false-negative and false-positive biopsy reports.

Many non-invasive techniques are commercially available for the detection of heart transplant rejection. These include the HeartsBreath™ test which measures breath markers of oxidative stress, the AlloMap® test which provides gene expression profiling of RNA obtained from peripheral blood samples, and Allosure® Heart, which measures donor derived cell-free DNA in peripheral blood.

Noninvasive Heart Transplant Rejection Tests

HeartsBreath™ Test

The Heartsbreath™ test (Menssana Research, Inc) measures breathe markers of oxidative stress non-invasively and is based on the understanding that in heart transplant recipients, oxidative stress appears to accompany allograft rejection. This rejection degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes, which are excreted as volatile organic compounds (VOC) in breath. The Heartsbreath™ test analyzes the breath methylated alkane contour (BMAC), which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes.

AlloMap® Test

Another approach, the AlloMap® test (CareDx, formerly Xdx, Inc.), focuses on patterns of gene expression of immunomodulatory cells as detected in the peripheral blood. For example, microarray technology permits the analysis of the gene expression of thousands of genes, including those with functions that are known or unknown. Patterns of gene expression can then be correlated with known clinical conditions, permitting a selection of a finite number of genes to compose a custom multi-gene test panel, which can then be evaluated using polymerase chain reaction (PCR) techniques. The test applies an algorithm to the results, which produces a single score that considers the contribution of each gene in the panel. The manufacturer website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cut-off for a positive test.[1]

Additional Tests

Other non-invasive laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, dd-cfDNA (discussed below), troponin, and soluble inflammatory cytokines. Most of these have had low diagnostic accuracy in diagnosing rejection. Preliminary studies have evaluated the association between heart transplant rejection and micro-RNAs or high-sensitivity cardiac troponin in cross-sectional analyses, but the clinical use has not been evaluated.[2, 3]

RENAL TRANSPLANT REJECTION

Allograft dysfunction is typically asymptomatic and has a broad differential, including graft rejection. Diagnosis and rapid treatment are recommended to preserve graft function and prevent loss of the transplanted organ. For a primary kidney transplant, graft survival at one year is 94.7%; at five years, graft survival is 78.6%.[4]

Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis.[5] Allograft dysfunction may also be demonstrated by a drop in urine output or, rarely, as pain over the transplant site. With clinical suspicion of allograft dysfunction, additional noninvasive workup including ultrasonography or radionuclide imaging may be used. Renal biopsy allows definitive assessment of graft dysfunction and is typically a percutaneous procedure performed with ultrasonography or computed tomography guidance. Biopsy of a transplanted kidney is associated with fewer complications than biopsy of a native kidney, as the allograft is typically transplanted more superficially than a native kidney. Renal biopsy is a low risk invasive procedure that may result in bleeding complications; loss of a renal transplant, as a complication of renal biopsy, is rare.[6] Kidney biopsies allow for diagnosis of acute and chronic graft rejection, which may be graded using the Banff scale.[7, 8] Pathologic assessment of biopsies demonstrating acute rejection allows clinicians to further distinguish between acute cellular rejection (ACR) and antibody-mediated rejection (AMR), which are treated differently.

The Pleximark™ test from Plexision measures the immune response of recipient lymphocytes to donor lymphocytes in cell culture and has been proposed to predict the likelihood of acute cellular rejection after renal transplantation.

The Clarava™ and Tuteva™ tests from Verici Dx, and the TruGraf® test from Eurofins Transplant Genomics are gene expression tests that use peripheral blood to generate risk scores for renal transplant rejection. The Clarava™ test is marketed for use prior to transplantation, while the Tuteva™ and TruGraf® tests are marketed for use following transplantation.

Measurement of urinary biomarkers, such as C-X-C motif chemokine ligand 10 (CXCL10) have been proposed as noninvasive tests for early detection of rejection that may reduce the need for unnecessary biopsies. Other urinary biomarkers that are under study for detection of renal transplant complications include CXCL9, urinary perforin levels, urinary mRNA transcripts, and urinary dd-cfDNA levels.

DONOR-DERIVED CELL-FREE DNA

Cell-free DNA (cfDNA), released by damaged cells, is normally present in healthy individuals.[9] In patients who have received transplants, donor-derived cfDNA (dd-cfDNA) may be additionally present. It is proposed that allograft rejection, which is associated with damage to transplanted cells, may result in an increase in dd-cfDNA. AlloSure®, Viracor TRAC™ dd-cfDNA, and myTAIHEART are commercially available assays which quantify the fraction of dd-cfDNA in transplant recipients, relative to total cfDNA, by measuring single nucleotide variants (SNVs). Separate genotyping of the donor or recipient is not required for some tests. Each test has a list of conditions that make the test not suitable for a given patient, such as receiving a transplant from a monozygotic (identical) twin and pregnancy. There are dd-cfDNA tests available for heart, kidney, and lung transplants.

Tests for Transplant Rejection that Evaluate Biopsy Specimens

The Molecular Microscope® Diagnostic System (MMDX, One Lambda, Thermo Fisher Scientific, Inc.) offers laboratory-developed tests that measure mRNA transcript levels in endomyocardial or kidney biopsy specimens and applies an algorithm to score the results.[10] The MMDx Kidney & Heart tests can help stratify the risk for conditions like T-cell mediated rejection (TCMR), antibody-mediated rejection (ABMR), acute and chronic injury, atrophy fibrosis, and arterial hyalinosis.

REGULATORY STATUS

Both the Heartsbreath™ and AlloMap® tests have received approval from the US Food and Drug Administration (FDA):

- In 2004, the Heartsbreath™ test received approval from the FDA through a humanitarian device exemption. The Heartsbreath™ test is indicated for use as an aid in the diagnosis of grade 3 (significant) heart transplant rejection in patients who have received heart transplants within the preceding year. The test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. It is also limited to patients who have had endomyocardial biopsy within the previous month.

- AlloMap® received 510k clearance from the FDA for use in conjunction with clinical assessment to identify heart transplant recipients with stable allograft function. The test is intended for patients at least 15 years-old who are at least two months post-transplant and who have a low probability of moderate/severe transplant rejection.

EVIDENCE SUMMARY

The principal outcomes associated with detection of acute heart transplant rejection or graft dysfunction include hemodynamic compromise, graft dysfunction, and/or death. Outcomes relating to use of laboratory tests (such as Heartsbreath™ or AlloMap®) proposed for adjunctive use in heart transplant rejection are best understood by comparing outcomes of patients receiving endomyocardial biopsy alone to those receiving biopsy with the laboratory

test. Data from adequately powered, blinded, randomized controlled trials (RCTs) are required to control for baseline differences between groups and determine whether additional testing provides a significant advantage over the standard of care in the proposed uses of these laboratory tests.

HEARTSBREATH™ TEST

A single non-randomized study was published in 2004 on the use of the Heartsbreath™ test. No subsequent studies that evaluated use of the Heartsbreath™ test to assess for graft rejection have been identified.

The FDA approval of the Heartsbreath™ test was based on the results of the National Heart Lung and Blood Institute-sponsored Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) study.[11] The HARDBALL study was a three-year multicenter study of 1,061 breath samples in 539 heart transplantation patients. Prior to scheduled endomyocardial biopsy, patient breath was analyzed by gas chromatography and mass spectroscopy for VOCs. The amount of C4 to C20 alkanes and monomethylalkanes was used to derive the BMAC. The BMAC results were compared with subsequent biopsy results as interpreted by two readers using the International Society for Heart and Lung Transplantation biopsy grading system as the "gold standard" for rejection.

The authors of the HARDBALL study reported that the abundance of breath markers of oxidative stress was significantly greater in grades 0, 1, or 2 rejection than in healthy normal subjects. However, in grade 3 (now grade 2R) rejection, the abundance of breath markers of oxidative stress was reduced, most likely due to accelerated catabolism of alkanes and methylalkanes that comprised the BMAC. The authors also reported that in identifying grade 3 rejection, the negative predictive value of the breath test (97.2%) was similar to endomyocardial biopsy (96.7%), and that the breath test could potentially reduce the total number of biopsies performed to assess for rejection in patients at low risk for grade 3 rejection. The sensitivity of the breath test was 78.6%, versus 42.4% with biopsy. However, the breath test had lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than biopsy (specificity 97%, positive predictive value 45.2%). Additionally, the breath test was not evaluated in grade 4 rejection.

GENE EXPRESSION PROFILING

AlloMap® Test

Clinical Validity

Kanwar (2021) published data from the Outcomes AlloMap Registry (OAR) indicating that asymptomatic or active cytomegalovirus infection is associated with significantly higher AlloMap scores among heart transplant recipients compared to those without infection, even in the absence of acute rejection, potentially resulting in unnecessary biopsies among surveillance patients.[12] Donor-derived cell-free DNA levels measured by the AlloSure Heart test available for a small subset of samples (5.3%) were not significantly different between groups. The authors concluded that further assessment of the combined use of AlloMap and AlloSure scores is required to determine if this will improve differentiating infection-related from rejection-related immune activation. The combined use of these tests, commercially available as HeartCare (CareDx), is addressed below.

Patterns of gene expression for development of the AlloMap® test were studied in the Cardiac Allograft Rejection Gene Expression Observation (CARGO) study, which included eight U.S. cardiac transplant centers enrolling 650 cardiac transplant recipients.[13] The study included discovery and validation phases. In the discovery phase, patient blood samples were obtained at the time of endomyocardial biopsy, and the expression levels of more than 7,000 genes known to be involved in immune responses were assayed and compared with the biopsy results. A subset of 200 candidate genes were identified that showed promise as markers that could distinguish transplant rejection from quiescence, and from there, a panel of 11 genes was selected that could be evaluated using polymerase chain reaction (PCR) assays. A proprietary algorithm is applied to the results of the analysis, producing a single score that considers the contribution of each gene in the panel.

The validation phase of the CARGO study, published in 2006, was prospective, blinded, and enrolled 270 patients.[13] Primary validation was conducted using samples from 63 patients independent from discovery phases of the study and enriched for biopsy-proven evidence of rejection. A prospectively defined test cutoff value of 20 resulted in a sensitivity of 84% for patients with moderate/severe rejection, but a specificity of 38%. Of note, in the “training set” used in the study, these rates were 80% and 59%, respectively. The authors evaluated the 11-gene expression profile on 281 samples collected at one year or more from 166 patients who were representative of the expected distribution of rejection in the target population (and not involved in discovery or validation phases of the study). When a test cutoff of 30 was used, the NPV (no moderate/severe rejection) was 99.6%; however, only 3.2% of specimens had grade 3 or higher rejection. In this population, grade 1B scores were found to be significantly higher than grade 0, 1A, and 2 scores, but similar to grade 3 scores. The sensitivity and specificity for determining quiescent versus early stages of rejection was not addressed in this study; however, it was addressed in a 2016 study.[14]

Crespo-Leiro (2016) published a reanalysis of the CARGO II data to clinically validate the GEP test performance.[14] Blood samples for AlloMap® were collected during post-transplant surveillance and were obtained at least 55 days post-transplantation; >30 days after transfusion of blood products; >21 days after administration of ≥20 mg/day of prednisone; and >60 days after treating a prior rejection. Four hundred and ninety-nine patients had 1,579 visits with paired endomyocardial biopsy histopathology rejection grades and GEP scores that met inclusion criteria for the study analyses. The reference standard for rejection status was based on histopathology grading of tissue from endomyocardial biopsy. Results indicated that a GEP test score of ≥34 (patients who are more than six months post-transplantation) corresponded to histology-based grade ≥3A (2R) rejection with a positive predictive value (PPV) of 4.0% at two to six months post-transplantation, and 4.3% at >6 months post-transplantation. The negative predictive values (NPVs) were 98.4% at two to six months post-transplantation and 98.3% at more than six months post-transplantation. In both time windows, the NPVs increased from 98.3 to >99.0% for decreasing threshold values below 34. The corresponding PPVs decreased from 4.3 to 2.1. Post-CARGO clinical observations have also been published.[15] The multicenter work group identified a number of factors that can affect AlloMap® scores, including the time post-transplant, corticosteroid dosing, and transplant vasculopathy.[15, 16] Scores of 34 or higher were considered positive. Analysis of data from a number of centers collected post-CARGO showed that at one year or more post-transplantation, an AlloMap® threshold of 34 had a PPV of 7.8% for scores of 3A/2R or more on biopsy and a NPV of 100% for AlloMap® scores below 34. There is insufficient information in this study to determine whether there are potential study biases in this report. These findings were limited due to a very low number of rejection events; only five biopsy samples (2.4%)

were found to have a grade of 2R or greater. At one year, 28% of the samples showed an elevated AlloMap® score (>34) even though there was absence of evidence of rejection on biopsy. The significance of chronically elevated AlloMap® scores in the absence of clinical manifestation of graft dysfunction and the actual impact on the number of biopsies performed is currently unknown.

A similar analysis by Fujita (2017) evaluated the longer-term predictive value of AlloMap® in a group of 46 patients from the CARGO II trial who survived at least one year after transplant.[17] Mean AlloMap® scores at 6, 9, 12, and 18 months posttransplant were not significantly different from one another, and there was no significant difference in mortality between those with scores about the median and those below at any time point. The authors also analyzed changes in Allomap® scores between different time points and found that only those with an increase in score between six and nine months posttransplant had higher mortality. Changes at all other times were not significantly associated with mortality. The authors concluded that a nine-month score that is less than 1.02-fold of the six-month score had a NPV of 100%, but that isolated scores at any of the time points were not correlated with survival.

Moayedi (2019) published results from the Outcomes AlloMap® Registry (OAR), a prospective, multicenter observational study, which included 1,504 heart transplant patients age 15 and older.[18] Among these patients, survival at one, two, and five years after transplant was 99%, 98%, and 94%, respectively. No association was seen between GEP score and coronary allograft vasculopathy, non-cytomegalovirus infection, or cancer.

Clinical Utility

Kobashigawa (2015) published results of a pilot RCT evaluating the use of the AlloMap® test in patients who were 55 days to six months posttransplant.[19] The study design was similar to that of the IMAGE RCT described below: 60 subjects were randomized to rejection monitoring with AlloMap® or with endomyocardial biopsy at prespecified intervals of 55 days and 3, 4, 5, 6, 8, 10, and 12 months posttransplant. The threshold for a positive AlloMap® test was set at 30 for patients two to six months posttransplant and 34 for patients after six months posttransplant, based on data from the CARGO study. Endomyocardial biopsy outside of the scheduled visits was obtained in either group if there was clinical or echocardiographic evidence of graft dysfunction and for the AlloMap® group if the score was above the specified threshold. The incidence of the primary outcome at 18 months posttransplant (composite outcome of first occurrence of death or retransplant, rejection with hemodynamic compromise, or allograft dysfunction due to other causes) did not differ significantly between the AlloMap® and biopsy groups (10% vs 17%, p=0.44). The number of biopsy-proven rejection episodes (ISHLT ≥2R) within the first 18 months did not differ significantly between groups (three in the AlloMap® group vs one in the biopsy group, p=0.31). Of the rejections in the AlloMap® group, one was detected after an elevated routine AlloMap® test, while two were detected after patients presented with hemodynamic compromise. In the AlloMap® group, 29 of 42 biopsies were performed due to elevated AlloMap® scores; four were performed due to signs, symptoms, or echocardiographic manifestations of graft dysfunction; five were performed as part of follow-up assessment for treatment for rejection; and four were performed outside the study protocol. In the biopsy group, 253 biopsies were performed, four of which were performed based on clinical need.

In 2010, results of the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study were published.[20, 21] This was an industry-sponsored noninferiority RCT that compared

outcomes in 602 patients managed with the AlloMap® test (n=297) or routine endomyocardial biopsies (n=305). The study was not blinded. The study included adult patients from 13 centers who underwent cardiac transplantation between one and five years previously, were clinically stable, and had a left ventricular ejection fraction (LVEF) of at least 45%. To increase enrollment, the study protocol was later amended to include patients who had undergone transplantation between six months and one year earlier; this subgroup ultimately comprised only 15% of the final sample (n=87). Each transplant center used its own protocol for determining the intervals for routine testing. At all sites, patients in both groups underwent clinical and echocardiographic assessments in addition to the assigned surveillance strategy. According to the study protocol, patients underwent biopsy if they had signs or symptoms of rejection or allograft dysfunction at clinic visits (or between visits) or if the echocardiogram showed a LVEF decrease of at least 25% compared with the initial visit. Additionally, patients in the AlloMap® group underwent biopsy if their test score was above a specified threshold; however, if they had two elevated scores with no evidence of rejection found on two previous biopsies, no additional biopsies were required. The AlloMap® test score varied from 0 to 40, with higher scores indicating a higher risk of transplant rejection. The investigators initially used 30 as the cutoff for a positive score; the protocol was later amended to use a cutoff of 34 to minimize the number of biopsies needed. Fifteen patients in the AlloMap® group and 26 in the biopsy group did not complete the study.

The primary outcome was a composite variable; the first occurrence of (1) rejection with hemodynamic compromise, (2) graft dysfunction due to other causes, (3) death, or (4) retransplantation. The trial was designed to test the noninferiority of gene expression profiling (GEP) with the AlloMap® test compared with endomyocardial biopsies with respect to the primary outcome. Use of the AlloMap® test was considered noninferior to the biopsy strategy if the one-sided upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) comparing the two strategies was less than the prespecified margin of 2.054. The margin was derived using the estimate of a 5% event rate in the biopsy group, taken from published observational studies, and allowing for an event rate of up to 10% in the AlloMap® group. Secondary outcomes included death, the number of biopsies performed, biopsy-related complications, and quality of life using the 12-Item Short-Form Health Survey (SF-12).

According to Kaplan-Meier analysis, the two-year event rate was 14.5% in the AlloMap® group and 15.3% in the biopsy group. The corresponding HR was 1.04 (95% CI, 0.67 to 1.68). The upper boundary of the CI of the HR (1.68) fell within the prespecified noninferiority margin (2.054); thus, GEP was considered noninferior to endomyocardial biopsy. Median follow-up was 19 months. The number of patients remaining in the Kaplan-Meier analysis after 300 days was 221 in the biopsy group and 207 in the AlloMap® group; the number remaining after 600 days was 137 and 133, respectively. The secondary outcome, death from all causes at any time during the study, did not differ significantly between groups. There were 13 (6.3%) deaths in the AlloMap® group and 12 (5.5%) in the biopsy group (p=0.82). During the follow-up period, there were 34 treated episodes of graft rejection in the AlloMap® group. Only six of the 34 (18%) patients with rejection presented solely with an elevated AlloMap® score. Twenty patients (59%) presented with clinical signs/ symptoms and/or graft dysfunction on echocardiogram, and seven patients had an elevated AlloMap® score plus clinical signs/symptoms with or without graft dysfunction on echocardiogram. In the biopsy group, 22 patients were detected solely due to an abnormal biopsy.

A total of 409 biopsies were performed in the AlloMap® group and 1,249 in the biopsy group. Most of the biopsies in the AlloMap® group, 67%, were performed because of elevated gene-

profiling scores. Another 17% were performed due to clinical or echocardiographic manifestations of graft dysfunction, and 13% were performed as part of routine follow-up after treatment for rejection. There was one (0.3%) adverse event associated with biopsy in the AlloMap® group and four (1.4%) in the biopsy group. In terms of quality of life, the physical-health and mental-health summary scores of the SF-12 were similar in the two groups at baseline and did not differ significantly between groups at two years.

A limitation of the study was that the threshold for a positive AlloMap® test was changed partway through the study; thus, the optimal test cutoff remains unclear. Moreover, the study was not blinded, which could have impacted treatment decisions such as whether or not to recommend biopsy, based on clinical findings. In addition, the study did not include a group that only received clinical and echocardiographic assessment, and therefore, the value of AlloMap® testing beyond that of clinical management alone cannot be determined. The uncertain incremental benefit of the AlloMap® test is highlighted by the finding that only 6 of the 34 treated episodes of graft rejection detected during follow-up in the AlloMap® group were initially identified due solely to an elevated gene-profiling score. Since 22 episodes of asymptomatic rejection were detected in the biopsy group, it is likely that the AlloMap® test is not a sensitive test, possibly missing more than half of the episodes of asymptomatic rejection. Because clinical outcomes were similar in the two groups, there are at least two possible explanations. The clinical outcome of the study may not be sensitive to missed episodes of rejection, or it is not necessary to treat asymptomatic rejection. In addition, the study was only statistically powered to rule out more than a doubling of the rate of the clinical outcome, which some may believe is an insufficient margin of noninferiority. Finally, only 15% of the final study sample had undergone transplantation less than one year before study participation; therefore, findings may not be generalizable to the population of patients 6 to 12 months post-transplant.

In a follow-up analysis of data from the IMAGE RCT, Deng (2014) evaluated whether variability in gene expression profiling results were predictive of clinical outcomes.[22] For this analysis, the authors included a subset of 369 patients who had at least two AlloMap® tests done before an event or the study end, and at least one endomyocardial biopsy and one echocardiogram. Patients were included from both arms of the IMAGE RCT. AlloMap® test results were expressed in three ways, as an ordinal score from 0 to 39, a threshold score of 1 or 0, depending on whether the score was 34 or more or not, and as a variability score, the standard deviation of all of the ordinal scores within a patient. The AlloMap® results were entered into a multivariable regression model to predict the composite end point, defined as a patient's first occurrence of: rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. AlloMap® ordinal score and AlloMap® threshold score were not predictive of the composite outcome. AlloMap® score variability was significantly associated with the composite outcome, with a hazard ratio for a one unit increase in variability of 1.76 (95% CI, 1.4 to 2.3). While this study implies that variability in AlloMap® score may be a prognostic factor, clinical application of this finding is uncertain.

Section Summary

The most direct evidence on the clinical utility of the AlloMap® test comes from one large RCT comparing an AlloMap®-directed strategy with an endomyocardial biopsy-directed strategy for detecting rejection, which found that the AlloMap®-directed strategy was noninferior. The high NPV of AlloMap enables the avoidance of surveillance endomyocardial biopsy and its inherent risks for certain heart transplant recipients who are at low risk for transplant rejection.

Additional Gene Expression Tests for Transplant Rejection

There are additional studies that have examined the use of gene expression testing to predict or detect organ transplant rejection, including renal transplant rejection.[23-26] However, these tests have mainly been used in the research setting and there is very limited evidence of clinical validity or utility.

DONOR-DERIVED CELL-FREE DNA TESTING

Knight (2019) published a systematic review of studies that investigated the use of dd-cfDNA post-transplantation.[27] A total of 95 publications representing 47 studies of kidneys (n=18), livers (n=7), hearts (n=11), kidney-pancreas (n=1), lungs (n=5) and multiorgans (n=5) met inclusion criteria. Besides one single case report, the studies were retrospective (n=19) and prospective (n=29) cohort studies. There was heterogeneity in methods for differentiating between donor-derived and recipient cfDNA and in calculating the proportion of dd-cfDNA. Trends from these studies were reported, but no meta-analysis was completed due to low study quality and high heterogeneity.

Renal Transplant

Xiao (2021) published a systematic review and meta-analysis which assessed the clinical validity of dd-cfDNA testing.[28] The review included nine observational studies of the diagnostic accuracy of dd-cfDNA as a potential marker of graft rejection following kidney transplantation. The review authors calculated a pooled sensitivity of 0.70 (95% CI, 0.57-0.81; I^2, 65) and specificity of 0.78 (0.70-0.84; I^2, 75) from six studies evaluating the diagnostic accuracy of dd-cfDNA for any rejection episode. The area under the receiver operating characteristics curve (AUC) was 0.81 (95% CI, 0.77 to 0.84; I^2, 65) with an overall diagnostic odds ratio (DOR) of 8.18 (95% CI, 5.11 to 13.09). Similar pooled estimates were calculated for five studies discriminating antibody-mediated rejection. The authors reported a pooled sensitivity of 0.84 (95% CI, 0.75 to 0.90; I^2, 0) and a specificity of 0.80 (95% CI, 0.75 to 0.84; I^2, 4) with an AUC of 0.89 (95% CI, 0.86 to 0.91) and overall DOR of 20.48 (95% CI, 10.76 to 38.99). Overall, the authors found greater value in dd-cfDNA as a biomarker for antibody-mediated rejection in patients with suspected renal dysfunction than in discriminating a main rejection episode and cite the need for more large-scale, prospective research on the topic.

Wijtvliet (2020) reported a systematic review and meta-analysis of dd-cfDNA as a biomarker for rejection after kidney transplant.[29] A total of 14 studies met inclusion criteria for the systematic review, of which nine were included in the meta-analysis. Huang (2019) and Bloom (2017), discussed in detail below, were included. Overall, the quality was rated moderate or high for each included study. Moderate heterogeneity was identified for antibody-mediated rejection versus no rejection (I^2=40.1%) and antibody-mediated rejection versus T cell-mediated rejection (I^2=31.5%). Median dd-cfDNA fractions were significantly higher in patients with antibody-mediated rejection than patients without rejection (n=283 samples; weighted minimum difference to mean 1.89%). Median dd-cfDNA values were intermediate for patients with T cell-mediated rejection and were not significantly different from either the antibody-mediated rejection or no-rejection groups.

Results from the ongoing Trifecta study (NCT04239703) published by Halloran (2023) provide an assessment of combined dd-cfDNA fraction and absolute values for prediction of active kidney allograft rejection.[30] The study reported data from 280 biopsies that were taken from 272 patients. 97 patients were female and 9% were Black or African-American; other race or

ethnicity data were not reported. The mean post-transplant time was 1,353 days. The study found that about half of all AMR is donor specific antibody (DSA)-negative. For specimens with histologically proven AMR, 51% were DSA-negative. Of specimens found to have AMR with the Molecular Microscope System, 56% were DSA-negative. In specimens with AMR, the percentage of dd-cfDNA (75%) was higher than DSA-positivity (44%). In cases with no rejection, 18% showed dd-cfDNA positivity, and 10% were DSA-positive. The authors conclude that dd-cfDNA is superior to DSA in predicting AMR, but the best performance was found with predictions that incorporated both dd-cfDNA and DSA tests.

Huang (2023) conducted a retrospective single institution study to evaluate the association of dd-cfDNA surveillance levels in adult renal transplant patients with transplant outcomes.[31] The study included 317 kidney transplant recipients with a median follow-up of 590 days. Participants were divided into three categories based on their baseline dd-cfDNA levels; low (n=239), moderate (n=43) and high (n=35). Patients in the high category were more likely to have had previous kidney transplant. There was no difference in the percentage of participants in each group that developed DSA (p=0.52). There was only one graft loss during the study period and it was in a low category participant. Ten participants died during the study period; all had functioning grafts and deaths were not associated with dd-cfDNA levels. Rejection was more likely to occur in patients with higher dd-cfDNA levels (p=0.02), but the researchers were unable to determine if high dd-cfDNA levels reflected actual graft injury or the higher immunologic risk related to previous transplant. The authors concluded that the role of routine dd-cfDNA surveillance in kidney transplant needs further study.

Dandamudi (2022) published a study of longitudinal cfDNA levels in pediatric kidney transplant patients.[32] The study used serial sampling of 290 plasma specimens from 57 children who had kidney transplant between January, 2013 and December, 2019 at a single institution. Using a one percent cutoff, and 109 samples with simultaneous biopsy data, dd-cfDNA had a 33% sensitivity (95% CI, 19% to 52%) in discriminating biopsy-proven acute rejection, but specificity was 96% (95% CI, 90% to 99%).

Puliyanda (2021) evaluated the use of dd-cfDNA in pediatric kidney transplant patients.[33] A total of 67 patients who underwent initial testing with dd-cfDNA as part of routine monitoring or in response to clinical suspicion for rejection were included. Two of the seven patients with clinical suspicion of rejection and a dd-cfDNA score <1% showed evidence of rejection on biopsy. Using a dd-cfDNA of >1% as a marker of rejection, sensitivity was 86% and specificity was 100% (Area Under the Curve [AUC]: 0.996, 0.98 to 1.00; p=0.002).

Stites (2020) assessed clinical outcomes in 79 patients diagnosed with T-Cell Mediated Rejection (TCMR) 1A/borderline rejection with simultaneous AlloSure assessment of dd-cfDNA across 11 centers between June 2017 and May 2019.[34] Timing of testing with respect to the date of transplantation was not reported. Elevated levels of dd-cfDNA (≥0.5%) were detected in 42 (53.2%) patients. No statistically significant differences between dd-cfDNA distributions when stratified by protocol versus for-cause biopsies was detected (p=0.7307). Elevated levels of dd-cfDNA were associated with adverse clinical outcomes compared to patients with low levels (< 0.5%), including decline in eGFR (8.5% versus 0%; p=0.004), de novo DSA formation (40% versus 2.7%; p<0.0001), and future or persistent rejection (21.4% versus 0%; p=0.003). The authors hypothesize that the use of dd-cfDNA may complement histological evaluation and risk stratify patients with TCMR 1A or borderline rejection identified on biopsy and propose the use of reference ranges as opposed to absolute dd-cfDNA cutoff thresholds.

Sigdel (2019) evaluated the diagnostic accuracy of the Prospera dd-cfDNA test in a retrospective analysis of 300 biorepository plasma samples from kidney transplant recipients at a single academic medical center.[35] Of the 300 samples (193 patients), 217 were biopsy-matched with 38 cases of active rejection, 72 cases of borderline rejection, 82 with stable allografts, and 15 cases of other kidney injuries. The sample cohort was demographically diverse, including women (42.5%), Hispanic and Latino patients (34.6%), Black or African American patients (14%), and pediatric patients (20%). Indication for renal transplantation was unknown in 45.6% of samples. The majority of samples (72.3%) were drawn on the day of surveillance (n = 114 [52.5%] patients) or clinically indicated biopsy (n=103 [47.5%] patients). Timing of tests with respect to the date of transplantation was not reported. Biopsies were evaluated by a single pathologist according to 2017 Banff criteria and classified as active rejection or non-rejection (i.e., borderline rejection, other injury, or stable allograft status). Median dd-cfDNA levels were significantly higher in biopsy-proven active rejection (2.32%) versus non-rejection subgroups (0.47%; p <.0001). All subtypes of active rejection could be detected, and median dd-cfDNA did not differ significantly between antibody-mediated (2.2%), T cell-mediated (2.7%), and combined subtypes (2.6%).

The 2019 report by Sigdel also assessed the performance characteristics of eGFR, which was calculated as a function of serum creatinine with adjustments for age, sex, and race based on the Modification of Diet in Renal Disease (MDRD) Study equation.[35] At a cutoff threshold of < 60, the sensitivity and specificity for eGFR were lower compared to dd-cfDNA, at 67.8% (95% CI, 51.3% to 84.2%) and 65.3% (95% CI, 57.6% and 73.0%), respectively, with a corresponding AUC of 0.74 (95% CI, 0.66 to 0.83). However, the relevance of absolute eGFR measurements is limited as dynamic changes in laboratory parameters (eg, serum creatinine elevation, eGFR decline) are used to flag impaired kidney function in clinical practice in the transplant population. Separate eGFR estimates in the for-cause subgroup were not reported. Major limitations of this study include its retrospective design and single-center setting. While the dd-cfDNA cutoff was prespecified, it was based on prior studies of the AlloSure test and may not be optimized for Prospera.

Huang (2019) conducted a single center study that recruited 63 renal transplant patients with suspicion of rejection that had AlloSure assessment of dd-cfDNA within 30 days of an allograft biopsy.[36] Median years from transplant to dd-cfDNA measurement was 2.0 (interquartile range, 0.3 to 6.5). Within this population, biopsy found acute rejection in 34 (54%) of patients; 10 (15.9%) were cell-mediated only, 22 (25.4%) were antibody-mediated only, and 2 (3.2%) were mixed cell-mediated and antibody-mediated. In contrast to the study by Bloom (2017) below, the optimal threshold for a positive dd-cfDNA result was identified as ≥0.74%. For the outcome of any rejection (i.e., cell-mediated, antibody-mediated, or mixed), use of this threshold was associated with an overall sensitivity of 79.4%, specificity of 72.4%, PPV of 77.1%, and NPV of 75.0%. Discrimination of rejection differed by biopsy findings, however. For the subgroup of patients with antibody-mediated rejection, the sensitivity was 100%, specificity was 71.8%, PPV was 68.6%, and NPV was 100%. The dd-cfDNA test did not discriminate rejection in patients with cell-mediated rejection, as evidenced by an AUC of 0.43 (95% CI, 0.17 to 0.66). Major limitations of this study are its small sample size and single-center setting.

The multicenter prospective DART study (Bloom, 2017) recruited both patients who were less than three months after renal transplant (n=245) and renal transplant patients requiring a biopsy for suspicion of graft rejection (n=139).[37] For the primary analysis, active rejection was defined as the combined categories of T cell−mediated rejection, acute/active AMR, and chronic/active AMR as defined by the Banff working groups. Only patients undergoing biopsy

were considered; further exclusion of biopsies which were not for cause, had inadequate or incomplete collection of biopsies or corresponding blood samples, or had prior allograft in situ resulted in the main study cohort (n=102 patients, 107 biopsies). Within this population, acute rejection was noted in 27 patients (27 biopsies). After statistical analysis accounting for multiple biopsies from the same patient, the threshold dd-cfDNA fraction corresponding to acute rejection was set to ≥1.0%. In the main study group, this resulted in a sensitivity of 59% (95% CI 44% to 74%) and specificity of 85% (95% CI 79% to 81%) for detecting active rejection vs no rejection. Returning to the original data set including all biopsies performed for clinical suspicion of rejection, 58 cases of acute rejection were diagnosed in 204 biopsies (170 patients). This prevalence was used to calculate the PPV (61%) and NPV (84%). Biopsies performed for surveillance (n=34 biopsies) were excluded from analysis in this study as only one biopsy for surveillance demonstrated acute rejection. Limitations of this study include the absence of a validation data set. Additional analyses of the DART study have reported on associations between first-year AlloSure dd-cfDNA fraction or serial variability and subsequent eGFR decline[38], and combined use of dd-cfDNA and DSA testing to diagnose active antibody-mediated rejection[39, 40]

A number of other studies have evaluated associations between dd-cfDNA assays and graft injury or rejection after kidney transplantation.[27, 39, 41-45] For individuals with a renal transplant who are undergoing surveillance or have clinical suspicion of allograft rejection who receive testing of dd-cfDNA to assess renal allograft rejection, the evidence includes small diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. The available evidence does not show how the use of these tests can impact patient health outcomes. Larger prospective studies validating the dd-cfDNA thresholds for active rejection are needed to develop conclusions for each test. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Heart Transplant

Richmond (2023) published data on pediatric (n=60) and adult (n=61) heart transplant recipients (median age, 24.3) prospectively enrolled at eight participating centers from August 2016 to October 2017 and followed patients for up to 12 months.[46] All patients had samples from one or more endomyocardial biopsies post-transplantation with Allosure dd-cfDNA testing within 24 hours prior to biopsy. dd-cfDNA level was blinded to participants and investigators over the study period. Median dd-cfDNA was significantly higher in the patients who had biopsy-defined allograft rejection (ACR or AMR) compared with healthy allograft participants (0.21% versus 09%, p<0.0001). An area under the curve (AUC) analysis yielded an AUC of 0.78 using a pre-defined dd-cfDNA threshold of 14% and resulted in a test sensitivity of 67% and a specificity of 79% (NPV = 94% and PPV = 34%), a sub-group analysis satisfying patients into adult of pediatric patients found similar results (AUC of the adult cohort = 0.81; AUC of the pediatric cohort =0.79).

Rodgers (2023) conducted a retrospective study that compared dd-cfDNA testing with Allosure, which examines 405 single nucleotide polymorphisms (SNPs), to Prospera, which evaluates 13,292 SNPs, in 112 heart transplant patients.[47] Participants were enrolled from October 2020 to January 2022 and had a median age of 60 years. Both tests used a dd-cfDNA threshold value of 15%. Testing with Allosure resulted in a low sensitivity (39%) and high specificity (82%) for identification of acute rejection; the Prospera test had similar characteristics with sensitivity at an identical 39% and a negligible difference in specificity (84%). Between-group comparisons showed no difference between the two tests. PPV with the

Allosure test was 6.2% compared to 7% in Prospera testing (p=0.7) and NPV was 98% for both tests (p=0.76). This study is limited by small sample size and retrospective design.

Feingold (2023) conducted a single institution study that compared pediatric and young adult heart transplant outcomes after implementation of dd-cfDNA surveillance to previous outcomes based on EMB-surveillance.[48] Heart transplant outcomes (graft losses, mortality, and EMB case volumes) from September 1, 2016 to July 15, 2019 were compared to outcomes from September 1, 2019 to July 15, 2022. Both cohorts had surveillance EMB at 2 weeks, 6 weeks, and 3 months. Then, the earlier cohort continued EMB surveillance at regular intervals and the later cohort had dd-cfDNA tests followed by EMB only if dd-cfDNA levels were elevated. From September 2019, 120 patients had 236 dd-cfDNA assessments. A total of 43 dd-cfDNA results triggered right heart catheterization/EMB, and of those, four patients were diagnosed with acute rejection. EMB volumes decreased after implementation of dd-cfDNA surveillance (p=0.002), and the incidence of graft loss (p=0.17) and mortality (p=0.23) were not significantly different. In addition to the lack of randomization and single institution data, the study is significantly limited by short follow-up time.

Kim (2022), assessed the clinical validity of the Prospera Heart dd-cfDNA test versus endocardial biopsy for prediction of acute heart transplant rejection.[49] The study included 811 samples (703 prospectively collected and 108 retrospectively collected) from 223 heart transplant patients with a planned biopsy from two U.S. centers. The median patient age was 54 years and 27% were female. Race/ethnicity of the study population was: 54% White, 21% Hispanic, 12% Black, 6% Asian and 5% other race/ethnicity. The majority (91% [737/811]) of reference standard biopsies were conducted for surveillance, and median dd-cfDNA was lower in the surveillance samples (0.04%) than the for-cause samples (0.22%). The time from transplant to biopsy was 10 weeks, and the total prevalence of acute rejection was 9.0%. Median dd-cfDNA % was 0.58% in patients with acute rejection, although fractions varied according to rejection type/grade and were higher in those with antibody mediated rejection (median range 0.44% to 3.43%) than those with acute cellular rejection (median range 0.045% to 0.13%). In patients without acute rejection, dd-cfDNA % was 0.04. Diagnostic accuracy for three dd-cfDNA fractions were explored: 0.12%, 0.15% and 0.20%. At a cut-off off of 0.12%, sensitivity was 86.6%, specificity was 72.0%, PPV was 23.4%, and NPV 98.2%. Corresponding values at a dd-cfDNA cut-of of 0.15% were 78.6%, 76.9%, 25.1% and 97.3%, and 78.6%, 82.1%, 30.3% and 97.5% at a dd-cfDNA cut-off of 0.20%. This resulted in an AUC for detection of acute rejection of 0.86 (95% CI 0.77 to 0.96). The optimal dd-cfDNA fraction for detection of heart transplant rejection has yet to be established. Limitations of the study include potential selection bias, as only patients with a scheduled biopsy were included in the study, and study authors noted that the prevalence of acute rejection in the study cohort was higher than in other cohorts.

Khush (2019) published performance characteristics for the AlloSure Heart dd-cfDNA test as assessed in the Derived Cell Free DNA in Association With Gene Expression Profiling (D-OAR) prospective, multicenter registry study.[50] Patients already undergoing AlloMap testing for surveillance were eligible for inclusion; however following a protocol amendment, dd-cfDNA specimens were only obtained in patients with clinical suspicion of rejection and a planned for-cause biopsy after 2016 through 2018. The majority of dd-cfDNA samples (81%) were drawn in the first-year post-transplant. The D-OAR cohort included 841 biopsy-paired dd-cfDNA results, of which 587 were performed for routine surveillance of rejection. Overall, cell-mediated rejection and antibody-mediated rejection were biopsy-confirmed in 17 and 18 cases, respectively. The AUC for detecting acute rejection was 0.64 (95% CI 0.52 to 0.75). At a 0.2%

cutoff for dd-cfDNA, the sensitivity, specificity, PPV, and NPV for detection of acute rejection was 80%, 44%, 8.9%, and 97.1% respectively. For the subgroup of patients undergoing surveillance, the sensitivity, specificity, PPV, and NPV were 38.1%, 84.0%, 8.1%, and 97.3%, with a corresponding AUC of 0.61 (95% CI 0.46 to 0.74). Among for-cause samples, the sensitivity, specificity, PPV, and NPV were 53.8%, 76.1%, 11.6%, and 96.6%, respectively. The study is limited by the protocol changes designed to increase the number of observed rejection events overall and low availability of concurrent dd-cfDNA results with respect to biopsy specimens (58%).

In study funded by TAI Diagnostics, Inc., North (2020) performed a blinded clinical validation study on 158 matched pairs of endomyocardial biopsy-plasma samples collected from 76 volunteer adult and pediatric heart transplant recipients (ages two months or older, and eight days or more post-transplant) between June of 2010 and Aug 2016 from two Milwaukee transplant centers.[51] Based on acute cellular rejection grade as defined by the 2004 International Society for Heart and Lung Transplantation (ISHLT) classification, Receiver Operating Characteristic (ROC) analysis was performed to evaluate diagnostic accuracy across all possible cutoffs. To maximize diagnostic accuracy, Youden's Index was used to select the optimal cutoff, found to correspond to a donor fraction value of 0.32%. Using this cutoff, clinical performance characteristics of the assay included a negative predictive value (NPV) of 100.00% for grade 2R or higher acute cellular rejection, with 100.00% sensitivity and 75.48% specificity; AUC for this analysis was 0.842, indicative of robust ability of the donor fraction assay to rule out 2R or greater acute cellular rejection for donor fraction values less than 0.32%. There was no statistically significant correlation of donor fraction with age. Donor fraction elevation can also be caused by other forms of injury to the donor heart such as acute cellular rejection 1R, acute antibody-mediated rejection (AMR), and presence of coronary artery vasculopathy (CAV), thereby requiring correlation of myTAIHEART results with other clinical indicators.

In study funded by a grant from the National Institutes of Health and TAI Diagnostics, Inc., Richmond (2019) assessed 174 postcardiac transplant patients from seven centers (ages 2.4 months to 73.4 years) days with myTAIHEART testing (before transplant; one, four, and seven days following transplant; and at discharge from transplant hospitalization) using blinded analysis of biopsy-paired samples.[52] All the patients were followed for at least one year. Donor fraction, defined as the ratio of cell free DNA specific to the transplanted organ to the total amount of cell free DNA present in a blood sample was higher in acute cellular rejection 1R/2R (n=15) than acute cellular rejection 0R (healthy) (n=42; p=0.02); an optimal donor fraction threshold (0.3%) was determined by the use of ROC analysis, revealing an AUC of 0.814 with a sensitivity of 0.65, specificity of 0.93, and an NPV of 81.8% for the absence of any allograft rejection.

Agbor-Enoh (2021) reported results of a multicenter, prospective cohort study of heart transplant recipients monitored using dd-cfDNA and EMB. A total of 171 subjects were followed for a median of 17.7 months post-transplant. The primary endpoint was AR defined by international standards as a composite endpoint of ACR or AMR, defined based on individual center histologic readings to be consistent with usual care and included the histopathology grades treated at individual centers. Secondary endpoints were ACR grade ≥2 and AMR grade ≥1. Quantification of dd-cfDNA was conducted using shotgun sequencing. SNPs were identified for each donor/recipient pair using genotype data and %dd-cfDNA was computed as percentage of reads with donor SNPs to total reads for donor plus recipient SNPs. Median %dd-cfDNA levels were highest post-surgery and reduced to 0.13% (interquartile range [IQR],

0.03% to 0.21%) by 28 days. In patients with AR, %dd-cfDNA increased again compared with control values (0.38%; [IQR, 0.31 to 0.83%], versus 0.03% [IQR, 0.01 to 0.14%]; p<0.001). The area under the receiver operator characteristic curve (AUROC) for AR was 0.92 and a 0.25% dd-cfDNA threshold had a negative predictive value for AR of 99% and would have safely eliminated 81% of EMB.

Lung Transplant

The use of dd-cfDNA to predict acute cellular rejection has also been proposed for use in lung transplant patients. Rosenheck (2022) assessed the predictive ability of dd-cfDNA testing using the Prospera test for lung transplant rejection.[53] The study included 195 samples from 103 patients, who were predominantly White (93%) and male (60%); mean age was 62 years. Black and Hispanic patients comprised 6% and 1% of the study population, respectively. The median time since lung transplant was 198 days, and most patients (85%) underwent lung biopsy for routine transplant surveillance. Consistent with other dd-cfDNA studies, median dd-cfDNA % was higher in patients with acute rejection (AR), which included acute cellular rejection (1.43%) or antibody-mediated rejection (2.50%), than those who were stable (0.46%). Prevalence of acute rejection was 28% (29/103), and prevalence of CLAD or neutrophilic-responsive allograft dysfunction (NRAD) was 21% (22/103); patients could be included in both diagnostic groups. Using a dd-cfDNA threshold of ≥1% for prediction of acute rejection, sensitivity was 89.1% and specificity was 82.9%, resulting in an AUC of 0.91 (95% CI 0.83 to 0.98). PPV was 51.9% and NPV was 97.3%. For a combined measure that included AR, CLAD/NRAD, and infection, sensitivity was 59.9%, specificity 83.9%, AUC 0.76, PPV 43.6%, and NPV 91.0%. As with other dd-cfDNA studies in lung transplantation, this study was limited by the small sample size though unlike other studies samples were collected prospectively.

Khush (2021) utilized samples from the biorepository derived from the Genome Transplant Dynamics study which included 38 unique bilateral or unilateral lung transplantation recipients 15 years of age or older.[54] A next-generation targeted sequencing assay was used to measure dd-cfDNA and acute cellular rejection was graded in trans-bronchial biopsies. Median dd-cfDNA was significantly elevated in acute cellular rejection samples (0.91%; IQR 0.39 to 2.07%) and chronic lung allograft dysfunction samples (2.06%; IQR 0.57 to 3.67%) compared to the samples from stable healthy allografts (0.38%; IQR 0.23 to 0.87%; p=0.021). The antibody-mediated rejection cohort was numerically but not statistically significantly different from the stable healthy allografts cohort (1.34%; IQR 0.34 to 2.40%), which was also not significantly different from the allograft infection group (0.39%; IQR 0.18 to 0.67%; p=0.56). No diagnostic cutoff for use of dd-cfDNA was proposed.

Sayah (2020) conducted a pilot study investigating the ability of AlloSure dd-cfDNA testing to detect acute cellular rejection.[55] Biopsy-matched biorepository samples from 69 lung transplant recipients who had previously enrolled in the multicenter Lung Allograft Gene Expression Observational (LARGO) Study were evaluated. Diagnostic cohorts included patients with respiratory allograft infection (n=26), normal histopathology without infection or rejection (n=30), and acute cellular rejection without concurrent infection (n=13). Samples were obtained between >14 days and <one1-year post-transplant, and samples associated with potential concurrent infection with rejection were excluded. Median dd-cfDNA levels were 0.485% (IQR, 0.220 to 0.790) in the normal cohort, 1.52% (IQR, 0.520 to 2.550) in the acute cellular rejection cohort, and 0.595% (IQR, 0.270 to 1.170) in the infection cohort. While dd-cfDNA levels were significantly higher in the acute cellular rejection cohort compared to the normal cohort (p=0.026), samples associated with infection were not significantly different from

the normal (p=0.282) or acute cellular rejection (p=0.100) cohorts. The AUC for detection of acute cellular rejection was 0.717 (95% CI 0.547 to 0.887; p 0.025). At a threshold of 0.87% dd-cfDNA and an estimated prevalence rate of 25%, sensitivity for acute cellular rejection was 73.1% (95% CI 52.2% to 88.4%), specificity was 52.9% (95% CI 27.8% to 77.0%), positive likelihood ratio was 1.55, negative likelihood ratio was 0.51, PPV was 34.1%, and NPV was 85.5%. The study is limited by the small sample size and use of archived samples, and raises concerns regarding the ability of AlloSure dd-cfDNA testing to detect antibody-mediated rejection and to discriminate between infection and rejection.

The evidence is insufficient to determine that dd-cfDNA results in an improvement in the net health outcome of patients after lung transplant. Larger and additional prospective studies validating the dd-cfDNA threshold for active rejection are needed to develop conclusions. At present, no studies evaluating the clinical utility for AlloSure or Prospera dd-cfDNA testing were identified.

HEARTCARE

The commercially available HeartCare (CareDx) test combines AlloMap GEP testing with AlloSure Heart measurement of percent dd-cfDNA. The combined use of GEP and dd-cfDNA testing for surveillance of acute rejection was assessed in a single-center, retrospective study conducted by Gondi (2021) between February 2019 and March 2020.[56] Patients (n=153) were required to be ≥55 days post-transplant, hemodynamically stable, ≥15 years of age, and single-organ recipients. The majority of patients were male (74.5%) and white (78.4%) with an average age of 54.5 years. Patients were assessed once monthly between 2 and 12 months, every three months between 12 and 24 months, and every six months between 24 and 36 months post-transplant. Pre-specified thresholds for GEP scores were ≥30 for patients under six months post-transplant and ≥34 for patients six or more months post-transplant. The pre-specified threshold for percent dd-cfDNA was ≥0.20% based on a prior study of the AlloSure test by Khush (2019),[50] described above. In patients under six months post-transplant, endomyocardial biopsy was performed regardless of test results. For patients six or more months post-transplant who received both GEP and dd-cfDNA testing, endomyocardial biopsy was canceled in patients with dd-cfDNA <0.20% regardless of AlloMap score. In patients with positive AlloMap scores but negative dd-cfDNA, endomyocardial biopsy could be performed or deferred in favor of repeat dd-cfDNA testing. Among 495 samples, overall test result distributions were 59.6% for patients negative on both tests, 12.3% for patients positive by dd-cfDNA only, 22.6% for patients positive by GEP only, and 5.5% positive by both GEP and dd-cfDNA. The combined testing approach resulted in a 12.7% reduction (48 biopsies) in endomyocardial biopsy volume compared to GEP testing alone. Among the 172 biopsies performed, two patients with cell-mediated rejection were identified, with corresponding dual-positive tests. Two patients with antibody-mediated rejection were identified, with corresponding tests that were only positive by dd-cfDNA. The study is limited by its retrospective design, incomplete evaluation of performance characteristics, and lack of reporting on health outcomes.

MOLECULAR MICROSCOPE® DIAGNOSTIC SYSTEM

The Molecular Microscope® Diagnostic System (MMDX) estimates the probability of rejection in endomyocardial or kidney biopsy tissue using microarray gene analysis. As previously described, the MMDX test has been used as a comparator to dd-cfDNA test for detecting renal transplant rejection.[30] Schachtner (2023) evaluated discrepant results between MMDX and

kidney histology using 72 biopsies from 51 patients. There was 65% concordance between MMDX and kidney biopsy.[57] In most cases of discordance, MMDX showed no rejection, but histology showed rejection. The authors note that histologic evidence drives treatment decisions.

MMDX testing for heart transplant rejection was evaluated by Alam (2022), who used paired results from heart transplant tests for comparisons. MMDX was paired with endomyocardial biopsy (EMBx), and a different pairing was of MMDX and dd-cfDNA.[58] The study used 228 specimens from 135 patients. Thirty percent of the specimens were associated with clinical concern for rejection. MMDX and EMBx showed 84% concordance. MMDX identified 32 specimens with rejection that were discordant with EMBx results. Five specimens were found to be negative for rejection with MMDX but showed rejection with EMBx. There was 72% concordance between MMDX and dd-cfDNA. Treatment for rejection was initiated in eight patients when MMDX results showed rejection and EMBx did not. These treatment changes were also influenced by clinical suspicion of rejection and/or elevated dd-cfDNA or DSA levels. The evidence is insufficient to determine whether MMDX test results can lead to improved health outcomes after heart or kidney transplantation.

IMMUNE RESPONSE OF RECIPIENT LYMPHOCYTES TO DONOR LYMPHOCYTES

Rohan (2020) evaluated the performance of allo-antigen-specific T-cytotoxic memory cells (TcM) for predicting the likelihood of rejection in renal transplant recipients.[59] A total of 22 adult primary renal transplant recipients were tested for allospecific CD154-positive TcM (Plemixmark™). Frequencies of CD154-positive TcM in recipient blood samples induced by overnight stimulation with donor-HLA-matched (donor) peripheral blood lymphocytes were measured with flow cytometry. The index of rejection was reported as donor-specific CD154-positive TcM expressed as a multiple of those induced by stimulation with HLA-mismatched PBL in parallel co-culture. Of the 22 patients, six experienced biopsy-proven T-Cell Mediated Rejection (TCMR) and one experienced antibody-mediated rejection. Six of the seven rejection patients had an index of rejection predicting rejection and 10 of 15 patients with no rejection had an index of rejection predicting no rejection. These results indicated a sensitivity of 83%, specificity of 67%, positive predictive value of 54%, and negative predictive value of 91%.

A study by Ashokkumar (2017) described the creation and validation of a similar test for predicting the likelihood of rejection in pediatric patients after liver or small bowel transplantation.[60] In this study, allo-antigen-specific T-cytotoxic memory cells were measured in a training set of 158 cryopreserved samples from 127 subjects to set threshold values for samples obtained before or after (within 60 days) transplantation. After the test was standardized for reproducibility, it was run on a validation set of 122 samples from 87 patients. Of these, only 97 samples from 72 patients were analyzable. There were no significant differences in donor-recipient HLA-matching between rejectors and non-rejectors. The sensitivity and specificity of the test in post-transplant samples were 84% and 80%, respectively in the validation set.

URINARY BIOMARKERS

Janfeshan (2024) published a systematic review and meta-analysis to determine the role of urinary CXCL10 in predicting renal allograft injury.[61] Of nine case-control studies, four assessed urinary CXCL10 to serum creatinine (Cr) ratio with and without other biomarkers (e.g., CXCL9). Five studies assessed urinary CXCL10 protein levels. The quality assessment of the included studies was deemed satisfactory using the Newcastle-Ottowa scale, but there

was significant heterogeneity. The study groups were too dissimilar to merge results. The authors concluded that assessing CXCL10 protein levels detected graft injury more effectively than measurement of the CXCL10/Cr ratio, but neither type of CXCL10 measurement is effective by itself.

Hirt-Minkowski (2023) performed a RCT that evaluated CXCL10 monitoring in 241 people who were immediate post-renal transplant.[62] Both study arms had CXCL10 testing, but the intervention arm monitored lab values and had triggers for biopsy and subsequent treatment adjustment, while the CXCL10 test results for the control arm were concealed. After one year, there were no significant differences in clinical outcomes, including intention to treat (p=0.80), death-censored graft loss (p=0.62), acute rejection (p=0.39), or chronic active TCMR in one-year surveillance biopsy (p=0.59). The authors concluded that no clinical benefit was demonstrated with urine CXCL10 monitoring.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL SOCIETY OF HEART AND LUNG TRANSPLANTATION

In 2023, the International Society of Heart and Lung Transplantation published updated guidelines for the care of heart transplant recipients.[63] The guidelines included the following recommendations regarding rejection surveillance:

Immunosuppression and Rejection:

Recommendations for Rejection Surveillance by Endomyocardial Biopsy in Heart Transplant Recipients:

- The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy (EMB) during the first 6 to 12 postoperative months for surveillance of heart transplant rejection. Class IIa, Level of Evidence: C
- The standard of care for adolescents should be similar to adults, including surveillance EMB for heart allograft rejection for 3 to 12 months after HT. In younger children, especially infants, the risks associated with EMB and required general anesthesia may outweigh the surveillance benefit for comparably rare acute rejection; therefore, it is reasonable to use a combination of noninvasive screening methods (echocardiography, ECG, biomarkers) instead. Class IIa, Level of Evidence: C
- After the first postoperative year, it is reasonable to continue EMB surveillance in patients who are at higher risk for late acute rejection. This group includes HT recipients with donor-specific antibodies (DSA), a history of recurrent acute rejection, calcineurin-inhibitor free immunosuppression, reduced immunosuppression due to post-transplant malignancy or chronic infection, African American descent. Class IIa, Level of Evidence: C
- Routine EMB later than 5 years after HT are not recommended. EMB should be performed only for cause in patients with signs or symptoms of cardiac allograft dysfunction. Class III, Level of Evidence: C
- Children receiving ABO incompatible cardiac allografts in the first 2 years of life with isohemagglutinin titers toward the donor blood group below 1:32 and without elevated titers post-transplant do not require more frequent EMB or non-invasive monitoring compared to recipients of ABO compatible organs. Class IIa, Level of Evidence: B

Recommendations for the Noninvasive Monitoring of Acute Heart Transplant Rejection:

- Ventricular evoked responses (VER) monitoring for rejection surveillance is no longer recommended as the technology has become obsolete. Class III, Level of Evidence: C
- Gene Expression Profiling (GEP) (i.e., AlloMap) of peripheral blood can be used in low-risk patients between 2 months and 5 years after heart transplant and to identify adult recipients who have the low risk of current acute cellular rejection (ACR) to reduce the frequency of EMB. Data in children does not allow a general recommendation of GEP as routine tool at present. Class IIa, Level of Evidence: B
- In pediatric patients, echocardiography, especially detailed assessment of diastolic function, shows reasonable correlation with significant acute rejection; however, it should not be considered as a sole surveillance method in patients who have a low risk of EMB complications. In younger children, echocardiographic surveillance represents an alternative monitoring modality to avoid or reduce the frequency of EMB. Class IIb, Level of Evidence B.
- The routine clinical use of electrocardiographic parameters for acute heart allograft rejection monitoring is not recommended. Class III, Level of Evidence: C
- Echocardiography may be an acceptable rejection monitoring strategy in patients at low risk for acute rejection and in whom EMB is not possible (i.e., tricuspid valve replacement or difficult vascular access). Class IIb, Level of Evidence: C
- MRI with gadolinium enhancement may be used as an adjunct modality in patients with unexplained graft dysfunction and low-grade or absent histologic evidence of rejection on EMB. Class IIb, Level of Evidence: C
- It is reasonable to integrate biomarkers such as B-type natriuretic peptide (BNP) and high-sensitivity troponins into a rejection monitoring strategy to identify higher risk patients who may benefit from additional evaluation for ACR, AMR or CAV. Class IIb, Level of Evidence: C
- Post-transplant monitoring for de novo donor specific antibodies (DSA) should be performed at 1, 3, 6, and 12 months post-operatively and annually thereafter. Sensitized patients should be monitored more frequently. Class IIa, Level of Evidence: C
- The use of systemic inflammatory markers such as C-reactive protein (CRP) for acute heart allograft rejection monitoring is not recommended. Class III, Level of Evidence: C
- In younger children, especially infants, the risks associated with EMB and required general anesthesia may outweigh the surveillance benefit for comparably rare acute rejection; therefore, it is reasonable to use a combination of non-invasive screening methods (echocardiography, ECG, biomarkers) instead. Class IIa, Level of Evidence: C
- Use of immune cell function assay (ImmuKnow) cannot be recommended in adult and pediatric heart transplant recipients for rejection monitoring. Class III, Level of Evidence: B

<u>Recommendation for the management of Late Acute Rejection:</u>

- After the first year, continued rejection surveillance (using a combination of noninvasive methods, GEP or EMB) is reasonable in patients at higher risk for late acute rejection. Risk factors for rejection include younger recipient age, prior history of acute rejection episodes, presence of donor-specific-antibodies, recipient female gender, rejection events occurring >6 months after transplantation, CNI-reduced or -free immunosuppression, and a history of medication of non-compliance. The optimal frequency and duration of rejection surveillance have not been defined. Class IIa, Level of Evidence: C
- Antibody mediated rejection is more commonly identified in late acute rejection

compared to acute cellular rejection and should be considered in the differential diagnosis of HT recipients presenting with signs or symptoms of heart allograft dysfunction. EMB with ISHLT immunopathologic evaluation, as well as measurement of circulating HLA donor-specific-antibodies should be obtained before initiating treatment. Class IIa, Level of Evidence: C

Long-term care of heart transplant recipients: Prevention and Prophylaxis:

Frequency of Routine Tests and Clinic Visits in Heart Transplant Recipients:

In addition to routine outpatient follow-up visits, HT recipients should have more prolonged visits every 1 to 2 years for more detailed clinical assessment. (Class I, Level of Evidence B). The purpose of the follow-up visits is to monitor for rejection and screen for adverse events and may include the following:

1. A complete physical examination;
2. Review of medications and changes to medications based on the results of the examinations;
3. Blood work;
4. Echocardiogram;
5. Coronary angiography. Adjunct Intravascular imaging can be considered if expertise available, as Maximal Intimal Thickening (MIT) > 0.3 mm in the first year has been shown to have prognostic value;
6. Surveillance EMB, and noninvasive rejection monitoring [Gene Expression Profiling (Allomap), DSA, BNP and high sensitivity troponins, donor-derived cell-free DNA]
7. Additional education and/or interaction with members of the multidisciplinary team. Class I, Level of Evidence B

In infants early after heart transplantation, far fewer biopsies are performed due to the need for general anesthesia and the difficulties with venous access and bioptome manipulation in small hearts and vessels. There is no consensus regarding the frequency of EMB. Ancillary noninvasive modalities for the assessment of rejection as surrogates to EMB should be considered. Class I, Level of Evidence B.

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

In 2009, the Kidney Disease Improving Global Outcomes issued guidelines for the care of kidney transplant recipients.[64] The guidelines did not address dd-cfDNA or gene expression profile testing.

AMERICAN SOCIETY OF TRANSPLANT SURGEONS

In 2023, the American Society of Transplant Surgeons (ASTS) issued a position statement on the role of dd-cfDNA in kidney transplant surveillance.[65] The following recommendations regarding the clinical utility and decision analysis were issued:

- "The most data have been accumulated in adult transplant recipients, and these recommendations are therefore most applicable to adult patient populations.
- We suggest that clinicians consider measuring serial dd-cfDNA levels in kidney transplant recipients with stable renal allograft function to exclude the presence of subclinical antibody-mediated rejection.

- We recommend that clinicians measure dd-cfDNA levels in kidney transplant recipients with acute allograft dysfunction to exclude the presence of rejection, particularly antibody-mediated rejection (ABMR).
- We do not recommend the use of blood gene expression profiling (GEP) in kidney transplant recipients for the purpose of diagnosing or excluding sub-clinical rejection, as adequate evidence supporting such use is still lacking.
- We do not recommend the use of blood GEP to diagnose or exclude the presence of acute graft rejection in kidney transplant recipients with acute allograft dysfunction given the paucity of data to support this practice.
- We recommend that dd-cfDNA may be utilized to rule out subclinical rejection in heart transplant recipients.
- We recommend that clinicians utilize peripheral blood GEP as a non-invasive diagnostic tool to rule out acute cellular rejection in stable, low-risk, adult heart transplant recipients who are over 55 days status post heart transplantation."

"Caveats and recommendations for future studies:

- None of these recommendations should be construed as recommending one biomarker over another in the same diagnostic niche.
- We strongly recommend ongoing clinical studies to clarify the scenarios in which molecular diagnostic studies should be utilized.
- We specifically recommend that studies be carried out to evaluate the potential role of dd-cfDNA surveillance in kidney transplant recipients to improve long-term allograft survival."

SUMMARY

There is enough research to show that gene expression profiling to predict heart transplant rejection improves health outcomes for patients who have had a heart transplant. Therefore, the use of gene expression profiling, including but not limited to the AlloMap® test, for prediction or detection of heart transplant rejection is considered medically necessary.

There is not enough research to show that gene expression profiling to predict transplant rejection improves health outcomes for patients who do not meet policy criteria. Therefore, the use of gene expression profiling tests in the management of transplant recipients who do not meet policy criteria is considered investigational.

There is not enough research to show that the Heartsbreath™ test or any test that measures volatile organic compounds improves health outcomes for patients that have had a heart transplant. Therefore, the measurement of volatile organic compounds to assist in the detection of heart transplant rejection, including use of the Heartsbreath™ test, is considered investigational.

There is not enough research to show that measurement of donor-derived cell-free DNA (dd-cfDNA) to assess rejection improves health outcomes for patients who have had a renal, heart, or lung transplant. Therefore, the use of dd-cfDNA testing, including the AlloSure® and myTAIHEART tests, to assist in the detection of kidney, heart, or lung transplant rejection is considered investigational.

There is not enough research to show that measurement of immune response of recipient lymphocytes to donor lymphocytes in cell culture to assess the likelihood of acute cellular rejection after transplantation improves health outcomes for patients who have had an organ transplant. Therefore, the use of measurement of immune response of recipient lymphocytes to donor lymphocytes in cell culture to assess the likelihood of acute cellular rejection after renal, liver, and/or small bowel transplantation is considered investigational.

There is not enough research to show that heart or kidney transplant risk of rejection estimates using gene expression profiling tests (e.g., Molecular Microscope® Diagnostic System) on biopsy specimens improves health outcomes for patients who have had heart or kidney transplant. Therefore, the use of gene expression profiling tests on biopsy tissue to predict rejection is considered investigational.

There is not enough research to show that measurement of the urinary chemokine CXCL10 improves health outcomes of people who have had kidney transplant. Therefore, use of urinary quantification of chemokine CXCL10 to monitor for rejection or determine the need for graft biopsy after renal transplant is considered investigational.

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CODES

Codes	Number	Description
		Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
	0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma
	0087U	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score
	0088U	Transplantation medicine (kidney allograft rejection) microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection
	0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA
	0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection
	0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection

Codes	Number	Description
	0493U	Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA
	0508U	Transplantation medicine, quantification of donor-derived cell-free DNA using 40 single-nucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cell-free DNA with risk for active rejection
	0509U	Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection
	0526U	Nephrology (renal transplant), quantification of CXCL10 chemokines, flow cytometry, urine, reported as pg/mL creatinine baseline and monitoring over time
	0540U	Transplantation medicine, quantification of donor-derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection
	0544U	Nephrology (transplant monitoring), 48 variants by digital PCR, using cell-free DNA from plasma, donor-derived cell-free DNA, percentage reported as risk for rejection
	81479	Unlisted molecular pathology procedure
	81558	Transplantation medicine (allograft rejection, kidney), mRNA, gene expression profiling
	81560	Transplantation medicine, measurement of donor and third party-induced CD154+T-cytotoxic memory cells
	81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score
	86849	Unlisted immunology procedure
HCPCS	None	

Date of Origin: *January 2005*

Regence

Medical Policy Manual Laboratory, Policy No. 65

Measurement of Serum Antibodies to Selected Biologic Agents

Effective: July 1, 2024

Next Review: April 2025
Last Review: May 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

Anti-drug antibodies to drugs such as infliximab, adalimumab, ustekinumab, and vedolizumab may be found in patients undergoing treatment for inflammatory diseases including inflammatory bowel disease, psoriasis, ankylosing spondylitis, or rheumatoid arthritis and are thought to be associated with a loss of treatment response.

MEDICAL POLICY CRITERIA

I. Measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, may be considered **medically necessary** for patients with inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis), when there is documentation of a loss of response to one of these medications.

II. Measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, is considered **not medically necessary** when there has not been a loss of response to the medication.

III. Measurement of serum antidrug antibodies, either alone or as a combination test that includes serum drug levels, is considered **investigational** for all of the following:

A. For any chronic inflammatory condition other than inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis), including but not limited to rheumatoid arthritis and psoriasis, and

B. For quantification of antibodies to ustekinumab, vedolizumab, certolizumab, etanercept, or golimumab for any condition.

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

CROSS REFERENCES

1. Medication Policy Manual, Note: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

INFLIXIMAB, ADALIMUMAB, USTEKINUMAB, AND VEDOLIZUMAB IN AUTOIMMUNE DISEASE

Therapy with monoclonal antibodies has revolutionized treatment of patients with inflammatory diseases such as inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]), rheumatoid arthritis and psoriasis. These agents are generally given to patients after conventional medical therapy fails, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to anti-drug antibodies (ADA).[1]

Infliximab (Remicade® by Janssen Biotech, Inflectra® by Pfizer, and Renflexis® by Merck Sharp & Dohme) is an intravenous tumor necrosis factor alpha (TNFα) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis (UC). Infliximab is a chimeric (mouse/human) anti-TNFα monoclonal antibody. Adalimumab (Humira® AbbVie) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of the above indications (CD and UC in adults only) plus juvenile idiopathic arthritis (JIA). Adalimumab is a fully human monoclonal antibody to TNFα. Certolizumab (Cimzia® by UCB) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and non-radiographic axial spondyloarthritis (nr-axSpA). Etanercept (Enbrel®, Immunex) is a TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, JIA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Golimumab (Simponi® by Janssen Biotech) is a subcutaneous TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, UC, and psoriatic arthritis. Vedolizumab (Entyvio®, Millennium Pharmaceuticals) is an intravenous blocking agent for integrin $\alpha_4\beta_7$ and is FDA-approved for adults with CD or UC. Ustekinumab (Stelara®, Janssen Biotech) is an antibody that blocks interleukins IL-12 and IL-23 and is FDA-approved to treat psoriasis and certain patients with Crohn's disease.

Following primary response to these medications, some patients become nonresponders (secondary nonresponse). The development of anti-drug antibodies (ADA) is thought to be a cause of secondary nonresponse. ADA are also associated with injection site reactions (adalimumab), and acute infusion reactions and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, such as infliximab.

DETECTION OF ANTI-DRUG ANTIBODIES

The detection and quantitative measurement of ADA has been fraught with difficulty owing to drug interference and identifying when antibodies are likely to have a neutralizing effect. First-generation assays, (i.e., enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay (RIA) method, and more recently, the homogenous mobility shift assay (HMSA) using high-performance liquid chromatography. Disadvantages of the RIA method are associated with the complexity of the test and prolonged incubation time, and safety concerns related to the handling of radioactive material. The HMSA has the advantage of being able to measure ADA when infliximab is present in the serum. A reporter-gene assay (RGA) is also available, which allows for the measurement of ADAs capable of neutralizing drug activity.[2] Cell-based assays typically have difficulty in standardization, take up to two days to complete, and with effects from the serum matrix. However, the RGA can quantify the anti-drug neutralizing antibody independent of matrix effects within two hours. Application of the RGA has recently been assessed for use in a clinical laboratory setting, and found to be a precise and high-throughput robust platform for detection of ADA.[3] Large randomized studies are still necessary to establish relevant clinical cut-off levels. Studies evaluating the validation of results among different assays are lacking, making inter-study comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between two different ELISA methods in patients with IBD (i.e., double antigen ELISA and antihuman lambda chain-based ELISA).[4] This study did not include an objective clinical and endoscopic scoring system for validation of results. A 2013 review by Seow and Panaccione, noted that the variability and lack of standardization in current assay tests has important implications for subsequent studies which report associations between antibodies-to-infliximab (ATIs) and infliximab levels and utilize these assays to predict treatment response.[5] These findings highlight the need for a validated gold standard test and established diagnostic parameters with which to measure levels of infliximab and ATIs.

TREATMENT OPTIONS FOR PATIENTS WITH SECONDARY LOSS OF RESPONSE TO ANTI-TNF THERAPY

A diminished or suboptimal response to infliximab or adalimumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different anti-TNF agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-anti-TNF agent.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be

licensed by the CLIA for high complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require regulatory review of these tests.

Prometheus® Laboratories Inc., a College of American Pathologists–accredited lab under CLIA, offers non-radiolabeled fluid-phase HMSA tests called the Anser® IFX test for infliximab. Anser® ADA for adalimumab, Anser® UST for ustekinumab, and Anser® VDZ for vedolizumab. None of these tests are ELISA-based and they can measure anti-drug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. All tests measure serum concentrations and anti-drug antibodies.

LabCorp has a portfolio of tests called DoseASSURE™ including DoseASSURE™ ADL for adalimumab, DoseASSURE™ UST for ustekinumab, DoseASSURE™ IFX for infliximab, DoseASSURE™ CTZ for certolizumab, DoseASSURE™ ETN for etanercept, and DoseASSURE™ GOL for golimumab. These tests are electrochemiluminescence immunoassay (ECLIA) and/or ELISA-based and report drug concentration and anti-drug antibody levels.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on analytic validity, diagnostic validity, and clinical utility. Analytic validity demonstrates technical feasibility as compared to a gold standard, including assessment of test reproducibility and precision. For comparison among studies, a common standardized protocol is necessary. Diagnostic utility is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known. Clinical utility is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes. This evidence review focuses on the clinical validity and clinical utility.

Most studies evaluating antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab report serum drug levels together with anti-drug antibody (ADA) levels, and correlate levels to disease response. Serum drug levels and disease response will not be addressed in this section and therefore the data reported on ADA will be highlighted from the identified studies. Most evidence concerning testing for ADA is derived from the data available for patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Less literature exists concerning other diseases comprising psoriasis and spondyloarthropathies (SpA; i.e., ankylosing spondylitis, psoriatic arthritis, IBD-associated arthritis, reactive arthritis, and undifferentiated and juvenile SpA). There is also a lack of literature on the measurement of anti-vedolizumab and anti-ustekinumab antibodies for patient management.

CLINICAL VALIDITY

There is a substantial body of evidence examining associations of ADA with nonresponse and injection or infusion site reactions; numerous systematic reviews and meta-analyses have been published. Accordingly, the review of evidence concerning clinical validity focuses on the most current systematic reviews (see Tables 3 through 5) and studies published since those reviews,[6] as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).

Systematic Reviews

A systematic review (SR) published by Vermeire (2018) evaluated studies on immunogenicity to adalimumab (ADM), certolizumab pegol (CZP), golimumab, infliximab (IFX), ustekinumab, and vedolizumab in patients being treated for inflammatory bowel disease (IBD).[7] Although 122 publications covering 114 studies were noted as included in the review, all study designs and abstracts from conference proceedings were included. Greater than 90% of studies involved administration of ADM or IFX. Of the studies involving IFX administration, only 12 were RCTs and 62 were non-randomized or observational studies. Across these studies, rates of ADA formation were highly variable, ranging from 0.0–65.3% in patients with IBD. While the authors reported that the proportion of patients achieving and maintaining a response to treatment with IFX was "generally lower" for patients with detected ADA than those without detected ADA, no pooled analyses were reported for any study outcomes. No analysis informing clinically useful thresholds or timing of antibody testing was provided. This review was funded by Pfizer, Inc, a manufacturer of Inflectra, which is an infliximab biosimilar and multiple study authors are employees and/or stakeholders in Pfizer, Inc.

Six SRs published from 2012 through 2017 were identified.[8-12] The number of studies included ranged from 11[11] to 68,[12] varying according to review objectives and conditions of interest. Although not detailed here, there was considerable overlap in included studies across reviews.

A SR with meta-analysis by Pecoraro (2017) selected 34 studies (total n=4,273 patients), including randomized controlled trials (RCTs, n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional studies (n=2).[13] Studies evaluated RA (n=18), ulcerative colitis (n=2), CD (n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), spondyloarthritis (n=1). Most of the patients (45%) received infliximab, 35% received adalimumab, and 21% received etanercept. None received golimumab or certolizumab. Reviewers identified studies published through August 2016 and rated study quality as good (n=17), fair (n=16), and poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant ($p<0.05$) reduction of response (relative risk [RR] 0.43, 95% confidence interval [CI] 0.3 to 0.63) in ADA-positive patients relative to ADA-negative patients, with adalimumab therapy demonstrating a greater reduction (RR 0.40, 95% CI 0.25 to 0.65, $p<0.001$) than infliximab (RR 0.37, 95% CI 0.2 to 0.7, $p<0.001$). Measures of heterogeneity were 84%, 57%, and 79%, respectively. Fourteen studies reported on the effect of ADA on clinical response (see Table 1). Eleven studies found the risk of developing ADA to be significantly ($p=0.03$) lower in patients treated with concomitant methotrexate therapy relative to treated those without methotrexate (RR 0.65, 95% CI 0.47 to 0.9). Studies comparing treatment response with nonresponse (n=15) found responders to have a significantly ($p<0.001$) lower risk of developing ADA relative to nonresponders (RR 0.31, 95% CI 0.18 to 0.52). The presence of ADA was associated with a significant reduction of anti-tumor necrosis factor α (TNF-α) serum concentration (see Table 2). Of the 20 studies (n>2,800 patients) reporting data on adverse events, 31% (n=2 studies) developed infections, 18% (n=12 studies) developed injection-site reactions, 8% (n=11 studies) discontinued treatment due to adverse events, and 5% (n=1 study) developed serious adverse events (5%). Although ADA significantly reduced TNF-α response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies included and considerable heterogeneity.

Freeman (2017) published a SR with meta-analysis evaluating the test accuracy estimates of levels of anti-tumour necrosis factor (anti-TNF) and antibodies to anti-TNF to predict loss of response or lack of regaining response in patients with anti-TNF managed Crohn's disease (CD).[14] Studies of patients with CD treated with infliximab or adalimumab as well as studies

with mixed Crohn's and ulcerative colitis populations were included if the proportion of Crohn's patients was at least 70%. Twenty-four full-test reports and seven conference abstracts were included in the SR; eleven of the 31 studies examined infliximab trough levels, 20 examined levels of antibodies to infliximab and five and six studies, respectively, investigated adalimumab levels and antibodies to adalimumab. The greatest identified threat to validity of the studies was high risk of bias in patient selection, which was present in nearly 80% of the included studies. The studies were heterogeneous with respect to the type of test used (eg, commercial or in-house ELISA, radioimmunoassay (RIA), homogeneous mobility shift assay (HMSA)), criteria for establishing response or lack of regaining response (e.g., use of the Crohn's Disease Activity Index score or the physician's global assessment score) and population examined (responders or patients with secondary loss of response). Summary point estimates for sensitivity and specificity were 56% and 79% for antibodies to infliximab, respectively, and results for antibodies to adalimumab were similar. Positive and negative predictive values across all pooled studies ranged between 70% and 80%, implying that between 20% and 30% of both positive and negative test results may be incorrect in predicting loss of response. The authors concluded that "higher quality head-to-head test accuracy studies are required to enable differentiation between different types of tests and cut-offs, with consistent outcome measurement in the same population" and "more clinical trial evidence from test–treat studies is required before the clinical utility of the tests can be reliably evaluated."

A SR and meta-analysis by Thomas (2015) included 68 studies (14,651 patients) with patients with RA (n=8,766), SpA (n=1,534), and IBD (n=4,351) and examined the immunogenicity of infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab (14), and certolizumab (8).[12] The review identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], or poor [n=10]). The pooled prevalence of ADA varied with disease and drug (see Table 3, highest with infliximab: 25.3%). Duration of exposure (reported in 60 studies) was examined for its potential effect on the development of ADA and most studies employed ELISA assays. The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 4). An exception was in studies of IBD (similar to that reported by Lee [2012]). The use of immunosuppressive agents substantially decreased the risk of ADA (odds ratio [OR] 0.26, 95% CI 0.21 to 0.32). Finally, infusion reactions and injection site reactions were more common (see Table 5) when ADA were detectable (OR 3.25, 95% CI 2.35 to 4.51). Evaluation of potential publication bias or overall assessment (e.g., GRADE or similar) for the body of evidence was not reported. Additionally, no measures of heterogeneity were reported.

A SR by Meroni (2015) included 57 studies of infliximab (n=34), adalimumab (n=18), and etanercept (n=5).[8] Studies included primarily patients with IBD and RA, but also SpA and psoriasis. Most studies were prospective cohort designs (n=42) and a formal assessment of study quality (bias) was not reported. The authors noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Varied antibody testing assay methods were used and included solid-phases RIA, traditional ELISA, fluid-phase RIA, and bridging ELISA; cutoffs for positive test results were also inconsistently reported. The ranges of patients with detectable ADA varied substantially (see Table 3) but were consistent with other reviews. Qualitatively, the presence of ADA was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ADA also increased the risk of infusion reactions. When ascertained, the time to development of ADA varied from as little as 16 weeks to over a year. The time to ADA positivity varied – fifty percent of patients with detectable ADA at 28 weeks to a median time of one year. Finally, for

both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. The authors concluded that "…the lack of homogeneity in study design and methodologies used in the studies analyzed limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development...." Although qualitative, the authors included many studies, and provided a detailed review of each study not reported by the other meta-analyses. The author's conclusions are consistent with the meta-analyses but with emphasis on important aspects of heterogeneity across studies.

Hsu (2014) published a SR of ADA in psoriasis that included 25 studies (n=7,969).[15] Inclusion criteria for the studies were: having at least 15 patients, documentation of serial assessments of psoriasis severity, and reporting ADA in patients with psoriasis receiving infliximab, etanercept, adalimumab, or ustekinumab. Ten of these studies reported on infliximab ADA: three found an association between ADA and lower serum infliximab levels, and five found an association between ADA and clinical response. Of the five studies that evaluated antiadalimumab antibodies, four found lower treatment efficacy for those with ADA. Six studies reported on ustekinumab ADA, and two of these found an association between ADA and Psoriasis Area and Severity Index (PASI) response. The remaining six studies in the review focused on antietanercet antibodies.

Nanda (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ADA in patients with IBD.[11] MEDLINE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus databases were searched to February 2012, EMBASE to August 2012; 11 studies involving 707 patients were included. Six of these studies (two RCTs, one prospective cohort study, three retrospective cohort studies) were included in the meta-analysis by Lee (2012) outlined below. In at least one quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), all the included studies had high risk of bias. The prevalence of detectable ADA in the included studies ranged from 22.4% to 46% (see Table 3). The outcome of interest was loss of response to infliximab, defined as "relapse of clinical symptoms in patients who were in clinical remission from, or had responded to, infliximab." Measures of loss of response varied across studies and included clinician assessment, standardized scales (Crohn's Disease Activity Index [CDAI], Harvey-Bradshaw Index, Simple Clinical Colitis Activity Index), and requirement for surgery or presence of nonhealing fistula. Patients with ATIs had a three-fold greater risk of loss of response than those without ATIs (RR 3.2, 95% CI 2.0 to 5.0) (shown in Table 3 as the RR of clinical response in treated vs. untreated patients to allow comparison with other meta-analyses). This result was influenced primarily by 532 patients with CD (RR 3.2, 95% CI 1.9 to 5.5); pooled results for 86 patients with ulcerative colitis (UC) were not statistically significant (pooled RR 2.2, 95% CI 0.5 to 9.0). Eighty-nine patients with unspecified IBD also were included in the meta-analysis. In addition to potential bias in included studies and heterogeneity in outcome assessment, the meta-analysis is limited by variability in the method of ADA detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA). Study investigators stated, "[t]he true incidence of ADA in IBD patients treated with infliximab remains unknown due to the different administration schedules, timing of ADA measurements, methods used in ADA detection, and the presence of serum infliximab." Finally, although the authors noted that the funnel plot "suggested the presence of publication bias," the small number of studies and plot appearance (only two of 11 studies suggesting asymmetry) preclude conclusions.

Garces (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis.[9] Databases were searched to August 2012, and 12

prospective cohort studies included involving 860 patients (540 with RA, 132 with SpA, 130 with IBD, 58 with psoriasis). The outcome of interest was response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or ASDAS for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable ADA were associated with a 68% reduction in drug response (pooled RR=0.32, 95% CI 0.22 to 0.48). Significant heterogeneity was introduced by varying use of immunosuppressant therapy (e.g., methotrexate) across studies. To assess ADA, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Lee (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ADA, effect of ADA on the prevalence of infusion reactions, and the effect of ADA on disease remission rates.[10] Databases were searched through October 2011, and 18 studies involving 3,326 patients were included. Studies included nine RCTs, five prospective cohort studies, and four retrospective cohort studies. The prevalence of ADA was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (see Table 3). Patients with ADA were less likely to be in clinical remission (Table 4), but this was not statistically significant (RR, 0.90, 95% CI 0.79 to 1.02, p=0.10). The rates of infusion reactions were significantly higher in patients with ADA (RR 2.07 [see Table 5], 95% CI 1.61 to 2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ADA (p<0.001). The meta-analysis concluded that patients with IBD who test positive for ATIs are at an increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATIs.

Table 1. Effect of Anti-drug Antibodies on Clinical Response

Outcome Measures	No. Studies	MD	95% Confidence Interval	I^2, %	p
Disease Activity Score 28	9	0.93	0.41 to 1.44	84	<0.001
BASDAI	2	-0.62	-1.51 to 0.27	0	0.17
ASDAS	2	0.96	-0.27 to 2.2	0	0.13
Psoriasis Area Severity Index	1	4.7	-1.15 to 9.25	NR	0.04

Adapted from Pecoraro (2017).[13]
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; I^2: heterogeneity measure; MD: mean difference; NR: not reported.

Table 2. Evaluation of Anti-TNF-α Concentration

Outcome Measures	No. Studies	MD, mg/L	95% Confidence Interval	I^2, %	p
ADA-positive vs ADA-negative	8	-7.07	-8.9 to -5.25	98	<0.001
Responders vs no responders	13	2.77	1.97 to 3.58	82	<0.001
Adalimumab therapy	6	5.07	3.77 to 6.36	62	<0.001
Infliximab	4	2.74	0.59 to 4.89	62	<0.001
Etanercept	3	0.85	0.41 to 1.13	82	<0.001
DAS28 change from baseline	8	-2.18	-2.91 to -1.44	97	<0.001

Adapted from Pecoraro (2017).[13]
ADA: anti-drug antibodies; DAS28: Disease Activity Score in 28 joints; I^2: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Table 3. Estimated Prevalence of Anti-drug Antibodies from Meta-Analyses

Author	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI)	Range in Studies
Lee (2012)	18[b]	●			●			20.8% (19.2 to 22.5)	
Episodic	5	●			●			45.8% (41.7 to 50.0)	
Maintenance	10	●			●			12.4% (10.8 to 14.1)	
Nanda (2013)	11	●			●				22.4%-46%
Thomas (2015)	39[c]	●			●	●	●	25.3% (19.5 to 32.3)	
	15[c]		●		●	●	●	6.9% (3.4 to 13.5)	
	20	●	●		●			15.8% (9.6 to 24.7)	
	44	●	●	●		●		12.1% (8.1 to 17.6)	
	11	●	●	●			●	8.9% (3.8 to 19.2)	
Meroni (2015)	14	●				●			19%-47%
	14	●			●				15%-61%
	5	●					●[d]		26%-50%
	12		●			●			5%-54%
	3		●		●				9%-46%
	3		●				●[d]		18%-45%

ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthropathy.
[a] Includes etanercept, golimumab, certolizumab.
[b] Includes three studies including both maintenance and episodic therapy
[c] Number of comparisons in table; did not report studies for pooled prevalence.
[d] Also psoriasis.

Table 4. Results from Meta-Analyses of Anti-drug Antibodies and Clinical Response

Author	Included Studies	Drugs			Disease			Clinical Response: ADA vs None		
		IFX	ADL	Other[a]	IBD	RA	SpA	RR (95% CI)	OR (95% CI)	I^2
Lee (2012)	18	●			●			0.90 (0.79 to 1.02)		37%
Nanda (2013)	11	●			●			0.33 (0.20 to 0.40)		70%
Garces (2013)	12	●	●		●	●	●[b]	0.32 (0.22 to 0.48)		46%
Thomas (2015)	4	●	●	●	●				1.16 (0.66 to 2.03)	NR
	13	●	●	●		●			0.27 (0.20 to 0.36)	NR
	4	●	●	●			●		0.18 (0.09 to 0.37)	NR
	9	●			●	●	●		0.42 (0.30 to 0.58)	NR

ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis;
RR: relative risk; SpA: spondyloarthropathy.
[a] Includes etanercept, golimumab, certolizumab.
[b] Also psoriasis.

Table 5. Increased Risk of Adverse Reaction Associated With the Presence of Anti-drug Antibodies

Author	Included Studies	Drugs			Disease			Adverse Reactions: ADA vs None	
		IFX	ADL	Others[a]	IBD	RA	SpA	OR (95% CI)	RR (95% CI)
Lee (2012)	18	●			●				2.07 (1.61 to 2.67)[a]
Thomas (2015)	NR	●	●	●	●	●	●	3.25 (2.35 to 4.51)	

ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis;
RR: relative risk; SpA: spondyloarthropathy.
[a] Infusion reaction.

Nonrandomized Studies

Recent publications not included in the SRs above are included, below.

Bellur (2023) evaluated the frequency and clinical relevance of ADAs in 54 patients undergoing treatment with either adalimumab or infliximab for noninfectious uveitis.[16] None of the 12 patients receiving infliximab developed ADAs after a mean time between therapy initiation and testing of 1.7 years. One patient was a nonresponder. Of the 42 patients receiving adalimumab, ADAs were detected in 15 (35.7%). Mean drug levels were lower in patients with ADAs than in those without (p<0.001). ADAs were detected in a higher proportion of partial responders (50%) and nonresponders (53.8%) than complete responders (21.7%). The authors concluded that ADA detection may be associated with an increased risk of TNFα ineffectiveness, and ADA monitoring may be useful for determining TNFα therapy use, dosage, and frequency, but more research is needed.

A multicenter prospective cohort study of 137 patients with plaque-type psoriasis was published by De Keyser (2019).[17] Serum samples and Psoriasis Area and Severity Index scores were obtained at baseline, week 16, 28, 40, 52, and/or ≥64 of ustekinumab treatment. Presence of anti-ustekinumab antibodies (prevalence of 8.7%) was significantly associated with a diminished clinical response (p=0.032). The median ustekinumab trough concentration was 0.3 mcg/mL (<0.02-3.80). No differences in serum concentrations were observed between moderate to good responders and nonresponders (p=0.948). Although the authors found that the presence of anti-ustekinumab antibodies was associated with treatment response in this patient population, serial measurements were collected in less than half (43.8%) of the patients. Anti-ustekinumab antibodies was reported to have developed during the first 52 weeks of treatment, however, the number of observations in the first year of treatment (n=191) was significantly higher than the number of observations in patients on treatment more than one year (n=38). This may underestimate the prevalence of anti-ustekinumab antibody formation after long-term treatments. Ultimately, the authors concluded that while measurement of anti-ustekinumab antibodies should be considered if treatment response is unsatisfactory, additional research is needed to identify tools for TDM in psoriasis patients on ustekinumab treatment.

As part of a RCT of treatment strategies in rheumatoid arthritis (RA), Hambardzumyan (2019) analyzed serum infliximab (sIFX) and anti-drug antibodies (ADAs) levels in study participants randomized to methotrexate + infliximab therapy and for whom serial serum sampling data at three, nine, and 21 months were available (n=101).[18] The primary and secondary outcome measures were low disease activity [LDA = 28-joint Disease Activity Score (DAS28) ≤ 3.2] and remission (DAS28 < 2.6). The frequencies of very low sIFX levels increased over time, with 15%, 23%, and 28% at 3, 9, and 21 months from IFX start, respectively, and the majority of patients with very low sIFX levels were ADA positive at these time-points [71% (10/14), 82% (18/22), and 68% (19/28), respectively]. The proportion of patients with LDA was numerically higher at all follow-up time-points among those with sIFX ≥ 0.2 µg/mL compared with patients who had sIFX < 0.2 µg/mL and positive ADAs, although only significant at 21 months (67% and 26%, p=0.002). Similar results were observed when remission was the outcome measure (47% vs 11%, p=0.004). The authors concluded that these findings support the monitoring of serum drug levels, however, these findings require validation in larger populations and for dose-adjustment studies.

Van den Berghe (2018) published a small study evaluating ADA to vedolizumab in a cohort of 40 patients with IBD.[19] This study included the development of an ELISA-based test to measure ADA in the presence of the drug. Antivedolizumab antibodies and vedolizumab trough levels were measured after six weeks of treatment and after treatment discontinuation. At the six-week follow-up, three (8%) of the patients were positive for ADA, but this appeared

to be transient. None of the patients who discontinued vedolizumab were positive for ADA at the time of their last infusion or after discontinuation. The authors concluded that immunogenicity did not appear to play a major role in vedolizumab treatment failure.

Cludts (2017) conducted a single-center retrospective cohort analysis of patients with RA (n=18), psoriatic arthritis (n=9), or ankylosing spondylitis (n=12) in Italy.[20] Serum samples were taken prior to adalimumab therapy and after 12 and 24 weeks of treatment. Psoriatic arthritis and ankylosing spondylitis patients were grouped together (SpA) due to axial involvement in all psoriatic arthritis patients. Although adalimumab levels varied among patients (0 to 30 µg/mL), median levels were significantly lower at 12 and 24 weeks in ATA-positive samples, and antibody formation was associated with decreasing levels of circulating adalimumab. A reporter gene assay detected neutralizing antibodies against TNF antagonists in ATA-positive, therapeutic-negative patients; however, neutralization could not be confirmed in all ATA-positive samples due to adalimumab interference. There was a negative correlation between ADA levels and adalimumab in all groups, with 43.6% and 41% of the adalimumab-treated patients developing antibodies at 12 and 24 weeks, respectively. These percentages increased to 48.7% and 46% after subjecting the samples to acid treatment. There was a negative correlation between adalimumab trough levels and DAS28 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores ($p<0.001$). There were no significant differences between BASDAI in ATA-positive compared with ATA-negative patients at 12 or 24 weeks. The study is consistent with others suggesting that adalimumab levels can serve as an indicator of ATA; however, limitations included small sample size, retrospective research design, and failure to confirm neutralization in all ATA-positive samples.

Using an observational, cross-sectional study design, Ara-Martin (2017) analyzed the impact of immunogenicity on response to anti-TNF therapy in 137 adults with moderate-to-severe plaque psoriasis at 35 centers in Spain between 2012 and 2014.[21] All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) after six or more months of treatment. Serum ADA was identified in 48%, 0%, and 42% of patients of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the PASI (PASI >5), 75% improvement in PASI score from baseline (PASI75), and/or the Physician Global Assessment (PGA, >2). PGA values for ADA-positive vs ADA-negative patients were significantly worse in the adalimumab group (3.7 vs 3.2, $p=0.02$) but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in both the adalimumab group ($p=0.001$) and among the three groups combined ($p=0.001$), and a significant ($p=0.019$) correlation between serum ADA titer and body surface area. Unlike the other studies, in this study, the use of concomitant antirheumatic drugs was not associated with anti-TNF immunogenicity in any of the groups. This study provided evidence of antibody development against adalimumab and infliximab (not against etanercept) in patients with psoriasis, with ADA formation accounting for half of the secondary nonresponse associated with these therapies. However, conclusions were limited due to the cross-sectional study design, use of ELISA to detect ADAs due to drug interference, the potential presence of neutralizing antibodies as confounding factors, and limited information about patients' health status prior to the study period.

A case-control, longitudinal study by Lombardi (2016) excludes possible confounding factors by analyzing adalimumab treatment for psoriasis in five distinct groups, including individuals who received: biologic therapies after switching from adalimumab (n=20); ongoing adalimumab therapy (n=30); novel adalimumab therapy (n=30); biologic therapies other than adalimumab (n=15); and no treatment with immunosuppressants or biologics (n=15), serving as a quasi-

control.[22] The clinical severity of psoriasis was scored using the Psoriasis Area Severity Index (PASI). At 12-month follow-up, ADA was highest (87%) in patients who received biologic therapies after switching from adalimumab. The false-positive rate was 23% for adalimumab detection and 22% for anti-adalimumab antibodies in individuals who were never treated with adalimumab. There was no significant difference in median PASI score between the anti-adalimumab antibody-negative patients (1.1) and the anti-adalimumab antibody-positive patients (4.0). There was no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumab. Additionally, there were no significant differences in TNF-α and C-reactive protein concentrations. Study limitations included its observational design, small sample size, use of ELISA to measure ADA, and high variability of results. The authors concluded that the assay has limited clinical utility.

Chiu (2015) published a prospective observational study investigating the role of ustekinumab ADA in psoriasis.[23] The study included 76 individuals with plaque psoriasis who were treated with ustekinumab for at least seven months (mean 13 months). Antibodies to ustekinumab were found in five (6.5%) of the patients, and the presence of these antibodies was associated with lower serum levels of the drug ($p<0.001$) and lower PASI 50 response ($p=0.004$). Among the 15 patients who switched to ustekinumab from adalimumab, no difference in ustekinumab ADA was found between patients who had previously developed adalimumab ADA and those who did not.

Menting (2015) reported on the association between serum ustekinumab trough levels, ADA, and treatment efficacy in a small prospective study that included 41 patients with RA.[24] The mean follow-up time was 32 weeks (range 4 to 52 weeks), and during this period ADA to ustekinumab were detected in three patients. No correlations were seen between ustekinumab trough levels and clinical response to the medication.

While many studies have evaluated clinical validity using single ADA measurements, at least one study assessed their persistence over time. Vande Casteele (2013) analyzed infliximab trough and ADA levels using an HMSA assay with banked serum obtained from 90 IBD patients treated between May 1999 and August 2011.[25] ADA levels had been previously assayed using an ELISA-based test. A total of 1,232 samples were evaluated (mean 14 per patient). Treatment decisions were made solely on clinical evaluation and C-reactive protein levels. ADA were detected in 53 of 90 (59%) of patients but subsequently were nondetectable in 15 of the 53 (28%). Persistent ATIs were associated with discontinuation of infliximab (RR 5.1, 95% CI 1.4 to 19.0), but the wide confidence interval reflects considerable uncertainty. Although transience of ADA in IBD has not been carefully scrutinized, if replicated, these results suggest interpreting a single ADA result cautiously.

Section Summary: Clinical Validity

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, IBD, and noninfectious uveitis.The presence of ADA has been consistently associated with an increased risk of an infusion-site reaction related to infliximab and injection-site reactions related to adalimumab. A concomitantly administered immunosuppressant agent may reduce the risk of developing ADA. Although ADA significantly reduced TNF-α response in a recent meta-analysis, considerable heterogeneity limits those findings. In addition, a recent observational study found no association between concomitant immunosuppressants and anti-TNF immunogenicity in patients with psoriasis; and a second cohort study found no association

between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumabto treat psoriasis.

CLINICAL UTILITY

Manceñido (2024) published a systematic review and meta-analysis to compare proactive therapeutic drug monitoring (TDM) to conventional management; i.e., reactive TDM, during maintenance treatment using anti-TNF-α factor for IBD.[26] The primary outcome measure was sustained clinical remission at 12 months. The analysis included nine studies, of which six were RCTs, and involved 528 patients. Proactive TDM was not found to be superior to conventional management in maintaining clinical remission at 12 months (RR 1.16; 95% CI 0.98-1.37, I^2=55%). The authors concluded that proactive TDM should not be recommended.

Several algorithms have been developed for management of patients with irritable bowel disease (IBD)[27-29] or rheumatoid arthritis (RA)[30] who have relapsed during TNF-inhibitor therapy. These algorithms are generally based on evidence that has indicated an association between ADA, reduced serum drug levels, and relapse. None has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response), using algorithmic rather than dose-escalation approaches.

Syversen (2021) reported results of a randomized, parallel-group, open-label trial of 411 adults with RA, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Chron's disease (CD), or psoriasis who received either proactive therapeutic drug monitoring of infliximab therapy based on serum infliximab level and ADA testing, or standard therapy without serum infliximab level or ADA testing (Norwegian drug monitoring [NOR-DRUM A]).[31] Serum trough infliximab levels and ADA levels were measured at each infusion in the therapeutic drug monitoring group. The infliximab dose or interval could be adjusted based on the therapeutic range during induction and during treatment. If ADA level was greater than 50 mcg/L at any point, therapy with infliximab was switched to a different agent. No significant difference between the therapeutic drug monitoring group and standard therapy group in clinical remission at week 30 was found (50.5% versus 53% of patients, respectively; p=0.78). During infliximab treatment, 36 (18%) patients in the therapeutic drug monitoring group and 34 (17%) in the standard therapy group developed ADAs ≥15 mcg/L. Antidrug antibodies ≥50 mcg/L (the threshold for discontinuation) occurred in 20 (10%) of patients in the therapeutic drug monitoring group and 30 (15%) in the standard therapy group. The remission rate in patients who developed ADAs was 56% in the therapeutic drug monitoring group and 35% in the standard therapy groups. The trial was limited by the small sample size of subjects who developed ADAs.Brun (2024) published a predefined exploratory analysis of data from the NOR-DRUM A and NOR-DRUM B studies. NOR-DRUM B, a 52-week trial, compared therapeutic drug monitoring to no monitoring (standard therapy) in 253 NOR-DRUM A participants and 205 newly enrolled participants on infliximab maintenance therapy.[32] The outcomes in accordance with therapeutic drug monitoring were remission at week 30, disease worsening during 52 weeks, infusion reactions, and infliximab discontinuation. Therapeutic monitoring was not associated with ADA positivity and remission at day 30 (16/39 therapeutic monitoring and remission vs. 9/34 standard therapy and remission p=0.86). Therapeutic monitoring was associated with a lower risk of disease worsening (p=0.0001). The rate of disease worsening was highest in patients with ADA/standard therapy and lowest in patients without ADA but with therapeutic monitoring. The rate of infusion reactions (35 reactions in 28 patients) was higher in patients with antidrug antibodies, (p<0.0001). Therapeutic drug monitoring was associated with a lower risk of infusion reactions compared to standard therapy, and independent of ADA status (p=0.0076).

Participants having therapeutic drug monitoring were more likely to discontinue infliximab and switch to another drug (p=0.037). The authors note that the treatment algorithm enabled switching therapy regardless of whether disease worsening had occurred, which is controversial. However, the authors point out that avoiding disease worsening is a worthwhile goal that may be achieved with therapeutic monitoring. The authors conclude that therapeutic monitoring may be of highest benefit to a subset of patients with ADA risk factors, such as predisposing HLA variants. Strengths of the study include its randomized design and high number of patients (n= 616). Limitations of the study includes its open-label design, its exploratory aim, and potential sparse data bias, especially regarding infusion reactions.

In a study of patients with IBD, Fernandex (2019) compared proactive monitoring of infliximab ADA and trough levels (n=56) to a retrospective control cohort (n=149).[33] The primary outcomes were hospital admission, surgery, treatment discontinuation, and rates of mucosal healing. A composite “unfavorable outcome” comprised of all of these was also analyzed. There was an association between treatment excalation rates and proactive monitoring (60.7% vs. 16.8% of controls, p<0.001). After two years of follow-up, surgery rates were lower in the proactive group (8.9% vs. 20.8%, p=0.030) and mucosal healing was more common (73.2% vs. 38.9%, p<0.0001). No significant differences were seen in hospitalization rate or treatment discontinuation.

A similar retrospective study by Papamichael (2019) evaluated proactive monitoring of serum adalimumab levels and ADA (n=53) with standard of care, defined as empirical dose excalation (n=279) or reactive monitoring (n=50).[34] Patients with early treatment failure (within eight weeks) were not included. After a median follow up of 3.1 years, fewer patients in the proactive monitoring group experienced treatment failure (hazard ratio [HR] 0.4, 95% CI 0.2 to 0.9). No significant difference was found for the probability of IBD-related surgery.

Kamperidis (2019) published retrospective observational study on the impact of therapeutic drug level monitoring (TDM) on outcomes of 291 patients with Crohn's disease treated with Infliximab (IFX).[35] Primary outcomes were clinicians' response to each TDM result and the rate of IFX discontinuation due to secondary loss of response or serious adverse event. Secondary outcomes included the intestinal surgery rate after IFX initiation and remission six months after TDM. Two hundred thirty-eight (81.8%) patients were tested for TDM at least once during their follow-up with 672 TDM results. 95/238 patients (39.9%) had undetectable levels and 76 (31.9%) had positive antibodies to infliximab (ATI) at least once. IFX was discontinued in 109 patients (37.5%). TDMs results were not followed by altered patient management in 526/672 (78.3%) of the observations. Treatment was discontinued in 40 (75.5%) patients never tested for TDM compared with 69 (29.0%) of those tested (p<0.01). Fewer TDM tested patients (29; 12.2%) required intestinal surgery post IFX initiation compared with those not TDM tested (15; 28.3%). In this retrospective study, data collected on clinical outcomes relied on record keeping and physician response was taken as the measure of clinical remission. These methods may be subject to interpretation bias.

Dong (2019) reported an observational study of 60 patients with ankylosing spondylitis (AS) taking a biosimilar of etanercept.[36] Serum drug levels and anti-drug antibody levels, as well as clinical measures of disease activity were assessed at baseline and after four, 12, and 24 weeks of treatment. The authors found that anti-drug antibodies had no effect on the Assessment of Spondylosis Arthritis International Society (ASAS) remission rates but reported that patients with ADA had lower drug levels and higher TNF-α levels.

Steenholdt (2014) reported results of a noninferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy.[37] Patients were randomized to infliximab dose intensification (5 mg/kg every four weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level (<0.5 µg/mL[38]) had infliximab dose increased if ADA were undetectable or were switched to adalimumab if ADA were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ADA levels if ADA were detectable or diagnostic reassessment if ADA were undetectable. Serum infliximab and ADA levels were measured in all patients using RIA in single-blind fashion (patients unaware but investigators aware of test results). Randomized groups were similar at baseline; overall, 55 (80%) of 69 patients had nonfistulizing disease. Most patients (70%) had therapeutic serum infliximab levels without detectable ATI; revised diagnoses in 6 (24%) of 25 such patients in the algorithm arm[39] included bile acid malabsorption, strictures, and IBS. In both intention-to-treat (ITT) and per-protocol analyses, similar proportions of patients in each randomized group achieved clinical response at week 12, defined as a minimum 70-point reduction from baseline CDAI for patients with nonfistulizing disease and a minimum 50% reduction in active fistulas for patients with fistulizing disease (ITT 58% in the algorithm group vs 53% in the control group, p=0.810; per-protocol, 47% in the algorithm group vs 53% in the control group, p=0.781). Only the ITT analysis fell within the prespecified noninferiority margin of -25% for the difference between groups.

Conclusions on the noninferiority of an algorithmic approach compared with dose intensification from this trial are limited. The noninferiority margin was arguably large and was exceeded in the conservative per-protocol analysis. Dropouts were frequent and differential between groups; 17 (51%) of 33 patients in the algorithm group and 28 (78%) of 36 patients in the control group completed the 12-week trial. A large proportion of patients (24%) in the algorithmic arm were potentially misdiagnosed (i.e., CD flare was subsequently determined not to be the cause of relapse); the comparable proportion in the control arm was not reported. In most patients (80% who had nonfistulizing disease), only a subjective measure of treatment response was used (minimum 70-point reduction from baseline CDAI).

Roblin (2014) conducted a single-center, prospective observational study of 82 patients with IBD (n=45 CD, n=27 UC) with clinical relapse (CDAI >220 or Mayo Clinic >5) during treatment with adalimumab 40 mg every two weeks.[40] For all patients, trough adalimumab levels and ADA were measured in a blinded fashion using ELISA, and adalimumab dose was optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI <150 or Mayo score <2) within four months underwent repeat trough adalimumab and anti-adalimumab antibody testing and were switched to infliximab. Clinical and endoscopic responses after adalimumab optimization and after infliximab therapy for six months were compared across three groups: (1) those with a therapeutic adalimumab level (>4.9 µg/mL[41]), (2) those with a subtherapeutic adalimumab level and undetectable ATA; and (3) those with a subtherapeutic adalimumab level and detectable ADA. After adalimumab optimization, more group 2 patients achieved clinical remission (16 [67%] of 24 patients) than group 1 (12 [29%] of 41 patients; p<0.01 vs group 2) and group 3 (2 [12%] of 17 patients, p<0.01 vs group 2) patients. Duration of remission was longest in group 2 (mean 15 months) compared with group 1 (mean five months) and group 3 (mean, four months, p<0.01 for both comparisons vs group 2). At one year, 13 (52%) of 24 patients in group 2 maintained clinical remission compared with no patients in groups 1 or 3 (p<0.01 for both comparisons vs group 2). Results were similar when remission was defined using calprotectin levels (<250 µg/g stool) or endoscopic Mayo score (<2).

Fifty-two patients (n=30 CD, n=22 UC) who did not achieve clinical remission after adalimumab optimization were switched to infliximab. More patients in group 3 achieved clinical remission (12 [80%] of 15 patients) than in group 1 (2 [7%] of 29 patients) or group 2 (2 [25%] of 8 patients, p<0.01 for both comparisons vs group 3). Duration of response after switching to infliximab was longest in group 3 (mean, 14 months) compared with group 1 (mean, three months) and group 2 (mean, five months, p<0.01 for both comparison vs group 3). At one year, 8 (55%) of 15 patients in group 3 maintained clinical remission compared with no patients in groups 1 or 2 (p<0.01 for both comparisons vs group 3). Results were similar using objective measures of clinical remission (calprotectin level, endoscopic Mayo score).

These results suggested that patients with IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ADA are undetectable or from a change to another TNF inhibitor if ADA are detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. Strengths of the study include its use of subjective and objective measures of remission and blinded serum drug level and ADA monitoring. However, results were influenced by the small sample size, use of ELISA for antibody testing, and lack of ADA levels for decision making. Studies comparing management using the algorithm proposed with usual care are needed.

Afif (2010) evaluated the clinical utility of measuring ADA (referred to as human antichimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing patient medical records.[42] Record review from 2003 to 2008 identified 155 patients who had had ADA, had data on infliximab concentrations, and met the study inclusion criteria. A single physician ordered 72% of the initial tests. The authors retrospectively determined clinical response to infliximab. Forty-seven percent of patients were on concurrent immunosuppressive medication. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune or delayed hypersensitivity reaction (10%). ADA were identified in 35 (23%) patients and therapeutic infliximab concentrations in 51 (33%) patients. Of 177 tests assessed, the results impacted treatment decisions in 73%. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation occurred in 17%. The authors concluded that measurement of ADA and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ADA was ineffective whereas in patients with subtherapeutic infliximab concentrations this strategy was a good alternative to changing to another anti-TNF agent. Study limitations included the retrospective design and using ELISA testing for ADA. Because there was no control group, one cannot determine what changes in management would have been made absent ADA measurement. Because clinicians are likely to change management for patients who do not achieve or maintain a clinical response, it is important to understand how these management decisions differ when ADA are measured.

Section Summary: Clinical Utility

Significant evidence for the clinical utility of ADA testing is currently lacking. Uncontrolled retrospective studies in IBD have demonstrated the impact of ADA testing on treatment decisions but cannot demonstrate improved patient outcomes compared with a no-testing strategy. Additional limitations of these studies included a lack of clinical follow-up after treatment decisions were made and a lack of clinical assessments to guide treatment decisions. Additionally, the determination of a clinically relevant threshold for the ADA level is

complicated by the use of various assay methods. A small, nonrandomized prospective study suggested that ADA levels may be informative in relapsed patients with IBD who have low serum adalimumab levels, but this finding requires confirmation in larger, randomized trials. Methodologic flaws, including relapse misclassification, limit conclusions from the RCT in patients with relapsed IBD. Direct or indirect evidence for clinical utility in patients with RA or SpA was not identified.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2019, the American College of Gastroenterology published a guideline on ulcerative colitis (UC).[43] The guideline stated: "In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence)."

In 2018, the American College of Gastroenterology published a guideline on Crohn's disease (CD).[44] Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: "If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2017, the American Gastroenterological Association published an evidence-based clinical practice guideline on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD).[45] The guideline was developed according to the GRADE framework to evaluate certainty of evidence, and a Technical Review was published to accompany the recommendations.[46] Regarding measurement of anti-drug antibodies, the Association made the following statement:

> "In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes." *Conditional recommendation, very low quality of evidence.*

According to the GRADE method, *very low quality* is defined as: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The guideline also stated:

> "In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring." *No recommendation, knowledge gap.*

AMERICAN COLLEGE OF RHEUMATOLOGY

The American College of Rheumatology published a clinical practice guideline on axial spondyloarthritis in 2019.[47] The guideline includes recommendations for treatment with TNFα inhibitors for people with active and stable ankylosing spondylitis. The guideline does not address the use of serum antibody measurement.

The American College of Rheumatology published a clinical practice guideline on the pharmacologic management of rheumatoid arthritis in 2021.[48] The guideline includes recommendations for treatment with TNFα inhibitors. The guideline does not address the use of serum antibody measurement.

SUMMARY

Antibodies to drugs for chronic inflammatory diseases including, but not limited to infliximab, adalimumab, ustekinumab, certolizumab, etanercept, golimumab, and vedolizumab, are present in a substantial number of patients treated with these medications. A correlation between the level of these antibodies and clinical response has been identified in patients with some chronic inflammatory conditions.

There is some evidence that, in patients with inflammatory bowel disease who have lost response to infliximab or adalimumab, measurement of serum drug antibodies can impact patient care decisions. Evidence-based clinical practice guidelines recommend reactive monitoring of serum drug levels and anti-drug antibodies to guide treatment changes in patients with active inflammatory bowel disease who are being treated with an anti-TNF agent. Therefore, measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, may be considered medically necessary for patients with inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis) when there is documentation of a loss of response to these medications.

There is not enough evidence to show that measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, improves net health outcomes when there has not been a loss of response to the medication. No evidence-based clinical practice guidelines recommend the measurement of serum drug antibodies when there has not been a loss of response to medication. Therefore, measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, is considered not medically necessary when there has not been a loss of response to the medication.

There is not enough research to determine whether measurement of serum anti-drug antibodies can be used in patient management to improve net health outcomes for all conditions. The optimal timing of when to measure antibody levels and measurement cutoff levels has not been established. No evidence-based clinical practice guidelines recommend testing for serum drug antibodies in the treatment of chronic inflammatory conditions other than anti-TNF agents in the treatment of inflammatory bowel disease. Therefore, measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, other than infliximab or adalimumab in the treatment of inflammatory bowel disease, is considered investigational.

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CODES

Codes	Number	Description
CPT	80145	Adalimumab
	80230	Infliximab
	80280	Vedolizumab
	80299	Quantitation of therapeutic drug, not elsewhere specified
	84999	Unlisted chemistry procedure
HCPCS	None	

Date of Origin: *January 2013*

Regence

Medical Policy Manual Medicine, Policy No. 14

Hyperbaric Oxygen Therapy

Effective: January 1, 2025

Next Review: September 2025
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

Hyperbaric oxygen therapy (HBOT) is a technique of delivering higher pressures of oxygen to the tissues. Two methods of administration are available, systemic and topical.

MEDICAL POLICY CRITERIA

I. Systemic hyperbaric oxygen therapy may be considered **medically necessary** when both of the following criteria (A. and B.) are met:

   A. Systemic hyperbaric oxygen therapy services must comply with the following guidelines which are consistent with the Undersea and Hyperbaric Medical Society criteria:

      1. Patient must breathe 100% oxygen intermittently or continuously while the pressure of the treatment chamber is increased above one atmosphere absolute; and
      2. Systemic hyperbaric oxygen pressurization should be at least 1.4 atmospheres absolute (atm abs) (20.5 psi); and
      3. Treatment is provided in a hospital or clinic setting; and

   B. Treatment meets one or more of the following conditions:

1. Acute carbon monoxide poisoning *(Recommended treatment review threshold*: 5 treatments); or
2. Acute traumatic ischemia (*Recommended treatment review threshold:* Reperfusion injury: one - two treatments; Crush injury: 12 treatments (three times per day for one day, then twice a day for two days, then daily for two days); Compartment syndrome, no fasciotomy: three treatments a day for 36 - 48 hours; Compartment syndrome, after fasciotomy: twice a day up to 14 days.
3. Chronic refractory osteomyelitis (*Recommended treatment review threshold*: 40 treatments; continuation based on clinical response); or
4. Cyanide poisoning, acute (*Recommended treatment review threshold*: five treatments); or
5. Decompression sickness (*Recommended treatment review threshold*: 10 treatments); or
6. Gas or air embolism, acute (*Recommended treatment review threshold*: 10 treatments); or
7. Gas gangrene (i.e., clostridial myositis and myonecrosis; *Recommended treatment review threshold*: 10 treatments); or
8. Non-healing diabetic wounds of the lower extremities as an adjunct to ongoing conventional wound care in patients who meet **all** of the following Criteria (a. – c.) (*Recommended treatment review threshold*: 30 treatments one or two treatments daily):
    a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes; and
    b. Patient has a wound classified as Wagner grade 3 or higher (see Policy Guidelines); and
    c. Patient has no measurable signs of healing after 30 days of an adequate course of standard wound therapy including **all** of the following:
        i. Assessment of vascular status and correction of any vascular problems in the affected limb if possible; and
        ii. Optimal glycemic control; and
        iii. Optimal nutritional status; and
        iv. Topical wound treatment (e.g., saline, hydrogels, hydrocolloids, alginates) with maintenance of a clean, moist bed of granulation tissue; and
        v. Debridement to remove devitalized tissue, any technique; and
        vi. Pressure reduction or offloading; and
        vii. Treatment to resolve infection (e.g., antibiotics); or
9. Pre- and post-treatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw (*Recommended treatment review threshold*: 40 sessions; 10 - 20 before surgery); or

10. Profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed (*Recommended treatment review threshold*: HBOT should be continued with taper of both time and frequency until red blood cells have been satisfactorily replaced by patient regeneration or the patient can undergo transfusion.); or
11. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and osteoradionecrosis *(Recommended treatment review threshold*: 60 treatments); or
12. Idiopathic Sudden Sensorineural Hearing Loss of greater than or equal to 41 decibels and an onset of treatment within 14 days (*Recommended treatment review threshold:* 20 treatments.); or
13. Necrotizing soft tissue infections (*Recommended treatment review threshold*: 30 sessions: twice daily sessions during the acute phase with continuation until extension of necrosis has been halted, typically 10 treatments: followed by once daily sessions; continuation based on clinical response); or
14. Actinomycosis (Recommended treatment review threshold: 20 treatments) or
15. Central retinal artery occlusion (Recommended treatment review threshold; 10 treatments with one to two treatments per day as soon as possible after symptom onset); or
16. Compromised skin grafts and flaps where hypoxia or decreased perfusion has compromised viability acutely (*Recommended treatment review threshold: 40 treatments;* 20 treatments when preparing recipient site and 20 treatments following flap or graft placement with evaluation for continuation based on initial response to hyperbaric oxygen therapy).

II. Systemic hyperbaric oxygen for non-healing diabetic wounds of the lower extremities as an adjunct to conventional wound care is considered **not medically necessary** when Criterion I.B.8 is not met.

III. Continuation of hyperbaric oxygen therapy beyond initial *recommended treatment review thresholds* may be **medically necessary** to reach treatment stabilization, a clinical plateau or continued wound healing. Documentation of initial HBOT treatment response is required for continuation. Note: HBOT treatment continuation will be approved for up to the initial recommended number of sessions at each subsequent review.

IV. Initial or continuing systemic hyperbaric oxygen therapy is considered **investigational** for all other indications including but not limited to other ophthalmologic conditions, non-diabetic wounds, and acute thermal burns.

V. Topical hyperbaric and topical normobaric oxygen therapies are considered **investigational**.

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

POLICY GUIDELINES

WAGNER CLASSIFICATION

- Grade 0: No open lesion
- Grade 1: Superficial ulcer without penetration to deeper layers
- Grade 2: Ulcer penetrates to tendon, bone, or joint
- Grade 3: Lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths
- Grade 4: Wet or dry gangrene in the toes or forefoot
- Grade 5: Gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at the below the knee level) is indicated

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 including type of HBOT planned
- Treatment plan including the following:
  - Percent of oxygen that the patient will breathe while receiving therapy
  - Pressurization (atm abs, psi)
  - Treatment setting (clinic or hospital)
- Condition being treated including how many treatments being requested
  - If a diabetic wound is being treated, then the request must include the following:
    - Type of diabetes
    - Location of wound
    - Wagner Classification
    - Measurable signs of healing following standard wound therapy including therapy length of time with documentation of the following:
      - Vascular assessment and correction, if possible, of vascular problems to affected area
      - Glycemic data for patient (e.g., A1C)
      - Nutritional status
      - Topical wound treatments utilized including wound bed description
      - Debridement
      - Pressure reduction or offloading
      - Any infection treatment utilized
  - If dental surgery, include description and diagnosis
  - If anemia, include blood loss and ability to transfuse patient
  - If necrosis, include type
  - If idiopathic sudden sensorineural hearing loss, include decibels of loss and onset of treatment
  - For continuation, include documentation of initial treatment response and number of requested treatments

CROSS REFERENCES

None

BACKGROUND

SYSTEMIC HYPERBARIC OXYGEN THERAPY (HBOT)

In systemic or large chamber hyperbaric oxygen therapy, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 atmosphere (atm, the pressure of oxygen at sea level). Thus, this technique relies on systemic circulation to deliver highly oxygenated blood to the target site, typically a wound. In addition, systemic HBOT can be used to treat systemic illness, such as air or gas embolism, carbon monoxide poisoning, clostridial gas gangrene, etc. Treatment may be carried out either in a monoplace (class B) chamber pressurized with pure oxygen or in a larger, multiplace (class A) chamber pressurized with compressed air, in which case the patient receives pure oxygen by mask, head tent, or endotracheal tube.

Mild hyperbaric oxygen therapy

Oxygen therapy delivered via soft-sided chambers is referred to as mild hyperbaric oxygen therapy. While this implies that these chambers provide HBOT, the therapy is not considered hyperbaric as they provide pressurization of only about 4.5 psi, compared with true HBOT which is defined as pressurization of 20.5 psi or higher.

TOPICAL OXYGEN THERAPY

Topical hyperbaric oxygen therapy

Topical hyperbaric oxygen therapy is a technique of delivering 100% oxygen directly to an open, moist wound at a pressure slightly higher than atmospheric pressure. It is hypothesized that the high concentrations of oxygen diffuse directly into the wound to increase the local cellular oxygen tension, which in turn promotes wound healing. This therapy has been investigated as a treatment of skin ulcerations resulting from diabetes, venous stasis, postsurgical infection, gangrenous lesion, decubitus ulcers, amputations, skin graft, burns, or frostbite.

Topical hyperbaric oxygen devices consist of an appliance to enclose the wound area (frequently an extremity) and a source of oxygen; conventional oxygen tanks may be used. Topical hyperbaric oxygen therapy may be performed in the office, clinic, or may be self-administered by well-trained patients in the home. Typically, the therapy is offered for 90 minutes per day for 4 consecutive days. After a 3-day break, the cycle may be repeated. The regimen may last for 8 to 10 weeks.

Topical normobaric oxygen therapy

Devices that deliver topical oxygen to a wound at normal atmospheric pressure (normobaric) are not considered hyperbaric oxygen therapy. These devices may also be called low dose tissue oxygenation systems. An example of a normobaric oxygen delivery system is the TransCu O2™, a small handheld device with an attached cannula. According to the manufacturer, the TransCu O2 is “intended for use with wound dressings to treat the following: skin ulcerations due to diabetes, venous stasis, post-surgical infections and gangrenous lesions; pressure ulcers; infected residual limbs; skin grafts; burns; and frostbite.” The device concentrates room air to 99.9% oxygen which is delivered via the cannula which is placed under the wound dressing.

REGULATORY STATUS

In 2013, U.S. Food and Drug Administration (FDA) published a statement warning that non-FDA approved uses of HBOT may endanger the health of patients.[1] "Patients may incorrectly believe that these devices have been proven safe and effective for uses not cleared by FDA, which may cause them to delay or forgo proven medical therapies. In doing so, they may experience a lack of improvement and/or worsening of their existing condition(s)."

The following are examples of oxygen therapy devices:

In February 1999, the Numobag™ Kit (Numotech, Inc) for application of topical hyperbaric therapy was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices. Another example is the AOTI Hyper-Box™ (AOTI Ltd., Galway, Ireland) which was cleared by FDA in 2008.

In August 2009, the TransCu O2 (Electrochemical Oxygen Concepts, Inc.) was cleared for marketing by the FDA through the 510(k) process as substantially equivalent to existing devices.

There are numerous FDA-approved hyperbaric oxygen chambers. In May 2005, the ATA Monoplace Hyperbaric System (ATA Hyperbaric Chamber Manufacturing, Inc.) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing hyperbaric devices.

EVIDENCE SUMMARY

Current evidence is sufficient to determine the effectiveness of hyperbaric oxygen therapy (HBOT) for the indications that meet the above medical necessity criteria. Assessing the effectiveness and safety of HBOT for the investigational indications requires randomized controlled trials comparing HBOT with the conventional treatments for each indication. Therefore, the following literature review on HBOT focuses on randomized controlled trials (RCTs) and systematic reviews of RCTs for the investigational indications.

Assessment of efficacy for therapeutic interventions involves a determination of whether the intervention improves health outcomes. The optimal study design for a therapeutic intervention is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. When the primary outcomes are subjective (e.g., pain, depression), sham-controlled RCTs are needed to assess the effect of the intervention beyond that of a placebo effect.

Due to the expansive conditions included in this policy, the evidence included below support only the investigational and not medically necessary conditions.

TOPICAL HYPERBARIC OXYGEN

Systematic Reviews

A 2015 Cochrane review of interventions for treating gas gangrene evaluated the safety and efficacy topical HBOT and Chinese herbs as treatments options.[2] Re-analysis if cure rate did not show beneficial effects from either treatment. In 1984, Heng published a controlled study of

topical hyperbaric oxygen therapy in 6 patients with 27 ulcers compared to no treatment in 5 patients with 10 ulcers.[3] Although a greater improvement was noted in the treated group, the results were calculated according to the number of ulcers rather than based on individual patients. Leslie reported on a trial that randomly assigned 18 patients with diabetic foot ulcers to receive either topical hyperbaric oxygen therapy plus standard wound care or standard wound care alone.[4] Changes in ulcer size and depth did not differ between the 2 groups. Other studies consist of anecdotal reports or uncontrolled case series.[5]

Randomized Controlled Trials

Pasek (2023) published a pilot randomized controlled study evaluating the application of topical hyperbaric oxygen therapy (THOT) and Atrauman Ag medical dressings (MD).[6] Patients (n = 30) with chronic arterial ulcers were randomly assigned to MD and THOT (n = 16) or MD alone (n = 14).The treatment was carried out for 4 weeks. The progress of healing ulcers was assessed by using the planimetric method, while the intensity of pain ailments was assessed by the visual analog scale (VAS). In both study groups, a statistically significant reduction in the mean surface area of the treated ulcers from 8.53 ± 1.71 cm2 to 5.55 ± 1.11 cm2 in the THOT group ($p < 0.001$) and 8.43 ± 1.51 cm2 to 6.28 ± 1.13 cm2 in the MD ($p < 0.001$). Intensity of pain reduced from 7.93 ± 0.68 points to 5.00 ± 0.63 points in the THOT group ($p < 0.001$) and 8.00 ± 0.67 points to 5.64 ± 0.49 points in the MD group ($p < 0.001$). The percentage change in ulcer area from baseline in the THOT group (34.6 ± 8.47%) was greater than in the MD group (25.23 ± 6.01%) ($p = 0.003$). The authors conclude that the addition of local hyperbaric oxygen therapy treatments as a supplement to the therapy with the use of specialized medical dressings improves the effectiveness the arterial ulcers treatment of the lower limbs in terms of reducing the ulceration area and pain.

Section Summary

Due to their different methods of delivery, topical and systemic hyperbaric oxygen are distinct technologies such that they must be examined separately.[7] There is minimal published literature regarding topical hyperbaric oxygen therapy.

SYSTEMIC HYPERBARIC OXYGEN THERAPY (HBOT)

In-home hyperbaric oxygen

A position statement from the National Board of Diving & Hyperbaric Medical Technology on in-home HBOT has been published on the Web site for The Undersea and Hyperbaric Medicine Society (UHMS).[8] The statement indicates that in-home HBOT “is inherently unsafe and cannot be condoned.” This position is based on concern for the safety and well-being of patients as well as those people in proximity to the HBOT delivery system because in-home provision of HBOT is likely to:

- Bypass otherwise mandatory federal, state, and local codes related to design, construction, installation, and operation of these devices; and
- Occur without adequate physician oversight and the operational support of appropriately qualified HBOT providers.

Acute Coronary Syndromes

Systematic Reviews

A 2012 Cochrane review by Bennett identified 6 trials with a total of 665 patients evaluating HBO for acute coronary syndrome.[9] All of the studies included patients with acute myocardial infarction (MI); one study also included individuals presenting with unstable angina. Additionally, all trials used HBOT as an adjunct to standard care. Control interventions varied; only 1 trial described using a sham therapy to blind participants to treatment group allocation. In a pooled analysis of data from 5 trials, there was a significantly lower rate of death in patients who received HBOT compared to a control intervention (RR: 0.58: 0.36 to 0.92). Due to variability of outcome reporting in the studies, few other pooled analyses could be conducted. A pooled analysis of data from 3 trials on improvements in left ventricular function did not find a statistically significant benefit of HBOT (RR: 0.09; 95% CI: 0.01 to 1.4). The authors noted that, although there is some evidence from small trials that HBOT is associated with a lower risk of death, larger trials with high methodologic quality are needed in order to determine which patients, if any, can be expected to derive benefit from HBOT. Therefore, HBOT is considered investigational in the treatment of acute coronary syndromes.

Autism Spectrum Disorders (ASD)

Systematic Reviews

A 2016 systematic review on hyperbaric oxygen therapy for treatment of children with autism identified one RCT[10] with a total of 60 children. The study quality was rated as low using GRADE criteria with small sample size and wide confidence intervals. The results indicated no improvement in social interaction and communication, behavioral problems, communication and linguistic abilities, or cognitive function. The authors reported minor-grade ear barotrauma as adverse events.

A 2012 systematic review[11] of RCTs on hyperbaric oxygen therapy for treatment of children with autism identified two RCTs[12, 13]with a total of 89 participants. In both RCTs the active hyperbaric treatment was 24% oxygen delivered at an atmospheric pressure of 1.3 atmospheres (atm). Although this regimen was referred to as HBOT in the article, it differed from standard HBOT which uses 100% oxygen and a pressure of at least 1.4 atm. A detailed analysis of these RCTs is provided below. Briefly, one of the two RCTs found better outcomes after hyperbaric oxygen compared with placebo treatment, and the other did not find significant differences in outcomes. The author concluded that additional sham-controlled trials with rigorous methodology are needed in order to draw conclusions about the efficacy of HBOT for treating autism.

Randomized Controlled Trials (RCTs)

The following is a summary of the 2 RCTs reported in the above systematic review:

One of the above two RCTs was by Rossignol.[12] This study was a double-blind RCT that included 62 children, ages 2-7, meeting DSM-IV criteria for autistic disorder. The active treatment was hyperbaric treatment at 1.3 atmospheres (atm) and 24% oxygen in a hyperbaric chamber. (This regimen differs from standard HBOT which uses 100% oxygen and a pressure of at least 1.4 atm). The other group received a sham treatment consisting of 1.03 atm and ambient air (21% oxygen). Both groups received 40 sessions of active or sham treatment lasting 60 minutes each over a period of 4 weeks. The equipment, procedures, etc. in the two groups were as similar as possible to maintain blinding. The investigators, participants, parents, and clinic staff were blinded to treatment group. Only the hyperbaric technician, who had no role in outcome assessment, was aware of group assignment. After completion of the

4-week study, families with children in the control group were offered the active intervention. When asked at the end of the study, there was no significant difference in the ability of parents to correctly guess the group assignment of their child.

The outcomes were change compared to baseline after 4 weeks on the following scales: Aberrant Behavior Checklist (ABC) total score and 5 subscales; Autism Treatment Evaluation Checklist (ATEC) total score and 4 subscales; and Clinical Global Impression-Improvement (CGI) overall functioning score and 18 subscales. P values of <0.05 were considered statistically significant; there was no adjustment for multiple comparisons. The analysis included all children who completed at least one complete session. Of the 33 children assigned to active treatment, 30 were included in the analysis and 29 completed all 40 treatments. Of the 29 children assigned to the control treatment, 26 completed all 40 sessions and were included in the analysis.

There was no significant between-group improvement on the ABC total score, any of the ABC subscales, or on the ATEC total score. Compared to the control group, the treatment group had a significant improvement in 1 of 4 subscales of the ATEC, the sensory/cognitive awareness subscale. The change from baseline on this subscale was a mean of 16.5 in the treatment group and a mean of 5.4 in the control group, a difference of 11.1 (p=0.037). (Note: due to an administrative error, baseline ATEC was not collected at one site, and thus data were not available for 23 children in the treatment group and 21 children in the control group). On the physician-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 (very much improved) or 2 (much improved) compared to 2/26 (8%) in the control group (p=0.047). On the parental-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 or 2 compared to 4/26 (15%) in the control group (p=0.22, not statistically significant). (The exact numbers receiving scores of 1 vs. 2 were not reported). Change in mean CGI scores were also reported, but this may be a less appropriate way to analyze these data. Among the parental-rated CGI subscales, significantly more children were rated as improved in the treatment group compared to control on 2 out of 18 subscales, receptive language (p=0.017) and eye contact (p=0.032).

A key limitation of this study was that the authors reported only outcomes at 4 weeks, directly after completion of the intervention. It is not known whether there are any long-term effects. Additional follow-up data cannot be obtained because members of the control group crossed over to the intervention after 4 weeks. Other limitations included lack of adjustment for multiple comparisons and unclear clinical significance of the statistically significant outcomes. The Undersea and Hyperbaric Medical Society (UHMS) issued a position paper after publication of the Rossignol et al. study stating that they still did not recommend routine treatment of autism with HBOT.[14]

The other RCT included in the systematic review was a double-blind RCT that began with 46 children with autism, ages 2-14 years, who were matched in pairs according to age and the number of hours of Applied Behavior Analysis (ABA) treatment they were receiving at the start of the study. Randomized[13] treatment allocation of the matched pairs was by coin toss. Both groups received 80 1-hour sessions of active treatment (24% oxygen at 1.3 atm) or sham treatment (room air at ambient pressure) for up to 15 weeks. Participants were allowed to undergo ABA, take any supplements, pharmacological interventions, and dietary modifications. Twelve patients withdrew from the trial, leaving 18 patients in the treatment group and 16 in the control group.

The primary outcome of change in symptoms was based on direct observation and the scales

noted in the Rossignol et al. study above in addition to the Behavior Rating Inventory of Executive Functioning (BRIEF), Parent Stress Index (PSI), Peabody Picture Vocabulary Test (PPVT-III), Repetitive Behavior Scale (RBS), and the Vineland Adaptive Behavior Scales (VABS-II). Direct observation and intention to treat analysis of test scores found no significant difference on any outcome measures between the treatment and sham groups. No participants experienced adverse effects attributable to barotrauma (e.g., pressure injury to tympanic membranes or sinuses).

A limitation of this study was the small sample size which was determined to be adequate to detect only large effects, which were not present in this study. In addition, since some patients in both groups received intensive ABA interventions during the study period, any potential effects of HBOT could not be isolated. The authors concluded that the active treatment had no significant beneficial effect on ASD and was not recommended for the treatment of ASD symptoms.

One additional RCT not included in the systematic review above was identified:

A 2012 RCT published after the systematic review randomly assigned 60 children with autism to receive 20 one-hour sessions with HBOT or sham air treatment (n=30 per group).[15] The primary outcome measures were change in the ATEC and CGI, evaluated separately by clinicians and parents. There were no statistically significant differences between groups on any of the primary outcomes. For example, post-treatment clinician-assessed mean scores on the ATEC were 52.4 in the HBOT group and 52.9 in the sham air group.

Section Summary

There is insufficient evidence from well-designed RCTs that HBOT improves health outcomes for patients with autism spectrum disorder; therefore, HBOT therapy for this indication is considered investigational.

Bell's Palsy

Systematic Review

In 2012, Holland published a Cochrane review evaluating HBOT in adults with Bell's palsy.[16] The authors identified one RCT with 79 participants, and this study did not meet the Cochrane review methodologic standards because the outcome assessor was not blinded to treatment allocation. Therefore, the evidence is insufficient to permit conclusions and HBOT is considered investigational for the treatment of Bell's palsy.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)

Randomized Controlled Trials (RCTs)

An unblinded RCT was published by Freiberger in 2012 on use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw.[17] Forty-nine patients were randomly assigned to HBOT in addition to standard care (n=22) or standard care alone (n=27). Five patients in the standard care group received HBOT and 1 patient assigned to the HBOT group declined HBOT. The investigators decided to do a *per* protocol

(PP) analysis (actual treatment received) because of the relatively large degree of crossover. Participants were evaluated at 3, 6 12 and 18 months. Data were available on 46 patients, 25 received HBOT in addition to standard care and 21 received standard care alone. The primary outcome measure was change in oral lesion size or number. When change from baseline to last available follow-up was examined, 17 of 25 (68%) of HBO-treated patients had improvement in oral lesion size or number compared to 8 of 21 (38%) in the standard care group, p=0.043. When change from baseline to 6, 12 or 18 months was examined, there was not a statistically significant difference between groups in the proportion of patients with improvement. In addition, the proportion of patients who healed completely did not differ significantly between groups at any time point. This single trial does not report consistent findings of benefit across outcome measures. It also has a number of methodologic limitations, e.g., unblinded, cross-over, and analysis performed on a *per-protocol* basis rather than intention to treat. A disadvantage of the *per-protocol* analysis is that randomization is not preserved, and the two groups may differ on characteristics that affect outcomes. As a result, this trial is insufficient to conclude that HBOT improves health outcomes for patients with bisphosphonate-related osteonecrosis of the jaw.

Section Summary

Current evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of bisphosphonate-related osteonecrosis of the jaw. Therefore, HBOT is considered investigational for this indication.

Cancer Treatment

Randomized Controlled Trials (RCTs)

In an RCT of 32 patients, Heys found no increase in 5-year survival in patients treated with HBOT prior to chemotherapy for locally advanced breast carcinoma to increase tumor vascularity.[18] This approach is being studied since studies in animal models have suggested that HBOT increases tumor vascularity and thus may make chemotherapy more effective. In a Cochrane review, Bennett concluded that HBOT given with radiotherapy may be useful in tumor control; however, the authors expressed caution since significant adverse effects were common with HBOT and indicated further study would be useful.[19]

Section Summary

Current evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of cancer of any type and location. Therefore, HBOT is considered investigational for this indication.

Cerebral Palsy

Randomized Controlled Trials (RCTs)

In 2012, Lacey published a double-blind RCT that included 49 children age 3-8 years with spastic cerebral palsy.[20] Participants were randomized to receive 40 treatments with either HBOT (n=25) or hyperbaric air to simulate 21% oxygen at room air (n=24). The primary efficacy outcome was change in the Gross Motor Function Measure (GMFM-88) global score after the 8-week treatment period. The study was stopped early due to futility, when an interim analysis indicated that there was less than a 2% likelihood that a statistically significant

difference between groups would be found. At the time of the interim analysis, there was no significant between-group difference in the post-treatment GMFM-88 global score (p=0.54).

In the largest RCT to date, Collet et al. randomly assigned 111 children with cerebral palsy to 40 treatments over a 2-month period of either HBOT (n=57) or slightly pressurized room air (n=54).[21] The authors found HBOT and slightly pressurized air produced similar improvements in both groups for outcomes such as gross motor function and activities of daily living.

Section Summary

HBOT is considered investigational as a treatment for cerebral palsy because it has not been shown to provide additional health benefits in this patient population.

Compromised Skin Grafts and Flaps

Systematic Reviews

In a 2010 Cochrane review, Estes found a lack of high quality evidence regarding HBOT in the treatment of skin grafts and flaps.[22, 23] The authors found one randomized controlled trial (RCT) on skin grafts for burn wounds (n=48) which reported significantly higher graft survival with HBOT, and one RCT on flap grafting (n=135) which reported no significant differences in graft survival with HBOT compared with dexamethasone or heparin. However, these data are unreliable due to various methodologic limitations such as biased analysis, omitted data, and small size.

In 2006, Friedman published a systematic review of literature on use of HBOT for treating skin flaps and grafts.[24] No RCTs were found. The authors identified 2 retrospective case series on use of HBOT for clinically compromised skin grafts and flaps. The series had sample sizes of 65 and 26, respectively; both were published in the 1980s based on treatment provided in the 1970s and 1980s.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the above systematic reviews.

Section Summary

Although the study of HBOT for compromised skin grafts and flaps goes back several decades, the clinical trial data is limited to noncomparative case series and a single randomized controlled trial. This evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of compromised skin grafts and flaps. Therefore, HBOT is considered investigational for these indications.

Carbon Monoxide Poisoning

A 2011 Cochrane review of seven RCTs concluded that the available evidence is insufficient to determine whether adverse neurologic outcomes in patients with carbon monoxide poisoning are reduced with HBOT.[25] In 2008, the American College of Emergency Physicians (ACEP) published a clinical policy on critical issues in carbon monoxide poisoning.[26] Their literature review indicated there was only level C evidence (preliminary, inconclusive, or conflicting evidence) for treatment of acute carbon monoxide poisoning. The 2008 UHMS guidelines, however, list carbon monoxide poisoning as an indication for HBOT.

Two blinded randomized trials were discussed in both the Cochrane and ACEP reviews. One is a study by Scheinkestel, a double-blind, RCT comparing HBOT with normobaric oxygen in patients with carbon monoxide poisoning.[27] The authors reported that HBOT did not benefit patient outcomes of neuropsychologic performance when HBOT was completed and at 1-month follow-up. This study was limited, however, by a high rate (46%) of patients who were lost to follow-up. Moreover, the trial has been criticized for administrating 100% normobaric oxygen for at least 72 hours between treatments, which has been called a toxic dose of oxygen.[28] The critiques also mention that there was an unusually high rate of neurologic sequelae after the treatment period, which could be due in part to the high dose of oxygen and/or the high rate of cognitive dysfunction in the study population (69% were poisoned by carbon monoxide through suicide attempts).

The other blinded trial, by Weaver, also compared hyperbaric and normobaric oxygen.[29] Patients received either 3 sessions of HBOT or 1 session of normobaric oxygen plus 2 sessions of exposure to normobaric room air. The primary outcome was the rate of cognitive sequelae at 6 weeks. Cognitive function was assessed using a battery of neuropsychological tests. At the 6-week follow-up, the intention- to-treat analysis found that 19 of 76 (25.0%) in the HBOT group and 35 of 76 (46.1%) in the control group had cognitive sequelae; the difference was statistically significant (p=0.007). There was a high rate of follow-up at 6 weeks, 147 of 152 (97%) of randomized patients. Enrollment in the study was stopped early because an interim analysis found HBOT to be effective. A follow-up study, which included 147 patients from the randomized trial and 75 who had been eligible for the trial but had not enrolled, was published in 2007.[30] Of the group treated with HBOT (n=75), cognitive sequelae were identified in 10 of 58 (17%) at 6 months and 9 of 62 (14%) at 12 months. Of the group not treated with HBOT (n=163), 44 of 146 (30%) at 6 months and 27 of 149 (18%) at 12 months had cognitive sequelae. (The follow-up rate was higher at 12 months because the investigators received additional funding for data collection.)

Delayed-Onset Muscle Soreness

Systematic Review

In a 2005 Cochrane review, Bennett concluded that available evidence is insufficient to demonstrate beneficial outcomes with HBOT for delayed-onset muscle soreness and closed soft-tissue injury.[31] It was noted that HBOT possibly even increases pain initially and further studies are needed. Therefore, use of HBOT for this indication is considered investigational.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2005 Cochrane review.

Dementia

Systematic Review

A 2012 Cochrane review identified 1 RCT evaluating HBOT for the treatment of vascular dementia.[32] The 2009 study compared HBOT plus donepezil to donepezil-only in 64 patients. The HBOT and donepezil group had significantly better cognitive function after 12 weeks of treatment, as assessed by the Mini-Mental State Examination. However, the Cochrane investigators judged the trial to be of poor methodologic quality because it was not blinded and the methods of randomization and allocation concealment were not discussed.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Section Summary

The current evidence for HBOT as a treatment of dementias of any cause is limited to a single short-term clinical trial on vascular dementia. This evidence is insufficient to permit conclusions about the safety and efficacy of HBOT on vascular dementia. No other randomized controlled trials were found for HBOT as a treatment of demential from any cause. Due to the lack of sufficient evidence, HBOT is considered investigational for treatment of dementias.

Femoral Neck Necrosis, Idiopathic

Randomized Controlled Trials (RCTs)

In 2010, Camporesi published the results of a double-blind RCT that evaluated HBOT in 20 adult patients with idiopathic unilateral femoral head necrosis.[33] Patients received 30 treatments over 6 weeks with either HBOT at 2.5 ATA (n=10) or a sham treatment consisting of hyperbaric air (n=10). The mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than the control group after 30 sessions ($p<0.001$) but not after 10 or 20 sessions. (The article did not report exact pain scores). Several range-of-motion outcomes were also reported. At the end of the initial treatment period, extension, abduction and adduction, but not flexion, were significantly greater in the HBOT group compared to the control group. Longer-term comparative data were not available because the control group was offered HBOT at the end of the initial 6-week treatment period.

Section Summary

The current evidence is limited to a single, small short-term RCT. Thus, there is insufficient data on which to draw conclusions about the efficacy of HBOT for treating femoral head necrosis, and it is considered investigational for this indication.

Fibromyalgia

Randomized Controlled Trials

Ablin (2023) published a RCT investigating the utility of HBOT in patients (n = 58) with fibromyalgia who had a history of traumatic brain injury (TBI).[34] They compared HBOT (n =29) to pharmacological intervention (n = 29). The HBOT protocol comprised 60 daily sessions, breathing 100% oxygen by mask at two absolute atmospheres (ATA) for 90 minutes. Pharmacological treatment included Pregabalin or Duloxetine. Results demonstrated a significant group-by-time interaction in pain intensity post-HBOT compared to the medication group ($p = 0.001$), with a large net effect size ($d = -0.95$) in pain intensity reduction following HBOT compared to medications. Fibromyalgia related symptoms and pain questionnaires demonstrated significant improvements induced by HBOT as well as improvements in quality of life and increase in pain thresholds and conditioned pain modulation. This study is limited by the small sample size, high dropout rate, no long-term follow-up, and lack of sham control.

In 2015, Efrati published an RCT that included 60 female patients who had fibromyalgia for at least two years and were symptomatic.[35] Patients were randomized to an immediate two month course of HBOT or delayed HBOT after two months. The HBOT protocol was forty 90-minute sessions of 100% oxygen at two ATA (one session per day, five d/wk). Forty-eight of 60

patients (80%) completed the study and were included in the analysis. After the initial two months, outcomes including number of tender points, pain threshold, and quality of life (SF-36) were significantly better in the immediate treatment group compared with the delayed treatment group (which received no specific intervention during this time). After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores prior to HBOT treatment. These findings are consistent with a clinical benefit of HBOT, but also with a placebo effect. A sham-control is needed to confirm the efficacy of HBOT in the treatment of fibromyalgia and other conditions where primary end points are pain and other subjective outcomes.

One quasi-randomized trial and 1 delayed-treatment RCT on HBOT for fibromyalgia were identified. In 2004, a study by Yildiz included 50 patients with fibromyalgia who had ongoing symptoms despite medical and physical therapy.[36] On an alternating basis, patients were assigned to HBOT or a control group. The HBOT consisted of fifteen 90-minute sessions at 2.4 ata (1 session per day, 5 d/wk). The control group breathed room air at 1 ata on the same schedule. Baseline values on the 3 outcomes were similar in the 2 groups. After the course of HBOT treatment, the mean (SD) number of tender points were 6.04 (1.18) in the HBO group and 12.54 (1.10) in the control group. The mean (SD) pain threshold was 1.33 kg (0.12) and 0.84 kg (0.12), respectively, and the mean VAS was 31.54 (8.34) and 55.42 (6.58), respectively. In the study abstract, the authors stated that there were statistically significant differences between the HBO and control groups after 15 therapy sessions, but the table presenting outcomes lacked the notation used to indicate between-group statistical significance. It is not clear whether the control group actually received a sham intervention that would minimize any placebo effect (i.e., whether or not the control intervention was delivered in a hyperbaric chamber). The authors stated that the study was double-blind but did not specify any details of patient blinding.

Section Summary

The above studies are few with relatively small sample sizes and have methodological limitations, e.g., quasi-randomization and no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect. Moreover, the HBO protocol varied (e.g., 15 vs 40 HBOT sessions). Thus, the evidence is insufficient to draw conclusions about the impact of HBOT on health outcomes for patients with fibromyalgia.

Fracture Healing

Systematic Review

In 2012, Bennett published a Cochrane review on HBOT to promote fracture healing and treat non-union fractures.[37] The investigators did not identify any published RCTs on this topic that compared HBOT to no treatment, sham treatment, or another intervention and reported bony union as an outcome.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Section Summary

Due to the lack of RCTs, it is not possible to conclude whether the use HBOT to promote fracture healing improves outcomes; therefore, the use of HBOT for this indication is considered investigational.

Headaches

When assessing any treatment focused on pain relief, randomized, placebo-controlled trials are necessary to investigate the extent of any placebo effect and to determine whether any improvement with the treatment exceeds that associated with a placebo.

The following is a summary of the available evidence:

Migraine headaches

Systematic Review

A 2008 Cochrane review by Bennett identified RCTs that evaluated the effectiveness of systemic hyperbaric oxygen therapy for preventing or treating migraine headache compared to another treatment or a sham control.[38] Five trials with a total of 103 patients were identified that addressed treatment of acute migraine with HBOT. A pooled analysis of 3 trials (total of 43 patients) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBOT (relative risk [RR] 5.97, 95% confidence interval [CI]1.46-24.38, p=0.001). No other pooled analyses were conducted due to variability in the outcomes reported in the trials. The meta-analysis did not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodologic quality of trials was moderate to low, e.g., randomization was not well-described in any trial. There was no evidence that HBOT could prevent episodes of migraine headache.

Randomized Controlled Trials (RCTs)

In 2004 Eftedal reported the results of a randomized, double-blind, placebo-controlled trial to assess whether HBOT had a prophylactic effect on migraine headache.[39] Forty patients were randomly assigned to either a treatment group receiving 3 sessions of HBOT or a control group receiving 3 hyperbaric treatments with room air. Thirty-four patients completed the study. Efficacy was measured as the difference between pre- and post-treatment hours of headache per week. There was no significant reduction in hours of headache with HBOT compared with hyperbaric air treatments. Nor was there a significant difference in either group in pre- and post-treatment levels of endothelin-1 in venous blood. The authors concluded that that HBOT had no significant prophylactic effect on migraine headache or on the endothelin-1 level in venous blood.

Cluster headaches

Systematic Reviews

Two 2008 systematic reviews, including the Cochrane review noted above, reported few studies comparing HBOT with sham treatment for cluster headaches.[38, 40] Available randomized, placebo-controlled trials measuring effect on symptoms are unreliable due to very small size.[41, 42]

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2008 systematic reviews.

Section Summary

Due to the lack of sufficient evidence from well-designed clinical trial, HBOT for the treatment of headaches from any cause is considered investigational.

Herpes Zoster

Randomized Controlled Trial (RCT)

In 2012, Peng published an RCT evaluating HBOT as a treatment of herpes zoster.[43] Sixty-eight patients with herpes zoster diagnosed within the previous 2 weeks were randomized to 30 sessions of HBOT (n=36) or medication treatment (n=32). Pharmacotherapy included antiviral, pain, nerve nutritive and antidepressive medication. Therapeutic efficacy was calculated at the end of the 3-week treatment period and included the proportion of patients who were healed (i.e., complete subsidence of pain and rash) or improved (i.e., significant pain relief and rash subsistence). Rates of therapeutic efficacy were 97.2% in the HBOT group and 81.3% in the medication group ($p<0.05$). Limitations of the study included a lack of blinding and lack of long-term follow-up.

Section Summary

The evidence from the single randomized controlled trial is insufficient to permit conclusions about the effect of HBOT on health outcomes for patients with herpes zoster; therefore, HBOT is considered investigational for this indication.

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL)

Systematic Reviews

Joshua (2021) published a SR which included 3 RCTs comparing HBOT with medical treatment, all published in 2018 and none of which were included in either the Bennett or Rhee systematic reviews below.[44] Inclusion criteria for studies in the Joshua review differed from the previous reviews in that: 1) only randomized studies were included and 2) diagnosis of ISSNHL was based on American Academy of Otolaryngology Head and Neck Surgery criteria. In addition, the literature search was limited to studies published beginning in January 2020. HBOT interventions were 60 or 90 minutes in duration, for time periods ranging from 10 to 20 days and medical treatment included a use of steroids (oral and/or intravenous) alone or in combination with antiviral medications and/or hemorheologic therapy. The patients included in the studies were clinically heterogenous, with baseline hearing loss ranging from moderate to profound in 2 studies and was unreported in the third study. The proportion of patients with hearing recovery, based on a ≥10 point audometric gain, was significantly higher with HBOT compared with control based on pooled analysis of 2 studies (OR, 4.32; 95% CI, 1.60 to 11.68; I2=0%). Limitations of these results include the fact that the included studies were judged to have moderate (2 studies) and high (1 study) risk of bias and the small number of participants in both HBOT (n=88) and medical treatment (n=62) groups.

Eryigit (2018) published a qualitative SR assessing the effectiveness of HBOT to treat patients with ISSNHL.[45] Sixteen clinical trials were included, with a total of 1759 operative ears, 580 of which received HBOT. All patients also received steroid treatment, (systemic, intravenous, or intratympanic injection). Most studies found that patients with severe or profound hearing loss who received steroids (any route of administration) plus HBOT saw statistically significant improvements (specified p-value range across studies:0.0014 to 0.012), whereas those with a

lower level of hearing loss did not see these improvements. Several studies reported no significant difference between case and control groups, but the studies that broke down the results by levels of hearing loss all showed that profound (or severe and profound) loss benefited from the addition of HBOT to steroid treatment.

Rhee (2018) published a systematic review and meta-analysis comparing HBOT plus medical therapy (HBOT + MT) with MT alone for ISSNHL treatment.[46] Randomized clinical trials and nonrandomized studies were included. The main outcomes considered were complete hearing recovery, any hearing recovery, and absolute hearing gain. Nineteen studies (3 randomized and 16 nonrandomized) with a total of 2401 patients (mean age, 45.4 years; 55.3% female) were included. In the HBOT+ MT group, rates of complete hearing recovery and any hearing recovery were 264/897 (29.4%) and 621/919 (67.6%), respectively, and in the MT alone group were 241/1167 (20.7%) and 585/1194 (49.0%), respectively. Pooled HBOT+MT also showed favorable pooled results from random-effects models for both complete hearing recovery (OR, 1.61; 95% CI, 1.05 to 2.44) and any hearing recovery (OR, 1.43; 95% CI, 1.20 to 1.67). Limitations include differences in clinical and methodological characteristics of selected studies heterogeneity, possible measurement confounder effects, and difficulty in evaluating the benefit of treatment due to a substantial proportion of patients experiencing spontaneous recovery.

A Cochrane review by Bennett (2012) on HBOT for ISSNHL and/or tinnitus identified seven RCTs (n = 392).[47] Six studies included time-based entry criteria for hearing loss and/or tinnitus (48 hours in 3 studies, 2 weeks in 2 studies, 6 months in 1 study). The dose of oxygen per treatment session and the treatment protocols varied across studies (eg, the total number of treatment sessions ranged from 10 to 25). All trials reported on the change in hearing following treatment, but specific outcomes varied. Two trials reported the proportion of participants with more than 50% and more than 25% return of hearing at the end of therapy. A pooled analysis of these studies did not find a statistically significant difference in outcomes between the HBOT and the control groups at the level of 50% or higher but did find a significantly higher rate of improvement at the level of 25% or higher. A pooled analysis of 4 trials found a significantly greater mean improvement in hearing over all frequencies with HBOT compared with control. Studies were small and generally of poor quality. Randomization procedures were only described in 1 study, and only 1 study stated they blinded participants to treatment group assignment using sham therapy.

Randomized Controlled Trial (RCT)

Cavaliere (2022) published a RCT comparing HBOT and oral steroids, alone and in combination, in adults (n = 171) with ISSNHL.[48] Pure tone audiometry (PTA) testing was conducted at baseline and 20 days after treatment. ISSNHL was characterized at baseline as upsloping (hearing loss affecting 250 to 500 herz [Hz] more), flat (<20 decibel [dB] difference between the highest and lowest pure tone average threshold), downsloping (hearing loss affecting 4000 and 8000 Hz more) or profound (thresholds of ≥90 dB in each test frequency) at baseline. In the study, total or partial hearing recovery was based on change in PTA test results at follow-up, but the magnitude of change that constituted either total or partial recovery was not clearly defined. The study reported that all patients, regardless of intervention group, had a statistically significant improvement in mean PTA scores from baseline, and that HBOT alone or combination therapy with HBOT plus steroids resulted in greater recovery relative to steroid use alone. Other outcomes, including harms of treatment, were not reported.

Section Summary

A Cochrane review of RCTs had mixed findings from studies that included individuals with tinnitus. Some outcomes (ie, improvement in hearing of all frequencies, >25% return of hearing) were better with HBOT than with a control intervention, but more than 50% return of hearing did not differ significantly between groups. There was important variability in the patients enrolled in the studies. A subsequent systematic review had similarly limited conclusions due to the inclusion of non-randomized studies. A third review that had stricter inclusion criteria found HBOT increased the rate of hearing recovery, the analysis was limited to 2 trials with methodological limitations. One RCT published subsequent to the systematic reviews found a positive effect of HBOT plus steroid combination therapy on measures of auditory function compared to either HBOT or steroids alone, other outcomes were not reported.

Inflammatory Bowel Disease (IBD)

Systematic Reviews

McCurdy (2022) published a SR examining the evidence on HBOT for a range of IBD phenotypes (Crohn disease, ulcerative colitis).[49] The review was not limited by study design, and included 3 small RCTs (total N=40 all with ulcerative colitis) and 16 case series.The included case series generally enrolled less than 30 patients each, with the exception of one study, conducted in Russia, that enrolled 519 patients. Overall, a total sample size for the SR across phenotypes was 844. Two RCTs found a benefit for HBOT compared with standard medical care, but they were small studies (n=10 and 20) and were likely underpowered to detect between-group differences. In addition, one of the trials only included prior HBOT responders and one was stopped early due to enrollment difficulties. The third RCT found no benefit of HBOT compared with standard care, and was also stopped early. Quality assessment of the included studies judged two of the three RCTs to be at high risk of bias. Study authors concluded that although HBOT was associated with high response rates across phenotypes, high-quality evidence was limited, and well-designed RCTs are needed to confirm the effect of HBOT in patients with IBD.

Singh (2021) published a SR on the efficacy of HBOT in patients with ulcerative colitis and Chron’s disease.[50] A total of 18 studies were included in the review consisting mainly of observational studies. The overall response rate of HBOT in ulcerative colitis was 83.24% (95% CI: 61.90-93.82), while the response in Crohn's disease was 81.89 (95% CI: 76.72-86.11). The results of randomized trials for HBOT as adjuvant therapy in ulcerative colitis were conflicting within the review. The complete healing of fistula in fistulizing Crohn's disease was noted 47.64% (22.05-74.54), while partial healing was noted in 34.29% (17.33-56.50%). This review is limited by inclusion of inadequately powered studies and lack of randomized trials.

McCurdy (2021) published a systematic review evaluating the efficacy of HBOT on various inflammatory bowel disease phenotypes.[51] There were 19 studies included in the review with 809 patients in three randomized trials and 16 case series. Rates of clinical remission included 87% (95% CI, 10-100) for ulcerative colitis (n = 42), 88% (95% CI, 46-98) for luminal Crohn's disease (CD, n = 8), 60% (95% CI, 40-76) for perianal CD (n = 102), 31% (95% CI, 16-50) for pouch disorders (n = 60), 92% (95% CI, 38-100) for pyoderma gangrenosum (n = 5), and 65% (95% CI, 10-97) for perianal sinus/metastatic CD. This review is limited by the inclusion of primarily case studies and studies with inadequate descriptions of the interventions and outcomes.

A 2014 systematic review by Dulai examined the evidence on HBOT for inflammatory bowel disease (Crohn disease and ulcerative colitis).[52] The review was not limited by study design. The authors included 17 studies: 1 RCT, 2 case-control studies, 3 case series, and 11 case reports. The studies reported on a total of 613 patients, 286 with Crohn disease and 327 with ulcerative colitis. The only RCT identified was published in 2013; it was open-label and included 18 patients with ulcerative colitis.[53] Patients were randomized to treatment with standard medical therapy only (n=8) or medical therapy plus HBOT (n=10) consisting of 90-minute treatments at 2.4 atm, 5 days a week for 6 weeks (total of 30 sessions). The primary outcome was the self-reported Mayo score which has a potential range of 0 to 12.[54] Patients with a score of 6 or more are considered to have moderate to severe active disease. At six months follow-up there was no significant difference between groups in the Mayo score, with a median score of 0.5 in the HBOT group and three in the control group (exact p value not reported). In addition, there were no significant differences in any of the secondary outcomes including laboratory tests and fecal weight. Overall, the authors found that the studies had a high risk of bias, particularly in the areas of attrition and reporting bias, and further study in well-controlled, blinded RCTs was recommended.

Randomized Controlled Trials (RCTs)

The RCTs for IBD are included in the Systematic Reviews above.

Section Summary

There is insufficient evidence that HBOT is effective for treating inflammatory bowel disease. Only three small RCT have been published, and these studies did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy.

In Vitro Fertilization

In a 2005 nonrandomized pilot study, Van Voorhis reported that HBOT was well tolerated in women undergoing ovarian follicular stimulation for in vitro fertilization; however no outcomes were reported.[55] Therefore, current evidence is insufficient to permit conclusions and HBOT is considered investigational for this indication.

Mental Illness

A Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health (CADTH) searched the literature through July 2014 on the clinical effectiveness of hyperbaric oxygen therapy for treatment of adults with posttraumatic stress disorder, generalized anxiety disorder, and/or depression.[56]

The review's inclusion criteria were health technology assessments, systematic reviews, meta-analyses, RCTs or nonrandomized studies comparing HBOT to any active treatment and reporting clinical outcomes. No eligible studies were identified.

Multiple Sclerosis

A Cochrane review of RCTs on HBOT for multiple sclerosis was published by Bennett in 2004.[57] The authors identified 9 RCTs, with a total of 504 participants that compared the effects of HBOT with placebo or no treatment. The primary outcome of the review was score on the Expanded Disability Status Scale (EDSS). A pooled analysis of data from 5 trials (N=271) did not find a significant difference in change in the mean EDSS after 20 HBOT

treatments versus control (mean difference [MD], -0.07; 95% CI, -0.23 to 0.09). Moreover, a pooled analysis of data from 3 trials (n=163) comparing HBOT and placebo did not find a significant difference in mean EDSS after 6 months of follow-up (MD = -0.22; 95% CI, -0.54 to 0.09).

Necrotizing Soft Tissue Infection

Systematic Reviews

Huang (2023) published a SR with meta-analysis examining the efficacy of HBOT in the treatment of necrotizing soft tissue infections (NSTI).[58] Retrospective cohort and case-control studies included 49,152 patients, 1448 who received HBOT and 47,704 in control. The mortality rate in the HBOT group was significantly lower than that in the non-HBOT group [RR = 0.522, 95% CI (0.403, 0.677), $p < 0.05$]. However, the number of debridements performed in the HBOT group was higher than in the non-HBOT group [SMD = 0.611, 95% CI (0.012, 1.211), $p < 0.05$]. There was no significant difference in amputation rates between the two groups [RR = 0.836, 95% CI (0.619, 1.129), $p > 0.05$]. The incidence of multiple organ dysfunction syndrome (MODS) was lower in the HBOT group than in the non-HBO group [RR = 0.205, 95% CI (0.164, 0.256), $p < 0.05$]. There was no significant difference in the incidence of other complications, such as sepsis, shock, myocardial infarction, pulmonary embolism, and pneumonia, between the two groups ($p > 0.05$).Due to the retrospective nature of the studies, the evidence is weak, and further research is needed to establish efficacy.The authors also comment that It is important to note that HBOT is not available in all hospitals, and its use should be carefully considered based on the patient's individual circumstances. Additionally, it is still worthwhile to stress the significance of promptly evaluating surgical risks to prevent missing the optimal treatment time.

A Cochrane review by Levett (2015) evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis.[59] No RCTs were identified. Hedetoft (2021) published a SR which included 31 retrospective cohort studies assessing the effect of adjunctive HBOT for treating necrotizing soft-tissue infections (necrotizing fasciitis, Fournier’s gangrene, and gas gangrene).[60] Ten studies assessed to have critical (very high) risk of bias were excluded from meta-analyses. Pooled results from the remaining 21 studies found HBOT associated with a reduced risk of in-hospital mortality (OR, 0.44; 95% CI, 0.33 to 0.58; I2=8%), but the duration of follow-up for mortality was not reported. Results were consistent when studies were stratified according to moderate (5 studies; OR, 0.39; 95% CI, 0.28 to 0.55; I2=0%) and serious (high) risk of bias (16 studies; OR, 0.51; 95% CI, 0.33 to 0.80; I2=17%). Publication bias favoring HBOT was present for this outcome based on funnel plot analysis. For other outcomes, including major amputation and length of hospital stay, there were no statistically significant differences between HBOT use and non-use. Evidence on adjunctive HBOT and the need for surgical debridement was mixed. One study with a low/moderate risk of bias reported a higher number of debridements with HBOT use versus non-use (mean difference, 1.8; 95% CI, 1.15 to 2.45), but the mean difference between HBOT use and non-use in a pooled analysis of 5 studies with methodological flaws was not statistically significant (mean difference, 0.63; 95% CI, -0.49 to 1.75).

Section Summary

No RCTs have evaluated HBOT for necrotizing soft tissue infection. Systematic reviews of retrospective studies with methodological limitations suggest that HBOT use may reduce the risk of in-hospital mortality.

Osteomyelitis

No prospective clinical trials on chronic refractory osteomyelitis or acute refractory osteomyelitis were identified in updated searches. Savvidou (2018) conducted a qualitative systematic review of HBOT as an adjunctive treatment of chronic osteomyelitis.[61] Adjuvant HBOT was effective in 16 (80%) of 20 cohort studies and 19 (95%) of 20 case series. Overall, 308 (73.5%) of 419 patients with complete data achieved a successful outcome with no relapses reported.

The justification for the use of HBOT in chronic osteomyelitis has been primarily based on case series. Among the larger case series, Maynor reviewed the records of all patients with chronic osteomyelitis of the tibia seen at one institution.[62] Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBO treatments (range, 6-99). Of the 26 patients with at least 2 years of follow-up after treatment, 21 (81%) remained drainage-free. Twelve of 15 (80%) with follow-up data at 60 months had remained drainage-free. A study by Davis reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution.[63] Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8-103). After a mean posttreatment follow-up of 34 months, 34 of 38 (89%) patients remained clinically free of infection (i.e., drainage-free and no tenderness, pain, or cellulitis). Success rates from several smaller case series, all conducted in Taiwan, are 12 of 13 (92%) patients, 11 of 14 (79%) patients, and 13 of 15 (86%) patients.[64-66] A high percentage of refractory patients in these series had successful outcomes.

Radiotherapy Adverse Effects

Systematic Review

A 2017 systematic review on the effectiveness of HBOT for the treatment of radiation-induced skin necrosis included eight articles with five case series studies, two case reports, and one observational cohort.[67] The authors investigated the change in symptoms and alteration in wound healing and reported that HBOT was a safe intervention with promising outcomes. However, the authors recommended additional high-quality evidence in order for HBOT to be considered as a relevant treatment for this indication.

A 2014 systematic review on the safety and effectiveness of HBOT for the treatment of non-neurological soft tissue radiation-related injuries (STRI) included 41 articles, 11 of which compared regimens with and without HBOT.[68] Serious adverse effects were rare and the more common adverse effects were minor and self-limiting. Evidence of a beneficial effect of HBOT was reported radiation proctitis and STRI of the head and neck, but not for post-radiation soft tissue edema or radiation cystitis. The authors recommended further studies to validate the use of HBOT as both a definitive and adjunctive treatment for individual STRI.

In 2010, Spiegelberg conducted a systematic review of studies on HBOT to prevent or treat radiotherapy-induced head and neck injuries associated with treatment of malignant tumors.[69] The authors identified 20 studies. Eight of the studies included control groups; their sample sizes ranged from 19 to 78 individuals. Four (50%) of the studies with a control group concluded that HBOT was effective, and the other 4 did not conclude that the HBOT was effective. The authors noted a paucity of RCTs but did not state the number of RCTs identified in their review.

Randomized Controlled Trials

Teguh reported on 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiation therapy.[70] Eight patients were randomly assigned to receive 30 sessions of HBOT, beginning within 2 days of completing radiation therapy, and 9 patients received no additional treatment. All patients were included in the analysis. Quality of life outcomes were assessed, and the primary outcome was specified as xerostomia at 1 year. Quality of life measures did not differ significantly between groups in the acute phase (first 3 months). For example, 1 month after treatment, the mean visual analog scale (VAS) score for xerostomia (0-to-10 scale) was 5 in the HBOT group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups; the mean VAS score for xerostomia was 4 in the HBOT group and 7 in the control group (p=0.002). Also at 1 year, the mean quality of life score for swallowing (0-to-100 scale) was 7 in the HBOT group and 40 in the control group (p=0.0001). The study is limited by the small sample size and the wide fluctuation over the follow-up period in quality-of-life ratings.

In 2010, Gothard randomized 58 patients with arm lymphedema (at least 15% increase in arm volume) following cancer treatment in a 2:1 ratio to receive HBOT (n=38) or usual care without HBOT (n=20).[71] Fifty-three patients had baseline assessments and 46/58 (79%) had 12-month assessments. No statistically significant difference was found in the change in arm volume from baseline to 12-month follow-up. The median change from baseline was -2.9% in the treatment group and -0.3% in the control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the contralateral arm. According to this definition, 9 of 30 (30%) patients in the HBOT group were considered responders compared with 3 of 16 (19%) in the control group; the difference between groups was not statistically significant. Other outcomes, e.g., quality-of-life scores on the Short-Form (SF)-36, were also similar between groups.

Section Summary

Due to the lack of sufficient evidence from well-designed clinical trial, HBOT for the treatment of adverse effects related to radiation therapy is considered investigational.

Radionecrosis and Osteoradionecrosis

Several systematic reviews of RCTs have been published. A 2008 Cochrane review by Esposito reviewed the use of HBOT in patients requiring dental implants.[30] The authors identified one randomized trial involving 26 patients. The authors concluded that despite the limited amount of clinical research available, it appears that HBOT in irradiated patients requiring dental implants may not offer any appreciable clinical benefits. They indicated that there is a need for more RCTs to ascertain the effectiveness of HBOT in irradiated patients requiring dental implants.

Lin (2023) published an updated Cochrane Review on HBOT for late radiation tissue injury.[72] This is the third update of the original Cochrane Review published in July 2005 and updated previously in 2012 and 2016. The purpose of the review is to evaluate the benefits and harms of HBOT for treating or preventing late radiation tissue injury (LRTI) compared to regimens that excluded HBOT. The study included 18 RCTs (1071 participants) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.They added four new studies to this updated review and evidence for the treatment of radiation proctitis, radiation cystitis, and the prevention and treatment of osteoradionecrosis (ORN). HBOT may not prevent death at one year (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.47 to 1.83; I2 = 0%; 3 RCTs, 166 participants; low-certainty evidence). There is some evidence that HBOT may result in

complete resolution or provide significant improvement of LRTI (RR 1.39, 95% CI 1.02 to 1.89; I2 = 64%; 5 RCTs, 468 participants; low-certainty evidence) and HBOT may result in a large reduction in wound dehiscence following head and neck soft tissue surgery (RR 0.24, 95% CI 0.06 to 0.94; I2 = 70%; 2 RCTs, 264 participants; low-certainty evidence). In addition, pain scores in ORN improve slightly after HBOT at 12 months (mean difference (MD) -10.72, 95% CI -18.97 to -2.47; I2 = 40%; 2 RCTs, 157 participants; moderate-certainty evidence). HBOT results in a higher risk of a reduction in visual acuity (RR 4.03, 95% CI 1.65 to 9.84; 5 RCTs, 438 participants; high-certainty evidence). There was a risk of ear barotrauma in people receiving HBOT when no sham pressurization was used for the control group (RR 9.08, 95% CI 2.21 to 37.26; I2 = 0%; 4 RCTs, 357 participants; high-certainty evidence), but no such increase when a sham pressurization was employed (RR 1.07, 95% CI 0.52 to 2.21; I2 = 74%; 2 RCTs, 158 participants; high-certainty evidence). The included studies have small sample sizes. The authors conclude that HBOT may be associated with improved outcomes (low- to moderate-certainty evidence for people with LRTI affecting tissues of the head, neck, bladder and rectum. HBOT may also result in a reduced risk of wound dehiscence and a modest reduction in pain following head and neck irradiation. However, HBOT is unlikely to influence the risk of death in the short term. And that the application of HBOT to selected participants may be justified. Limitations include a small number of studies with small sample sizes and methodological and reporting inadequacies of some of the primary studies. More information is required on the subset of disease severity and tissue type affected that is most likely to benefit from this therapy, the time for which we can expect any benefits to persist and the most appropriate oxygen dose. Further research is required to establish the optimum participant selection and timing of any therapy.

Stroke

Acute Stroke

Systematic Reviews

In a 2005 Cochrane systematic review, Bennett evaluated HBOT for acute stroke.[73] The investigators identified 6 RCTs with a total of 283 participants that compared HBOT to sham HBOT or no treatment. The authors were only able to pool study findings for 1 outcome, the mortality rate at 3-6 months. A pooled analysis of 3 trials found no significant benefit of HBOT compared to the control for this outcome. Based on the available evidence, acute ischemic stroke is considered investigational

In a 2005 systematic review, Carson concluded that current evidence did not demonstrate any benefit with the use of HBOT for the treatment of stroke.[74] The authors noted it was undetermined whether there were any benefits with HBOT that would outweigh potential harms, and further study was required.

In a 2014 update of a Cochrane systematic review, Bennett evaluated HBOT for acute ischemic stroke. The investigators identified 11 RCTs with a total of 705 participants that compared HBOT with sham HBOT or no treatment. The authors were only able to pool study findings for 1 outcome; mortality at 3 to 6 months. A pooled analysis of data from 4 trials with a total of 106 participants did not find a significant benefit of HBOT compared with a control condition for this outcome (RR=0.97; 95% CI, 0.34 to 2.75).

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2005 systematic reviews.

Stroke-related motor dysfunction

Randomized Controlled Trials (RCTs)

In 2013, Efrati published an RCT evaluating HBOT for treatment of neurologic deficiencies associated with a history of stroke.[75] The study included 74 patients with at least one motor dysfunction who had an ischemic or hemorrhagic stroke 6-36 months prior to study participation. Participants were randomly assigned to receive 2 months of HBOT (40 daily sessions, 5 days per week, n=30) or delayed treatment (n=32). Patients were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing over and receiving HBOT. Twenty-nine of 32 patients (91%) in the delayed treatment group crossed over to the active intervention. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to treatment group, and several patient-reported quality-of-life and functional status measures.

At 2 months' follow-up, there was statistically significantly greater improvement in function in the HBOT group compared to the control group as measured by the NIHSS, quality-of-life scales and the ability to perform activities of daily living (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography (SPECT) imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBOT compared to before treatment. This RCT raises the possibility that HBOT may induce improvements in function and quality of life for post-stroke patients with motor deficits. However, the results are not definitive for a number of reasons. This RCT is small and enrolled a heterogeneous group of post-stroke patients. The study was not double-blind and the majority of outcome measures, except for the NIHSS, were patient reported and thus prone to the placebo effect. Also, there was a high total dropout rate of 20% at the 2-month follow-up point. Therefore, larger, double-blind studies with longer follow-up are needed to corroborate these results. Because of these limitations in the evidence, HBOT is considered investigational for treating motor dysfunction associated with stroke.

Section Summary

Current evidence is insufficient to permit conclusions about whether HBOT improves health outcomes in the treatment of stroke or stoke-related functional limitations.

Traumatic Brain Injury

Systematic Review

Harch (2022) published a systematic review of the evidence for hyperbaric oxygen therapy (HBOT) in Persistent Postconcussion Syndrome using a dose-analysis.[76] Eleven studies were included: six randomized trials, one case-controlled study, one case series, and three case reports. Whether analyzed by oxygen, pressure, or composite oxygen and pressure dose of hyperbaric therapy statistically significant symptomatic and cognitive improvements or cognitive improvements alone were achieved for patients treated with 40 HBOTS at 1.5 atmospheres absolute. Alashram (2022) included ten studies in his systematic review; six studies were randomized controlled trials, and four were pilot studies.[77] As reported by the author, the benefits of HBOT were limited for traumatic brain injury and more RCTs with larger sample sizes are required to make any conclusion.

The systematic review and pooled analysis by Hart (2019) evaluated HBOT for mild traumatic brain injury (mTBI) associated post-concussive symptoms (PCS) and posttraumatic stress disorder (PTSD).[78] Data were aggregated from four Department of Defense (DoD) studies that included participant level data on 254 patients assigned to either HBOT or sham intervention. An additional three studies with summary-level participant data were summarized (N=135). The authors assessed changes from baseline to post-intervention on PCS, PTSD, and neuropsychological measures. The DoD data analyses indicated improvements with HBOT for PCS, measured by the Rivermead Total Score. Statistically significant improvements were seen for PTSD based on the PTSD Checklist Total Score, as well as for verbal memory based on CVLT-II Trial 1-5 Free Recall.

A 2016 meta-analysis by Wang (2016) assessed HBOT for TBI including eight studies with 519 participants that met the eligibility criteria.[79] HBOT protocols varied across studies in the levels of oxygen and the length and frequency of treatments. The primary outcome was change in the Glasgow Coma Scale score. A pooled analysis of two studies found a significantly greater improvement in the mean Glasgow Coma Scale score in the HBOT group compared with control groups. Mortality (a secondary outcome) was reported in 3 of the 8 studies. Pooled analysis of these 3 studies found a significantly lower overall mortality rate in the HBOT group than in the control group.

A 2012 Cochrane systematic review addressed HBOT as adjunctive treatment for traumatic brain injury.[80] The investigators identified 7 RCTs with a total of 571 participants comparing a standard intensive treatment regimen to the same treatment regimen with the addition of HBOT. The review did not include studies in which interventions occurred in a specialized acute care setting. The HBOT regimens varied among studies; for example, the total number of individual sessions varied from 3 to 30-40. No trial used sham treatment or blinded the staff members who were treating the patients, and only 1 had blinding of outcome assessment. Allocation concealment was inadequate in all of the studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials that reported this outcome found a statistically significantly greater reduction in mortality when HBOT was added to a standard treatment regimen. However, when data from the 4 trials were pooled, the difference in the proportion of patients with an unfavorable functional outcome at final follow-up did not reach statistical significance. Unfavorable outcome was commonly defined as a Glasgow Outcome Score (GOS) of 1, 2 or 3, which are described as ‘dead’, ‘vegetative state’ or ‘severely disabled’. Studies were generally small and were judged to have substantial risk of bias.

Randomized Controlled Trials

Hadanny (2022) conducted an RCT to assess the effect of hyperbaric oxygen therapy in children (age 8 to 15) suffering from persistent post-concussion syndrome (PPCS) from mild-moderate traumatic brain injury six months to 10 years prior.[81] 25 children were randomized to receive 60 daily sessions of HBOT (n = 15) or sham (n = 10) treatments. Following HBOT, there was a significant increase in cognitive function including the general cognitive score ($d = 0.598$, $p = 0.01$), memory ($d = 0.480$, $p = 0.02$), executive function ($d = 0.739$, $p = 0.003$), PPCS symptoms including emotional score ($p = 0.04$, $d = - 0.676$), behavioral symptoms including hyperactivity ($d = 0.244$, $p = 0.03$), global executive composite score ($d = 0.528$, $p = 0.001$), planning/organizing score ($d = 1.09$, $p = 0.007$).

A 2014 double-blind sham-controlled trial 2014 RCT by Cifu included 61 male Marines who had a history of mild traumatic brain injury and postconcussive syndrome. To maintain

blinding, all patients were pressured inside a hyperbaric chamber to 2.0 ata. They were randomized to breathe 1 of 3 oxygen p[nitrogen gas mixes equivalent to: (1) 75% oxygen at 1.5 ata (n=21); (2) 100% oxygen at 2.0 ata (n=19); and (3) sham treatment with surface room air (n=21). Patients underwent 40 once daily 60-minute sessions. Outcomes were assessed 3 months after the last exposure. The primary outcome was a clinically meaningful improvement, defined as a 10% difference between groups in the score on the Rivermead Post-Concussion Questionnaire (RPQ)–16 (scale range, 50-84; higher values indicate more severe symptoms). At follow-up, there was no statistically significant difference among groups on RPQ-16 score (p=0.41). A variety of secondary outcomes were also assessed. None of these, including measures of attention, cognition, or depression, differed significantly among groups at follow-up.

Also in 2014, Miller evaluated HBOT in 72 military service members with continuing symptoms at least 4 months after mild traumatic brain injury. Patients were randomized to receive 40 daily HBO sessions at 1.5 ata, 40 sham sessions consisting of room air at 1.2 ata or standard care with no hyperbaric chamber sessions. The primary outcome was change in the RPQ. A cutoff of 15% improvement was deemed clinically important, which translates to a change score of at least 2 points on the RPQ-3 subscale. The proportion of patients who met the prespecified change of at least 2 points on the RPQ-3 was 52% in the HBOT group, 33% in the sham group and 25% in the standard care-only group. The difference between rates in the HBOT and sham groups was not statistically significant (p=0.24). None of the secondary outcomes significantly favored the HBOT group. A criticism of this study, as well as the other military population studies, was that the response in the sham group was not due to a placebo effect but to an intervention effect of slightly increased atmospheric pressure (1.2 ata).43 Other researchers have noted that room air delivered at 1.2 ata would not be considered an acceptable therapeutic dose for any indication, and especially for a condition with persistent symptoms like postconcussive syndrome.

A 2012 sham-controlled double-blind trial evaluating HBOT was published after the 2012 Cochrane review.[82] The study included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBOT over 8 weeks (n=25) or a sham intervention (room air at 1.3 ATA) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post-Traumatic Disorder Check List- Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks post-exposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total mean score or the PCL-M composite score at any time point. While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.

Several trials on mild traumatic brain injury in military populations have been published and these did not find significant benefits of HBOT compared with sham treatment. The first trial, published by Wolf in 2012, included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBOT over 8 weeks (n=25) or a sham intervention (room air at 1.3 atmosphere, absolute [ata]) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post- Traumatic Disorder Check List–Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks postexposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total

mean score or the PCL-M me point. For example, at the 6-week follow-up, mean composite PCL-M scores were 41.6 in the HBOT group and 40.6 in the sham-control group (p=0.28). While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.

Section Summary

Three systematic reviews with cognitive improvement, no significant improvements and a mortality reduction with HBOT but no significant improvement in patient function among survivors of traumatic brain injury were found. One RCT in 2022 reported the usefulness of HBO six months to 10 years post-brain injury in children. Two double-blind, sham-controlled RCTs of HBO treatment in a military population with mild traumatic brain injury did not find a statistically significant benefit with HBOT. Thus, the evidence is insufficient that HBOT improves health outcomes in patients with traumatic brain injury, and this indication is considered investigational.

Wounds Unrelated to Diabetes

Systematic Reviews

Idris (2024) published a SR analyzing the efficacy of HBOT in the post-operative care of patients undergoing nipple-sparing mastectomy (NSM) as a method of treating breast cancer.[83] The SR included seven included studies; two case reports, one observational case series, two cohort studies, and two retrospective studies. The initiation of HBOT varied among the 63 patients included, with specific post-operative HBOT timeframes reported for 27 individuals. Notably, 10 patients received HBOT within an optimal 48 h window following NSM. Within this early-intervention subgroup, a 90% success rate in resolving threatened skin flap necrosis (TSFN) was observed, with only one patient experiencing unresolved complications. The authors assessed efficacy for various surgical complications related to NSM: Re-operation: Twenty-three patients across four studies required re-operation; Flap loss: Four patients across two studies experienced flap loss. Re-operation and Flap loss rates were higher in the pre-HBOT group than in the post-HBOT group. Sinus pain: No reported sinus pain was noted in the pre-HBOT group. One of the seventeen patients (5.9%) in the post-HBOT group experienced sinus pain. Significant limitations include the absence of rigorous clinical trials and well-defined control groups. None of the studies that were incorporated in this review exceeded Level III of the ASPS' Evidence Rating Scale for Therapeutic Studies.

Keohane (2023) published a SR evaluating the efficacy of HBOT in the treatment of chronic venous ulcers. Six studies were included.[84] There was significant heterogeneity across the studies, with no standard control intervention, method of outcome reporting, or duration of follow up. Two studies reported 12 week follow up results and pooled analysis of complete ulcer healing showed no statistically significant difference between HBOT and controls for the outcome of complete ulcer healing OR 1.54 (95%CI = .50-4.75) (p = 0.4478). A similar non-significant result was seen in four studies reporting 5-6 week follow up; OR 5.39 (95%CI = .57-259.57) (p = 0.1136). Change in VLU area was reported in all studies, and pooled standardized mean difference was 1.70 (95%CI = .60 to 2.79) (p = 0.0024), indicating a statistically significant benefit of HBOT in reducing ulcer area. There was significant heterogeneity across the studies, with no standard control intervention, method of outcome reporting, or duration of follow up. The authors concluded that the limited evidence does not justify widespread use of HBOT for venous leg ulcers.

Dauwe (2014) published a SR that included eight studies with sample sizes ranging from five to 125 patients. Four studies were randomized, three were prospective non-RCTs, and one was a retrospective non- RCT. Data were not pooled due to the heterogeneity described below. The authors noted that seven of the eight studies reported achieving statistical significance in their primary end points, but the end points differed among studies (eg, graft survival, length of hospital stay, wound size). Moreover, the studies were heterogeneous in terms of treatment regimens, patient indications (eg, burns, face lifts), and study designs, making it difficult to draw conclusions about the effect of HBOT on acute wound treatment

A 2013 updated Cochrane review analyzed randomized controlled trials comparing either HBOT with a different intervention, or two HBOT regimens for acute wounds (e.g., surgical wounds, lacerations, traumatic wounds, and animal bites).[85] The four studies that met inclusion criteria ranged in size from 10 to 135 subjects. Reported outcomes were mixed. Meta-analysis of pooled data was not possible due to differences among studies with respect to patient characteristics, interventions studied, and outcome measures. Also identified was a high risk of bias due to insufficient disclosure of randomization methods and selective reporting of outcome data. Findings of individual studies were mixed.

Kranke (2012) published an update to the 2007 Cochrane review of randomized controlled trials (RCTs) on HBOT for chronic wounds.[86] The authors identified nine RCTs with a total of 471 participants that compared the effect of HBOT on chronic wound healing compared with an alternative treatment approach that did not use HBOT. Eight of the nine trials included in the review evaluated HBOT in patients with diabetes. The remaining trial addressed HBOT for patients with venous ulcers; that study had only 16 participants and the comparator treatment was not specified. In a pooled analysis of data from three trials, a significantly higher proportion of ulcers had healed at the end of the treatment period (6 weeks) in the group receiving HBOT compared to the group not receiving HBOT (RR: 5.20: 95% CI: 1.25 to 21.7). Pooled analyses, however, did not find significant differences between groups in the proportion of ulcers healed in the HBOT versus non-HBO-treated groups at six months (two trials) or 12 months (three trials). There were insufficient data to conduct pooled analyses of studies evaluating HBOT for treating patients with chronic wounds who did not have diabetes.

The primary outcome examined by Cochrane reviewers, wound healing was not reported in either of the 2 trials comparing HBOT with usual care[87, 88] or in the 1 trial comparing HBOT with dexamethasone or heparin.[89] Complete wound healing was reported in the 1 RCT comparing active HBOT with sham HBOT.[90] In this small study (n=36), there was a statistically higher rate of wound healing in the active HBOT group. The time point for outcome measurement in this study was unclear, but there was no statistically significant difference between groups in the meantime to wound healing. Adverse effects included 2 additional surgical procedures in 1 patient in the HBOT group compared with 8 in 6 patients in the sham group. The HBOT group had significantly fewer patients who developed necrotic tissue (1 and 8, respectively). There were no amputations in the HBOT group compared with 2 amputations in the sham group, but this difference did not reach statistical significance. The authors concluded that evidence remains insufficient to support the routine use of HBOT for acute surgical or traumatic wounds. They recommended further evaluation in high quality RCTs that include outcomes measures of complete wound closure and accelerated wound closure.

Randomized Controlled Trials (RCTs)

No RCTs have been published since those included in the systematic reviews summarized above.

Section Summary

Published clinical trial data is insufficient to determine the effectiveness of HBOT for wounds that are not related to diabetes. The UHMS does not include these wounds in their list of indications for HBOT, noting the lack of available evidence.[91] As shown in studies of adjunctive HBOT for treatment of severe diabetic lower extremity ulcers, this treatment is well suited to randomized, controlled comparative trials.

Wounds Related to Diabetes

Sharma (2021) conducted a systematic review and meta-analysis of 14 studies (N=768) comparing the effect of HBOT with standard care on diabetic foot ulcers.[92] Study authors noted that various modalities can be considered standard care including, but not limited to, debridement, antibiotics and blood sugar control. However, the specific standard care modality in each included study was not reported. HBOT duration ranged from 45 to 120 minutes (median 90 minutes). All included studies had methodological limitations, including selection, performance, detection, attrition and reporting bias. The review found those treated with standard care were less likely to have complete ulcer healing versus HBOT, based on pooled analysis of 11 studies (OR 0.29, 95% CI 0.14 to 0.61; I2=62%). Results were consistent when stratified according to duration of followup of less than one year (seven studies; OR 0.63, 95% CI 0.39 to 1.02; I2=1%) and at one year (four studies; OR 0.16, 95% CI 0.03 to 0.82; I2=83%), although the risk estimate wasn't statistically significant for studies with less than one year followup. A funnel plot analysis for this outcome was asymmetrical, suggesting publication bias. Risk of major amputation was also significantly lower with HBOT compared to standard care based on pooled analysis of seven studies (OR 0.60, 95% CI 0.39 to 0.92; I2=24%). There were no clear differences between groups in minor amputation (9 studies; OR 0.89, 95% CI 0.71 to 1.12) or mortality (three studies; OR 0.55, 95% CI 0.25 to 1.24). Standard care was associated with an increased risk of adverse events compared with HBOT (seven studies; OR 1.68, 95% CI 1.07 to 2.65).

In 2013, O'Reilly[93] published a systematic review of studies on HBOT for treatment of diabetic ulcers. The authors identified 6 RCTs and 6 non-RCTs that compared HBOT with standard wound care or sham therapy in patients with diabetes who had nonhealing lower-limb ulcers. Pooled analyses of observational studies found statistically significant benefits of HBOT on rates of major amputation, minor amputation and the proportion of wounds healed at the end of the study period. However, in pooled analyses of RCT data, the stronger study design, there were no statistically significant differences between groups on key outcomes. This included the rate of major amputation (RR=0.40; 95% CI, 0.07 to 2.23; p=0.29), minor amputation (RR=0.79; 95% CI, 0.19 to 3.30, p=0.75), and the proportion of unhealed wounds at the end of the study period (RR=0.54, 95% CI, 0.26 to 1.13, p=0.1).

Randomized Controlled Trials (RCTs)

No RCTs have been published since those included in the systematic reviews summarized above.

Section Summary

Published clinical trial data is insufficient to determine the effectiveness of HBOT for wounds that are not related to diabetes. The UHMS does not include these wounds in their list of indications for HBOT, noting the lack of available evidence.[91] As shown in studies of adjunctive HBOT for treatment of severe diabetic lower extremity ulcers, this treatment is well

suited to randomized, controlled comparative trials. In spite of this, only 1 small (n=16) randomized, controlled trial was found for non-diabetic wounds.[94] This trial is too small and short-term to be reliable.

Other Indications

No data from well-designed randomized, controlled clinical trials were found that supported HBOT for any other investigational indication, including but not limited to refractory mycoses and acute peripheral arterial insufficiency.

For the indications listed below, insufficient evidence to support the use of HBOT was identified. Since 2000, there have been no published controlled trials or large case series (i.e., ≥ 25 patients):

- bone grafts;
- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- pseudomembranous colitis (antimicrobial agent-induced colitis);
- radiation myelitis;
- sickle cell crisis and/or hematuria;
- amyotrophic lateral sclerosis;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- pyoderma gangrenosum;
- tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy;

SUMMARY OF EVIDENCE

There is sufficient published evidence to determine that use of hyperbaric oxygen therapy (HBOT) in selected patients with nonhealing diabetic wounds of the lower extremities, acute traumatic ischemia, soft-tissue radiation necrosis (eg, radiation enteritis, cystitis, proctitis), osteoradionecrosis (ie, pre- and posttreatment) for patients undergoing dental surgery (non-implant-related) of an irradiated jaw, gas gangrene, idiopathic sudden sensorineural hearing loss, and profound anemia with exceptional blood loss when blood transfusion is impossible or must be delayed improves the net health outcome. There is insufficient evidence for patients all other indications included in the Rationale section that HBOT improves the net health outcome.

PRACTICE GUIDELINE SUMMARY

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

In 2013, the FDA published a position statement with a warning that HBOT has not been proven safe and effective for uses not cleared by the agency.[1] This statement was developed due to numerous complaints from consumers and health care professionals that unproven claims made by some HBOT centers may mislead consumers and ultimately endanger their health. The statement included the following conditions for which patients may be unaware that safety and effectiveness of HBOT have *not* been established:

- AIDS/HIV
- Alzheimer's Disease
- Asthma
- Bell's Palsy
- Brain Injury
- Cerebral Palsy
- Depression
- Heart Disease
- Hepatitis
- Migraine
- Multiple Sclerosis
- Parkinson's Disease
- Spinal Cord Injury
- Sport's Injury
- Stroke

In 2021 the FDA provided a consumer update which includes a list of FDA cleared uses of approved hyperbaric chambers (monoplace or multiplace) for the following disorders:[95]

- Air and gas bubbles in blood vessels
- Anemia (severe anemia when blood transfusions cannot be used)
- Burns (severe and large burns treated at a specialized burn center)
- Carbon monoxide poisoning
- Crush injury
- Decompression sickness (diving risk)
- Gas gangrene
- Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
- Infection of the skin and bone (severe)
- Radiation injury
- Skin graft flap at risk of tissue death
- Vision loss (when sudden and painless in one eye due to blockage of blood flow)
- Wounds (non-healing, diabetic foot ulcers)

HBOT is being studied for other conditions, including COVID-19. However, at this time, the FDA has not cleared or authorized the use of any HBOT device to treat COVID-19 or any conditions beyond those listed above.

UNDERSEA AND HYPERBARIC MEDICAL SOCIETY (UHMS)

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published a guideline on the use of HBOT for treatment diabetic foot ulcers.[96, 97] Recommendations are as follows:

- Suggest against using HBOT in patients with Wagner Grade 2 or lower diabetic foot ulcers
- Suggest adding HBOT in patients with Wagner Grade 3 or higher diabetic foot ulcers that have now shown significant improvement after 30 days of standard of care therapy
- Suggest adding acute post-operative HBOT to the standard of care in patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had foot surgery related to their diabetic ulcers.

- Appropriate Indications for HBOT[98]

  In 2023, the UHMS updated their guidelines and included the following list of indications considered *appropriate* for hyperbaric oxygen therapy:

  - Acute thermal burn injury
  - Air or gas embolism
  - Arterial insufficiencies (central retinal artery occlusion; enhancement of healing in selected problem wounds)
  - Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning
  - Clostridial myositis and myonecrosis (gas gangrene)
  - Compromised grafts and flaps
  - Crush injury, compartment syndrome, and other acute traumatic ischemias
  - Decompression sickness
  - Delayed radiation injury (soft tissue and bony necrosis)
  - Intracranial abscess
  - Idiopathic sudden sensorineural hearing loss (ISSNHL) (patients with moderate to profound ISSNHL who present within 14 days of symptom onset)
  - Necrotizing soft tissue infections
  - Osteomyelitis (refractory)
  - Severe anemia

- Autism Spectrum Disorder (ASD)[14]

  The 2009 UHMS position paper included a critical appraisal of the available literature, in particular the 2009 Rossignol RCT[12] which was the only RCT available at that time. The paper concluded that “the UHMS cannot recommend the routine treatment of ASD with HBO_2T outside appropriate comparative research protocols.”

- Chronic Brain Injury[99]

  The most recent UHMS position statement on chronic brain injury (e.g., traumatic brain injury, cerebral palsy, stroke) is from 2003. The statement considered the evidence to be insufficient to support a recommendation for HBOT for the chronic sequelae of traumatic or non-traumatic brain injury but noted that continued monitoring of data is warranted.

- Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)[100]

  In October 2011, the UHMS Executive Board approved ISSNHL as an additional indication. According to treatment guidelines, patients with moderate to profound ISSNHL who present within 14 days of symptom onset should be considered for HBOT treatment.

- Multiple Sclerosis[57]

A 2010 UHMS position paper reported that most RCTs have failed to show clinical benefit for HBOT therapy for multiple sclerosis. “We conclude that, while there is some case for further investigation of possible therapeutic effects in selected sub-groups of patients (well-characterized and preferably early in the disease course) and for the response to prolonged courses of HBOT, this case is not strong. At this time, the UHMS cannot recommend the routine treatment of MS with HBOT outside appropriate comparative research protocols.”

- Topical Oxygen for Chronic Wounds[101]

  A 2005 UHMS position statement reported that, “to date, mechanisms of action whereby topical oxygen might be effective have not been defined or substantiated. Conversely, cellular toxicities due to extended courses of topical oxygen have been reported, although, again these data are not conclusive, and no mechanism for toxicity has been examined scientifically...The only randomized trial for topical oxygen in diabetic foot ulcers actually showed a tendency toward impaired wound healing in the topical oxygen group. Contentions that topical oxygen is superior to hyperbaric oxygen are not proven.” Therefore, the UHMS recommends against application of topical oxygen outside a clinical trial setting, noting that topical oxygen “should be subjected to the same intense scientific scrutiny to which systemic hyperbaric oxygen has been held.”

NATIONAL BOARD OF DIVING & HYPERBARIC MEDICAL TECHNOLOGY[8]

As noted above, the current position statement concluded that “the installation and provision of in-home hyperbaric oxygen therapy is inherently unsafe and cannot be condoned.” This position is based on concern for the safety and well-being of patients as well as those people in proximity to the HBOT delivery system because in-home provision of HBOT is likely to:

1. Bypass otherwise mandatory federal, state, and local codes related to design, construction, installation, and operation of these devices; and
2. Occur without adequate physician oversight and the operational support of appropriately qualified HBOT providers.

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY (AAO-HNS)

In 2019, the American Academy of Otolaryngology-Head and Neck Surgery updated clinical guidelines on the treatment of sudden sensorineural hearing loss (SSNHL).[102] They give the following options regarding HBOT:

- "Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy within two weeks of onset of SSNHL."
- "Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy as salvage within 1 months of onset of SSNHL.”

The guideline provided a comprehensive list of evidence gaps and future research needs on the use of HBOT for SSNHL. These included, among others, the need for a standardized, evidence-based definition of SSNHL, the assessment of the prevalence of SSNHL, and the need for the development of standardized HBOT treatment protocols and standardized outcome assessments.

The International Society of Oral Oncology-Multinational Association for Supportive Care in Cancer (ISOO-MASCC) and American Society of Clinical Oncologists (ASCO)

In 2024 the ISOO-MASCC along with ASCO published a guideline for the Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy.[103] They include the following recommendation:

3.6. Routine use of prophylactic hyperbaric oxygen (HBO) therapy prior to dental extractions in patients who received prior head and neck radiation therapy is not recommended Evidence-based Low Weak

Qualifying statement: Prophylactic HBO may be offered to patients undergoing invasive dental procedures at site(s) where a substantial volume of mandible and/or maxilla received >50 Gy.

SUMMARY

Systemic hyperbaric oxygen therapy (HBOT) has been studied for a wide variety of clinical indications. There is enough evidence to show that systemic HBOT is safe and effective for a variety of indications. There are guidelines based on research that recommend the use of systemic HBOT for a variety of indications. Therefore, the use of systemic HBOT may be considered medically necessary when policy criteria are met.

Due to insufficient positive health outcomes for certain patients with non-healing diabetic wounds of the lower extremities, the use of hyperbaric oxygen therapy is considered not medically necessary when criteria for non-healing diabetic wounds of the lower extremities are not met.

There is not enough evidence to permit conclusions concerning the effects of systemic hyperbaric oxygen therapy (HBOT) on final health outcomes for any other indication. Therefore, the use of systemic hyperbaric oxygen therapy for all other indications is investigational.

There is not enough evidence to permit conclusions concerning the effects of topical hyperbaric and topical normobaric oxygen therapies on health outcomes. Therefore, the use of topical hyperbaric and topical normobaric oxygen therapies for any indication is investigational.

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CODES

Codes	Number	Description
CPT	99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session Note: This code is not intended for reporting systemic oxygen therapy in chambers that provide oxygen at less than hyperbaric pressure (eg, “mild hyperbaric” oxygen therapy) which should be reported using code 99199.
	99199	Unlisted special service, procedure or report
HCPCS	A4575	Topical hyperbaric oxygen chamber, disposable
	E0446	Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories NOTE: This code is intended for devices such as the TransCu 02 that deliver oxygen at normal atmospheric pressure under wound dressings; it should not be used to report topical hyperbaric oxygen therapy devices.
	E1399	Durable medical equipment, miscellaneous
	G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval

Date of Origin: *January 1996*

Regence

Medical Policy Manual Medicine, Policy No. 65

Neurofeedback

Effective: December 1, 2024

Next Review: September 2025
Last Review: October 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

Neurofeedback describes techniques for providing feedback about neuronal activity, as measured by electroencephalogram biofeedback, functional magnetic resonance imaging, or near-infrared spectroscopy, to teach patients to self-regulate brain activity. Neurofeedback may use several techniques in an attempt to normalize unusual patterns of brain function in patients with various psychiatric and central nervous system disorders.

MEDICAL POLICY CRITERIA

The use of neurofeedback as a treatment for any disorder is considered **investigational**.

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

CROSS REFERENCES

1. Biofeedback, Allied Health, Policy No. 32
2. Sphenopalatine Ganglion Block for Headache and Pain, Medicine, Policy No. 160

BACKGROUND

Behavioral (non-drug) treatments, including neurofeedback, result in both nonspecific and

specific therapeutic effects. Nonspecific effects, sometimes called placebo effects, 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 neurofeedback on health outcomes (specific effects) and properly control for nonspecific treatment effects, well-designed clinical trials with the following attributes are necessary:

- Randomization helps to achieve equal distribution of individual differences by randomly assigning patients to either neurofeedback or sham 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 placebo effects as well as for the variable natural history of the condition being treated.
- Blinding of study participants, caregivers, and investigators to the 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.
- A large study population is needed to ensure 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.

REGULATORY STATUS

Several electroencephalogram (EEG) feedback systems (EEG hardware and computer software programs) have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. For example, the BrainMaster™ 2E (BrainMaster Technologies) is "…indicated for relaxation training using alpha EEG Biofeedback. In the protocol for relaxation, BrainMaster™ provides a visual and/or auditory signal that corresponds to the patient's increase in alpha activity as an indicator of achieving a state of relaxation." Although devices used during neurofeedback may be subject to FDA regulation, the process of neurofeedback itself is a procedure, and, therefore, not subject to FDA approval. FDA product codes: HCC, GWQ.

EVIDENCE SUMMARY

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Systematic Reviews

Louthrenoo (2022) published a systematic review (SR) with meta-analysis on the potential effects of neurofeedback to improve functional outcomes in people with Attention Deficit/Hyperactivity Disorder (ADHD).[1] The review focused on randomized controlled studies of children and adolescents aged 5 to 18 years. Data from 10 studies (n=383) were included in the review. Participants received 18 to 40 sessions of neurofeedback across 3 to 25 weeks. No significant effect of neurofeedback on response inhibition, sustained attention, or working memory domains was found. Meta-regression revealed a trend-level association between

response inhibition and number of neurofeedback sessions (p=0.06). Limitations to existing data are noted as small sample sizes and lack of appropriate control.

Lee (2022) published a SR with meta-analysis focusing on theta/beta-based neurofeedback (T/B NF) training in children and adolescents aged 6 to18 with ADHD. Nineteen studies (13 RCTs and 6 non-RCTs) met selection criteria for systematic review (n=1059), 12 of which (7 RCTs and 5 non-RCTs) were included in the meta-analysis. Methodological quality of the RCTs ranged from 4 to 10 on the PEDro scale, indicating fair-to-excellent quality. Risk of bias assessment of the RCTs found four had an overall low risk of bias, seven had some concern of bias, and two had high risk of bias. Within-group effects on attention were medium at post-treatment (pooled Hedge's g=0.65) and large at follow-up (pooled Hedge's g=0.87). Between-group analyses revealed neurofeedback had a larger effect than no treatment, waitlist control, physical activities, and sham neurofeedback, however, the effect of neurofeedback was not superior to stimulant medication (Hedge's g=-0.25).

Riesco-Matias (2021) published a SR of RCTs of neurofeedback applied to children with ADHD.[2] The review included 17 trials (16 RCTs) of neurofeedback compared to active and nonactive controls in children and adolescents with a primary diagnosis of ADHD. The study designs were unblinded evaluation in 11 trials (n=674) and blinded evaluation in nine trials (n=573). RCTs were found to support the efficacy of neurofeedback to improve inattention symptoms when blinded evaluators assess symptoms. The meta-analysis also found results suggesting stimulant medication is more effective than neurofeedback. Additional RCT data are needed to evaluate symptom measurement and longer-term outcomes.

A SR published by Sampedro Baena (2021) evaluated nine RCTs comparing neurofeedback to control or other interventions in 620 children and adolescents with ADHD.[3] This was a qualitative review of trials; no pooled analysis was conducted. Comparing neurofeedback to methylphenidate (MPH) treatment, teachers reported significantly lower ADHD symptoms in the MPH group, but there were no differences between groups in parental report. Combined treatment of neurofeedback and MPH improved ADHD symptoms (p=0.01), which was more effective compared to single medication treatment in one study. Mixed outcomes were found on the superiority of neurofeedback or medication with respect to attention, hyperactivity, impulsivity, and visual attention capacity. Small trial sample size, variability in the duration of the intervention and limited longer-term outcomes are noted limitations across trials.

Lambez (2020) published a SR with meta-analysis of the effectiveness of non-pharmacological interventions for in ADHD, with a specific focus on objective cognitive outcomes.[4] A total of 18 RCTs (n=618) were included in the analyses. Interventions were categorized into neurofeedback, cognitive-behavioral therapy, cognitive training, and physical exercises. Among these interventions, physical exercises had the highest average effect size (Morris d=0.93). Across trials, a homogenous, medium to large effect size of improvement across interventions was found, with inhibition having the largest average effect size (Morris d=0.685, standardized mean difference (SMD), 0.61 [-3.77 to 4.82], I^2 (p)=0% [<0.05]). Six trials (n=203) evaluated the domain of inhibition.

A SR with meta-analysis by Van Doren (2019) sustainability of neurofeedback and control treatment effects in RCTs which included neurofeedback or control treatment in children and adolescents with ADHD.[5] The analysis included data from ten studies on neurofeedback (n=256) and nine studies with control data (n=250). Parent behavior ratings were calculated and analyzed. Within-group neurofeedback effects on inattention were of medium in size (ES)

(SMD=0.64) at post-treatment and increased to a large effect size (SMD=0.80) at follow-up (range 2 to 12 months). For hyperactivity/impulsivity, effect sizes for neurofeedback were medium at post-treatment (SMD=0.50) and follow-up (SMD=0.61). Non-active control conditions yielded small significant effects on inattention at post-treatment (SMD=0.28) but no significant effects at follow-up. Active treatments (mainly methylphenidate) had large effects for inattention (post: SMD=1.08; follow-up: SMD=1.06) and medium effects for hyperactivity/impulsivity (post: SMD=0.74; follow-up: SMD=0.67). Between-group analyses favored neurofeedback over non-active controls [inattention (post: SMD=0.38; follow-up: SMD = 0.57); hyperactivity/impulsivity (post: SMD=0.25; follow-up: SMD=0.39)] and favored active controls for inattention only at pre-post (SMD=- 0.44). The authors note limitations in existing data including challenges in blinding the intervention and limited data on longer-term follow-up.

Yan (2019) published a SR with meta-analysis comparing neurofeedback and pharmacological treatment with methylphenidate (MPH) for the treatment of ADHD.[6] The analysis included data from 18 RCTs were included (778 individuals with ADHD in the neurofeedback arm and 757 in the MPH group, respectively) with follow-up ranging from one to six months. MPH was significantly more effective than neurofeedback on ADHD core symptoms (ADHD symptoms combined: SMD=-0.578, 95% confidence interval [CI] (-1.063 to -0.092)) and on neuropsychological parameters of inattention: -0.959 (-1.711 to -0.208) and inhibition: -0.469 (-0.872 to -0.066). Study attrition, however, was significantly lower in neurofeedback than MPH (odds ratio [OR]=0.412, 0.186 to 0.913). Removing Chinese studies and non-funded studies from the analysis resulted in no differences between MPH and neurofeedback. Treatment-specific outcomes at study follow-up were mixed, with no significant difference in neuropsychological measures between groups, teachers' evaluation favoring MPH in total score and HI (Hyperactivity/Impulsivity), but parents' evaluation favoring neurofeedback. Heterogeneity in drug dosing, feedback protocols, and outcome rating scales was noted as limiting. High risk of bias was found for allocation concealment and blinding of participants/personnel in all studies.

Catalá-López (2017) published a SR comparing pharmacological, psychological and alternative medicine treatments for ADHD, one of which was neurofeedback.[7] There was lack of methodologically sound evidence to support neurofeedback and results should be interpreted cautiously. In addition, the authors stated the balance between benefits, costs, and harm should be weighed when selecting therapies for ADHD.

Cortese (2016) published a SR evaluating RCT outcomes on the efficacy of neurofeedback, for attention deficit/hyperactivity disorder.[8] 13 RCTs, with 520 participants were included. Neurofeedback was not found to be an effective treatment for ADHD.

Micoulaud-Franchi (2014) published an updated SR with meta-analysis of RCTs published through August 2014.[9] Five studies[10-14] (n=263) that compared standard neurofeedback with either a semi-active or sham neurofeedback control group in children with ADHD met inclusion criteria. Parent assessment reported significant improvement in all scores with neurofeedback compared to controls; however, the authors noted that the parents were probably not blinded to the treatment assignments. In blinded teacher assessment, significant improvement with neurofeedback compared to controls was reported only in inattention scores. No significant effect was found for overall ADHD scores or hyperactivity/impulsivity scores. The methodological strengths of this meta-analysis were noted to be the stringent inclusion criteria and the inclusion of inattention and hyperactivity/impulsivity scores in addition to overall ADHD scores. The principal limitations included the small number of studies, the small number of

subjects enrolled in the individual studies, and the heterogeneous methodological protocols between studies. The authors also noted the inclusion of studies with somewhat non-standard protocols[10, 11] such as the use by Maruizio[11] of tomographic neurofeedback that is rarely used in the clinical setting, as well as the exclusion of a study[15] that was not based on the basic learning theory used in standard neurofeedback protocol. The authors concluded that the studies included in their meta-analysis reported efficacy of neurofeedback only for the inattention dimension of ADHD and recommended additional studies in which parents and teachers are blinded to the treatment assignments.

Randomized Controlled Trials

Purper-Ouakil (2022) published the results of the NEWROFEED trial, a prospective multicenter RCT of personalized at-home neurofeedback training versus methylphenidate in children aged 7 to 13 years with ADHD.[16] The trial randomized participants from nine study sites across five European countries to the neurofeedback and methylphenidate groups in a 3:2 ratio; the neurofeedback group (n=111) underwent eight visits and two treatment phases of 16 to 20 at-home sessions and the control group (n=67) received optimally titrated long-acting methylphenidate. Data from a total of 149 participants were included in the per-protocol analysis. Reduction in the Clinician ADHD-RS-IV total score was found between baseline and final visit for both groups, with 26.7% (SMD=0.89) in the neurofeedback and 46.9% (SMD = 2.03) in the control group. Noninferiority of neurofeedback versus methylphenidate was not demonstrated (mean between-group difference 8.09 90% CI [8.09; 10.56]). Study limitations include absence of sham neurofeedback or another nonactive group and lack of mid- or long-term follow-up.

Hasslinger (2022) published the results of a multi-arm RCT in 202 children and adolescents (age 9 to 17 years) with ADHD that evaluated two neurofeedback treatments (slow cortical potential [SCP, standard neurofeedback protocol] and Live Z-score (LZS, nonstandard neurofeedback protocol) compared to working memory training (WMT, active comparator) and treatment as usual (passive comparator).[17] The active conditions (SCP/LZS/WMT) consisted of daily working week sessions (five sessions/week) during five consecutive weeks (25 sessions in total). The prespecified primary outcome measure was the self-, teacher- and parent-reported assessment of ADHD symptoms post-treatment and at six months using the Conners 3rd Edition scale. Neither neurofeedback treatment was superior to working-memory training for these outcome measures. Significant differences between SCP and treatment as usual were observed post-treatment for teacher- and parent-rated inattention, with no difference for other outcome measures at either timepoint. A statistically significant difference in Live Z-score over treatment as usual was only observed at the six-month endpoint for teacher-rated inattention and hyperactivity/impulsivity. No other differences between Live Z-score and treatment as usual were observed. Secondary outcomes in this study included measures of teacher- and parent-rated executive function and self-assessed health-related quality of life using the Behavior Rating of Executive Functions (BRIEF) and KIDSCREEN-27 scales, respectively. There were no consistent differences between neurofeedback interventions and control interventions for these outcomes except for teacher-assessed executive function at six months follow-up, which found both neurofeedback interventions superior to working-memory training and treatment as usual. Limitations in the study include lack of blinding of parents of, presence of missing data, limited measures of functioning and impairment, and patients being drawn from a single site.

Arnold (2021) published the 13-month outcomes of a two-site double-blind RCT in 144 children with moderate to severe ADHD randomized to neurofeedback and sham control.[18] Both groups showed significant improvement (p<0.001, d=1.5) in parent/teacher-rated inattention from baseline to treatment end and 13-month follow-up and neurofeedback was not significantly superior to the control condition at either time point on this primary outcome (d=0.01, p=0.965 at treatment end; d=0.23, p=0.412 at 13-month follow-up). No significant difference in responder rate, defined as Clinical Global Impression-Improvement [CGI-I] = 1-2 was found between groups. At 13-month follow-up, a nonsignificant improvement from treatment end for was found for neurofeedback (d 0.1) and a mild deterioration was found for controls (d=-0.07). Neurofeedback participants required significantly less medication at follow-up (p=0.012). Longer-term (25-month) follow-up data are anticipated.

Aggensteiner (2019) published the six-month outcomes of a multisite RCT of slow cortical potential (SCP)-neurofeedback or electromyogram biofeedback (EMG-BF) in the treatment of ADHD in 144 children age 7 to 9.[19] Participants were not blinded to study condition. Both groups showed improvement of ADHD symptoms compared to baseline at six-months follow-up with large effect sizes for SCP-NF (d=1.04) and EMG-BF (d=0.85). No between-group differences were found. A group-by-time interaction was found with SCP-NF showing stable improvement following treatment up to six months, but EMG-BF showing a relapse from post-test timepoint one to post-test timepoint two, and subsequent remission at follow-up (p<0.05). Power estimates were not reported.

Lim (2019) published a RCT of 172 participants age 6 to 12 years old diagnosed with ADHD not receiving concurrent pharmacotherapy or behavioral intervention from a single site in Singapore.[20] The participants were randomized to eight weeks of neurofeedback attention training or untreated waitlist control for eight weeks followed by neurofeedback attention training for 20 weeks. Modified intention to treat analyzes conducted on 163 participants with at least one follow-up rating. At eight weeks, clinician-rated inattentive symptoms (ADHD-Rating Scale. ADHD-RS) was reduced by 3.5 (SD 3.97) in the intervention group compared to 1.9 (SD 4.42) in the waitlist-control group, which was a difference of 1.6; 95% CI 0.3 to 2.9 p=0.018). Patients, parents, and investigators were unblinded.

Lee and Jung (2017) published a small RCT that compared neurofeedback with medication to medication alone in 36 children 6 to12 years of age, with ADHD.[21] Neurofeedback consisted of 20 sessions. Outcome measures (cognitive performance scores, ADHD rating scores completed by parents, and brain indices) pre- post-treatment occurred. Neurofeedback patients had improved symptom variables and reduced theta waves, but no additional intelligent functioning when compared to patients on medication management alone. Although the authors stated neurofeedback can be considered a possible effective treatment option for ADHD, this study was limited in size. Larger RCTs, with longer follow-up times are needed.

In addition to the initial report from the RCT by Steiner[12] included in the meta-analyses above, a secondary analysis[22] was also reported. This article was excluded from the meta-analysis in order to ensure that patients were not included more than once. In this RCT,104 children with ADHD age 7 to 11 years were randomized to receive neurofeedback, cognitive training, or a no-intervention control condition in their elementary school. Both the neurofeedback and cognitive therapies were administered with commercially available computer programs (45-min sessions three times per week), monitored by a trained research assistant. The neurofeedback EEG sensor was embedded in a standard bicycle helmet with the grounding and reference sensors located on the chin straps on the mastoids. No data was presented on the technical

performance of this system. There were some differences in baseline measures between the groups, although these differences were not large. The slope of the change in scores over time was compared between groups. Children in the neurofeedback group showed a small improvement on the Conners 3-Parent Assessment Report (effect size [ES] = 0.34 for inattention, ES=0.25 for executive functioning, ES = 0.23 for hyperactivity/impulsivity) and subscales of the Behavior Rating Inventory of Executive Function Parent Form (BRIEF global executive composite, ES=0.23) when compared with baseline. Interpretation of these findings is limited by the use of a no-intervention control group and lack of parental blinding. Evaluator-blinded classroom observation (Behavioral Observation of Students in Schools) found no sustained change with a linear growth model but a significant improvement with a quadratic model. No between-group difference in change in medication was observed at the six-month follow-up.

In 2012, Duric reported a comparative study of neurofeedback versus methylphenidate in 91 children with ADHD.[23] The children were randomized into three groups, consisting of 30 sessions of neurofeedback, methylphenidate, or a combination of neurofeedback and methylphenidate. The neurofeedback sessions focused on the theta/beta ratio. Parental evaluations found improvements in ADHD core symptoms for all three groups, with no significant differences between groups. Alternative reasons for improvement with neurofeedback include the amount of time spent with the therapist and cognitive-behavioral training introduced under neurofeedback. In a 2014 publication of self-reports from this study, there was no improvement in attention, hyperactivity, or school achievement when adjusted for age and sex.[24] Only the neurofeedback group showed a significant improvement in self-reported school performance.

Nonrandomized Studies

Additional studies have compared neurofeedback to medication (stimulant) and/or behavioral therapy in patients with ADHD.[25-27] In these nonrandomized studies, patients in both groups reported improvements in various measures of attention; however, nonrandomized studies limit the ability to reach scientific conclusions concerning the efficacy of neurofeedback in the treatment of AD/HD due to the lack of design attributes described above.

Section Summary

Several systematic reviews and meta-analyses as well as additional moderately sized RCTs have compared neurofeedback with methylphenidate, biofeedback, cognitive behavioral therapy, cognitive training, or physical activity These studies found either small to moderate or no benefit of neurofeedback and sustained long-term benefit has not been consistently demonstrated. Studies using active controls have suggested that at least part of the effect of neurofeedback might be due to attention skills training, biofeedback, relaxation training, and/or other nonspecific effects. Two of the RCTs indicated that any beneficial effects were more likely to be reported by evaluators unblinded to treatment (parents), than by evaluators blinded (teachers) to treatment, which would suggest bias in the nonblinded evaluations. Moreover, a meta-analysis found no effect of neurofeedback on objective measures of attention and inhibition. Additional research with blinded evaluation of outcomes is needed to demonstrate the effect of neurofeedback on ADHD.

AUTISM SPECTRUM DISORDER

Systematic Reviews

Vasa (2014) published a SR that included studies of the safety and effectiveness of psychopharmacological and non-psychopharmacological treatments, including NF, for anxiety in children with autism spectrum disorder (ASD).[28] While neurofeedback showed a possible benefit, studies were small and short-term; outcomes must be verified in large RCTs with adequate blinding and appropriate controls.

Frye (2013) conducted a SR on the treatment of seizures in patients with autism spectrum disorder.[29] Studies were selected systematically from major electronic databases and then reviewed by a panel of ASD treatment experts. Authors concluded there was limited evidence to support the use of neurofeedback in patients with seizures associated with ASD.

In a 2009 single-author SR of novel and emerging treatments for ASD, neurofeedback received a grade C recommendation (Grade C recommendation: supported by one nonrandomized controlled trial).[30] The author reviewed literature in the PubMed and Google Scholar databases for clinical trial reports on numerous biological (e.g., nutritional supplements, special diets, medications) and nonbiological (e.g., neurofeedback, massage) treatments. Due to the extensive amount of literature, a critical analysis of the quality of the studies was not included. The study referenced for neurofeedback was a nonrandomized pilot study that included 12 children with ASD who received neurofeedback and an untreated control group of 12 children who were matched by sex, age, and disorder severity.[31] The study found a greater reduction in ASD symptoms based on the Autism Treatment Evaluation Checklists (A TEC) and parental assessments in the group treated with neurofeedback compared with the control group. While this trial is useful in informing hypothesis formation, it does not permit conclusions on efficacy due to the lack of randomized treatment allocation, small patient population, lack of a sham control group, and short-term follow-up period. Randomized sham-controlled trials in larger numbers of patients are required to validate these findings due to the possibility of nonspecific effects (e.g., attention training) and confounding variables (e.g., parental engagement and expectation).

Randomized Controlled Trials

Kouijzer (2013) performed a small RCT to evaluate the effects of EEG-neurofeedback in ASD.[32] Thirty-eight participants were randomly allocated to the EEG-biofeedback (n=13), skin conductance (SC)-biofeedback (n=12) or waiting list (sham control) group (n=13). At six months follow up, 54% of the patients in the EEG-biofeedback group were able to influence their own EEG activity, with significantly reduced delta and/or theta power during EEG-biofeedback sessions. However, within this group no statistically significant reductions of symptoms of ASD were observed, but they did show significant improvement in cognitive flexibility as compared to participants who managed to regulate SC. Overall, the EEG- and SC-biofeedback groups, regardless of whether they could regulate their own activity, showed no improvement in clinical symptoms of ASD.

COGNITIVE PERFORMANCE

Systematic Reviews

Renton (2017) published a SR evaluating the impact of neurofeedback therapy on cognitive rehabilitation for stroke patients.[33] Eight studies met inclusion criteria. The authors stated although cognitive benefits were found with neurofeedback, the studies had methodological limitations. Additional studies should attempt to standardize neurofeedback protocols, so that the relationship between neurofeedback and improved health outcomes can be understood.

Emmert (2016) published a review evaluating twelve studies that examined nine different target regions in the brain, for 175 subjects.[34] The studies showed real-time functional magnetic resonance imaging (fMRI) activates regions of the regulation network in the brain, but the authors stated it was unclear why and could have been related to successful regulation versus the regulation process. More studies are needed to determine if neurofeedback can impact the regulation network.

Randomized Controlled Trials

In a three arm, assessor-blinded RCT, Chen (2023) tested the effects of low-resolution tomography Z-score neurofeedback and theta/beta neurofeedback on cognitive impairment, return to productive activity, and quality of life in patients with traumatic brain injury.[35] Patients 20 to 65 years old received weekly one hour training sessions of six pre-designed animated games, ten minutes each, with a five to ten minute break between games. Training sessions occurred over 10-weeks. Participants were randomized to receive low-resolution tomography Z-score neurofeedback (n=29), theta/beta neurofeedback (n=31), or standard care for traumatic brain injury (n=27). Cognitive performance was assessed using the Ruff2 and 7 Test, Rey Complex Figure Test, and the Symbol Digit Modalities Test. The low-resolution Z-score neurofeedback group exhibited significantly greater improvements in immediate recall, delayed recall, recognition memory, and selective attention compared to the control group, while the theta/beta group exhibited improvements in immediate memory and selective attention only ($p<0.05$). This study is limited by lack of participant blinding, lack of a sham or placebo group and small sample size.

De Ruiter (2016) published a double-blinded placebo-controlled RCT that evaluated the impact of neurofeedback on neurocognitive function, for pediatric brain tumor survivors (PBTS).[36] Patients age 8 to 18 years old were given 30 sessions (two/week) of neurofeedback (n=40) or placebo feedback (n=40). An assessment was performed six months after the sessions ended. The authors stated neither neurofeedback nor placebo feedback was superior.

One small (n=6) quasi-randomized, double-blind pilot study was identified that examined whether increasing peak alpha frequency would improve cognitive performance in older adults (70 to 78 years of age).[37] Control subjects were trained to increase alpha amplitude or shown playback of one of the experimental subject's sessions. Compared to controls, the experimental group showed improvements in speed of processing for two of three cognitive tasks (Stroop, Go/No-Go) and executive function in two tasks (Go/No-Go, n-back); other functional measures, such as memory, were decreased relative to controls.

EPILEPSY

Systematic Reviews

Tan (2009) published a SR that identified 63 studies on neurofeedback for treatment of epilepsy.[38] Ten of the 63 studies met inclusion criteria; nine of these studies included fewer than 10 subjects. The studies were published between 1974 and 2001 and utilized a pre-post design in patients with epilepsy refractory to medical treatment; only one controlled study was included. The meta-analysis showed a small effect size for treatment (-0.233), with a likelihood of publication bias based on funnel plot. Randomized placebo-controlled trials are needed to evaluate the effect of neurofeedback on seizure frequency in patients with epilepsy.

Randomized Controlled Trials

A RCT by Morales-Quezada (2019) randomized 44 children with focal epilepsy to sensorimotor rhythm (SMR) neurofeedback (n=15), slow cortical potentials (SCP) neurofeedback (n=16), or sham neurofeedback (n=13) for 25 sessions over five weeks.[39] Outcomes including the attention switching task (AST), Liverpool Seizure Severity Scale (LSSS), seizure frequency (SF), EEG power spectrum, and coherence were measured at baseline, postintervention, and at three-month follow-up. At the end of the intervention period, only the sensorimotor rhythm neurofeedback group demonstrated significant improvement in the activity switching task and all groups demonstrated significant improvements in quality of life ($p<0.05$).

FIBROMYALGIA

Systematic Reviews

In 2015 a Cochrane SR evaluated therapies for fibromyalgia, identifying five RCTs on biofeedback, including the Kayiran study described below, as well as four studies published prior to 2010.[40] There were two studies, both ranked with very low quality of evidence, which compared biofeedback versus usual care.[41] Neither of these studies found significant advantage of using biofeedback versus usual care for any of the major outcomes assessed, including self-reported physical functioning, pain, mood and overall quality of life. Both studies only assessed outcomes post-intervention, and only one reported three-month follow-up. No long-term follow-up was reported. There only one study, ranked with very low quality of evidence, which compared biofeedback versus attention control.[42] Although this study found significant differences between groups in terms of self-reported functioning and pain, the sample size was small (n=30) for each outcome, and the outcomes were only assessed post-intervention (no three- and six-month follow-up was reported). Overall, the review concluded that no advantage was observed for biofeedback in comparison to usual care controls and no studies reported any adverse events, however the quality of the evidence was so low that it is uncertain if there is any effect or not.

Randomized Controlled Trials

Kayiran (2010) reported a randomized single blind study of neurofeedback versus escitalopram in 40 patients with fibromyalgia.[43] Patients in the neurofeedback group were instructed to widen a river on a computer monitor which corresponded to increasing sensory motor activity and decreasing theta activity. Patients received five sessions per week for four weeks. The control group received escitalopram for eight weeks. Outcome measures at baseline and at weeks two, four, eight, 16, and 24 included visual analog scale (VAS) for pain, Hamilton and Beck Depression and Anxiety Inventory Scales, Fibromyalgia Impact Questionnaire and Short Form-36. Mean amplitudes of EEG rhythms and the theta/sensory motor rhythms were also measured in the neurofeedback group. At baseline, the control group scored higher on the Hamilton and Beck Anxiety Scales and the Hamilton Depression Scale; all other baseline measures were similar between groups. Both groups showed improvements over time, with significantly better results in the neurofeedback group. There were no changes over time in mean amplitudes of EEG rhythms and essentially no change in the theta/sensory motor rhythm ratio (reduced only at week four). This study is limited by the difference in intensity of treatment and contact with investigators between the neurofeedback and escitalopram groups. As previously noted, sham-controlled trials are needed when assessing the effect of neurofeedback on subjective outcome measures.

FOOD CRAVING OR BINGE EATING

Systematic Reviews

No SRs have been identified using neurofeedback for food craving.

Randomized Controlled Trials

Hilbert (2024) published a single-center assessor-blinded feasibility RCT of neurofeedback for the treatment of binge-eating disorder.[44] The study included 72 patients who were randomly assigned to receive either functional near-infrared spectroscopy-based real-time neurofeedback (rtfNIRS-NF), high-beta electroencephalography-based NF (EEG-NF), or waitlist (WL). The results showed that NF was feasible in terms of recruitment, attrition, adherence, compliance, acceptance, and assessment completion. However, the study found no significant difference in binge-eating frequency between the NF and WL groups post-treatment. The study showed that neurofeedback was superior to the waitlist control group in reducing food craving, anxiety symptoms, and body mass index, but the overall effects were mostly small, and brain activity changes were near zero. The authors concluded that while neurofeedback may be a feasible treatment for binge-eating disorder, additional studies with a double-blind randomized design long-term follow-up are needed to assess neurofeedback for the treatment of binge-eating disorder.

Blume (2022) published a RCT that evaluated efficacy of two EEG neurofeedback paradigms in the reduction of binge eating.[45] Participants were 18 to 60 years old and had full syndrome binge eating disorder or binge eating disorder of low frequency and/or limited duration, and body mass index greater than or equal to 25. Participants were randomized to either food cue-specific (n=20) or control, general neurofeedback (n=19) training and received 10, 1 hour EEG neurofeedback sessions. Sessions occurred approximately two times per week in the first four weeks and once per week during weeks five and six. Participants were assessed at each session by a trained psychologist using the Eating Disorder Examination interview and a series of questionnaires to assess eating disorder and determine the number of objective binge-eating episodes. A significant reduction in binge-eating episodes was observed in both groups posttreatment, and there was no significant difference in the magnitude of reduction between the two groups. This study is limited by small sample size, short-term outcomes, and lack of blinding.

Imperatori (2017) evaluated how EEG power spectra associated with alpha/theta (A/T) training reduces food craving.[46] 50 participants were randomly assigned to receive 10 sessions of either EEG power spectra associated with A/T training [neurofeedback group (NFG)] or to a control group. All participants were administered the same questionnaires, at the end of 10 sessions. The NFG showed a statistically significant reduction in desire to consume food, up to four months post-treatment. Although A/T training appeared to positively affect areas of the brain associated with food desires, the remaining study data was self-reported. Therefore, additional RCTs are needed to evaluate objective long-term outcomes.

Schmidt (2016) published a small RCT evaluating the efficacy of neurofeedback on female binge eating.[47] 75 subclinical threshold participants were assigned to EEG neurofeedback, mental imagery, or a waitlist group. The EEG neurofeedback group was the only one that had reduced binge eating, at a three-month follow-up. The authors stated EEG neurofeedback should be tested as a potential treatment option for binge eating.

MEDICATION OVERUSE HEADACHES

Systematic Reviews

No SRs have been identified using neurofeedback for medication overuse headaches.

Randomized Controlled Trials

Rausa (2016) evaluated the effectiveness of electromyographic (EMG) biofeedback, for medication overuse headache (MOH).[48] Twenty-seven participants were randomly assigned to receive EMG biofeedback with prophylactic pharmacological therapy (n=15) or to a control group that received pharmacological treatment alone (n=12). At the end nine weekly sessions and at four months post-study, participants who received EMG biofeedback had longer symptom free periods and statistically significant improved outcomes, but as the authors noted, additional larger RCTs are needed to validate these findings and determine the long-term effects.

MAJOR DEPRESSIVE DISORDER

Systematic Reviews

González Méndez (2022) conducted a SR and meta-analysis of the effect of real-time fMRI neurofeedback (rtfMRI-NF) on symptom reduction in patients with clinical depression.[49] 11 reports on four RCTs including journal articles, pre-print articles, trial registries, and poster and conference abstracts were analyzed. Most sources reported positive effects of rtfMRI-NF on depression symptoms, but the authors' meta-analysis yielded a non-significant effect immediately after neurofeedback treatments (SMD: -0.32 [95% CI -0.73 to 0.10]) and at follow-up (SMD: -0.33 [95% CI -0.91 to 1.25]). The authors concluded that effects of rtfMRI-NF training on depression symptoms are based on low certainty evidence and that more studies are necessary to evaluate quality of life, acceptability, adverse effects, cognitive tasks, and physiology measures.

Trambaiolli (2021) published a SR of neurofeedback studies employing electroencephalography or functional magnetic resonance-based protocols in patients with major depressive disorder (MDD).[50] There were 24 studies included in the review (n=480 patients in experimental and n=194 in the control groups). While symptom improvements were found in the experimental group compared to control, the authors note that study quality and reporting practices were not stringent. High-quality studies that are adequately powered and appropriately controlled are needed to determine the impact of the technology on health outcomes for people with major depressive disorder.

Randomized Controlled Trials

Young (2017) evaluated the impact rtfMRI-NF had on amygdala hemodynamic response, which the authors stated is blunted in patients with depression.[51] In a small double-blinded, placebo-controlled RCT, unmedicated adults received either two sessions of rtfMRI-NF from the amygdala (n=19) or from a parietal control region (n=17). Clinical scores and autobiographical memory performance evaluations took place at baseline and one week after the last rtfMRI-NF session. No additional follow-up was found. Even though the authors stated rtfMRI-NF increases the amygdala response to positive memories and that data suggests amygdala may play a role in depression recovery, this study was limited in size and larger RCTs with longer follow-up timeframes are needed.

MIGRAINE HEADACHES

Systematic Reviews

Miro (2016) performed a SR to evaluate the efficacy of neurofeedback, meditation, and hypnosis for chronic pain in young participants.[52] Only one RCT and one case series were evaluated for neurofeedback. The additional articles evaluated meditation (n=5) and hypnosis (n=8). Participants for neurofeedback ranged from 9 to 21 years of age. The authors concluded that the neurofeedback RCT showed no statistically significant differences in migraine intensity or treatment regime, for those receiving neurofeedback. The study had methodological limitations limiting the conclusions that can be drawn.

Randomized Controlled Trials

Walker reported quantitative EEG (QEEG) for the treatment of migraine headaches in a RCT of 46 patients.[53] Results were compared with 25 patients who chose not to do neurofeedback and continued anti-migraine drug therapy. Since baseline QEEG assessment in all 71 patients showed a greater amount of the high frequency beta band (21 to 30 Hz), the five neurofeedback sessions focused on increasing 10 Hz activity and decreasing 21 to 30 Hz targeted individually to brain areas where high frequency beta was abnormally increased. Patient diaries of headache frequency showed a reduction in migraines in a majority of patients in the QEEG group but not the drug therapy group. Fifty-four percent of the QEEG group reported complete cessation of migraines over one year, with an additional 39% reporting a greater than 50% reduction. In comparison, no patients in the drug therapy group reported a cessation of headaches, and 8% had a reduction in headache frequency of greater than 50%. Limitations of this study include the patient self-report of headache status through diary logs which may not be the most reliable measure of symptom improvement. Randomized sham-controlled trials are needed to adequately evaluate this treatment approach.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Systematic Reviews

No SRs have been identified using neurofeedback for OCD.

Randomized Controlled Trials

Deng (2014) reported the outcomes of a randomized comparison of sertraline and weekly cognitive behavioral therapy with (n=40) versus without (n=39) NF.[54] Treatment was considered effective after eight weeks of therapy in 86.5% and 62.9% of participants, respectively (p=0.021). The authors concluded additional studies are needed to determine the long-term effects of neurofeedback for OCD including the need for booster sessions after the initial training period.

Koprivova (2013) reported a double-blind randomized sham-controlled trial of independent component neurofeedback in 20 patients with obsessive-compulsive disorder.[55] Independent component neurofeedback is based on the individual diagnosis of pathological EEG sources and was directed at down-training of abnormally high activity. All patients were hospitalized and participated in a six-week standard treatment program that included cognitive-behavioral therapy and 25 neurofeedback or sham biofeedback sessions. The neurofeedback group showed greater reduction of compulsions compared to the sham group (56% vs. 21%). However, clinical improvement was not associated with a change in EEG. Larger, long-term RCTs are needed in order to assess the efficacy of neurofeedback treatment on patients with OCD.

POST TRAUMATIC STRESS DISORDER

Systematic Reviews

Voigt (2024) published a systematic review and meta-analysis of 17 RCTs of adults, adolescents, and children (n=628, ages 10 to 77) with PTSD treated with neurofeedback.[56] Three RCTs compared neurofeedback with yoked feedback, four compared neurofeedback to a waitlist control group that received neurofeedback after the trial, five RCTs compared neurofeedback to standard of care, two RCTs compared neurofeedback to no treatment, and one RCT compared neurofeedback to biofeedback, one RCT compared neurofeedback with relaxation, and one RCT compared neurofeedback to a sham control. Treatment duration ranged from 3 to 20 weeks. 10 studies were included in the meta-analysis. The meta-analysis found significant reductions in PTSD symptoms using various health instruments, including the Beck Depression Inventory (BDI), Clinician-Administered PTSD Scale (CAPS-5), and PTSD Checklist (PCL-5). The effect size of neurofeedback was found to be clinically meaningful, with an increased effect size at follow-up. Study quality was rated as moderate to high quality evidence. Limitations of this review include small sample size of included studies, heterogeneity among study designs and outcome measures, and many studies included short follow-up times.

Hong (2022) conducted a systematic review and meta-analysis of seven RCTs of adults with post-traumatic stress disorder (PTSD) treated with neurofeedback.[57] Three studies used fMRI-based neurofeedback, and four studies used EEG-based neurofeedback. Pooled analysis of studies demonstrated a significant improvement in PTSD symptoms with neurofeedback compared to sham neurofeedback, no treatment, or other treatment. When analyzed by type of neurofeedback, EEG-based neurofeedback significantly improved PTSD symptoms, but fMRI-based neurofeedback did not. Five studies assessed anxiety and depression with various validated scales. Overall, there was no significant impact on anxiety and depression with neurofeedback compared to control groups. Two studies demonstrated a high risk of performance or detection bias, while all other studies demonstrated overall low risk of bias.

A meta-analysis by Steingrimsson (2020) evaluated four RCTs of 123 adults with PTSD treated with neurofeedback.[58] Follow-up ranged from four weeks to 30 months. Compared with sham neurofeedback, no treatment or other treatment, neurofeedback was associated with significant improvement in PTSD symptoms. Other primary outcomes were only reported in one trial each, and the authors conclude there is uncertainty regarding the ability of neurofeedback to improve PTSD symptoms, self-rated suicidality, executive cognitive functioning, or medication use. All studies were at moderate to high risk for bias and were assessed as having some indirectness and imprecision.

Reiter (2016) published a SR that evaluated five studies to determine neurofeedback's effectiveness and which protocol is preferred for patients with PTSD.[59] Neurobiological changes were noted in three of the studies. However, the authors stated that even though there differences and methodological limitations amongst the studies, neurofeedback may be an effective treatment for PTSD.

Randomized Controlled Trials

Zhao (2023) evaluated the efficacy of real-time fMRI neurofeedback to control amygdala activity following trauma recall in a double-blind RCT.[60] Twenty-five participants with PTSD

completed three sessions of neurofeedback training in which they attempted to downregulate the feedback signal after exposure to personalized trauma scripts. The active treatment group received the feedback signal from a functionally localized region of the amygdala associated with trauma recall (n=14). The control group received yoked-sham feedback recorded from a matched participant in the active treatment group (n=11). Participants were instructed to try different mental regulation strategies to control feedback signals. Activity in the amygdala region of interest was measured by fMRI before neurofeedback training sessions, immediately after training sessions, and 30 days after training sessions. In each session, participants completed four amygdala neurofeedback control tasks while listening to audio clips related to a specific traumatic event. There was no significant difference in amygdala activity control between the two treatment groups immediately after the neurofeedback training sessions. At 30-day follow-up, the active treatment group experienced a greater reduction in amygdala activity compared to the control group (p=0.047). PTSD symptoms were measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Both treatment groups showed improvements in PTSD symptom scores. The active treatment group did not experience a significantly greater decrease in symptoms compared to the sham-neurofeedback control group. This study is limited by small sample size and heterogeneity in activity regulation strategies.

Van der Kolk (2016) evaluated neurofeedback and its effects on PTSD symptoms.[61] Fifty-two participants with chronic PTSD were randomly assigned to receive neurofeedback for 12 weeks or to a control group. Psychological and behavioral functioning were evaluated at baseline, six weeks, 12 weeks, and 16 weeks. The authors stated PTSD symptoms improved in individuals who received neurofeedback but concluded more long-term sham-controlled studies are needed.

PRIMARY INSOMNIA

Systematic Review

A systematic review by Melo (2019) of biofeedback techniques such as neurofeedback in adults with chronic insomnia included seven RCTs (N=244).[62] Conflicting results were found in comparisons of neurofeedback with other cognitive behavioral therapy techniques, placebo, and no treatment; a majority of outcomes demonstrated no significant differences between comparison groups. A majority of studies had high risk of bias related to blinding of participants and study personnel and incomplete outcome data. The authors conclude higher quality RCTs are needed to assess the effectiveness of biofeedback on chronic insomnia treatment.

Randomized Controlled Trials

Schabus (2017) published a double-blinded placebo-controlled study evaluating the efficacy of sensorimotor rhythm neurofeedback on sleep quality and memory.[63] Patients spent nine nights in the laboratory and received 12 sessions of neurofeedback and 12 sessions of placebo-feedback training (sham). The authors stated they did not find neurofeedback to be more effective than cognitive behavioral therapy.

Cortoos (2010) published a small (n=17) RCT on the effect of neurofeedback training or biofeedback training (placebo control) on objective and subjective sleep in patients with primary insomnia.[64] Of 158 subjects with sleep complaints who were interested in participating, 131 (89%) were excluded due to study criteria or unwillingness to remain medication free during the study period. Following polysomnograph (PSG) recorded sleep in

the laboratory, all subjects received 20 sessions of therapist-controlled telefeedback training at home over a period of eight weeks. The neurofeedback group was trained to increase the sensory-motor rhythm (12-15 Hz) and inhibit theta power (4-8 Hz) and high beta power (20-30 Hz). The biofeedback group was trained to decrease electromyographic (EMG) activity, which was equated with the reinforcement of relaxation (placebo control). Both treatments reduced sleep latency by 40% to 45% (22 minutes at baseline) on post-treatment PSG, measured two weeks after the end of training. Neurofeedback training reduced wake after sleep onset (54% vs. 13% decrease, respectively; however, no interaction was found on the two-way ANOVA) and increased total sleep time (40 minutes vs. less than 5 minutes, respectively, $p<0.05$). This study is limited by the small number of subjects, differences in sleep parameters at baseline, and short follow-up. Additional studies are needed to evaluate this novel treatment approach.

SUBSTANCE USE DISORDER

Systematic Reviews

A 2008 SR of neurofeedback as a treatment for substance abuse disorders described difficulties in assessing the efficacy of this and other substance abuse treatments, including the lack of clearly established outcome measures, differing effects of the various drugs, presence of comorbid conditions, absence of a gold standard treatment, and use as an add-on to other behavioral treatment regimens.[65] The authors concluded that alpha-theta training, when combined with an inpatient rehabilitation program for alcohol dependency or stimulant abuse, would be classified as level three or “probably efficacious.” This level is based on beneficial effects shown in multiple observational studies, clinical studies, wait-list control studies, or within-subject or between-subject replication studies. The authors also noted that few large-scale studies of neurofeedback in addictive disorders have been reported, and a shortcoming of the evidence for alpha-theta training is that it has not been shown to be superior to sham treatment.

Randomized Controlled Trials

Faridi (2022) published the results of a RCT that assessed efficacy of Low-Resolution Brain Electromagnetic Tomography (LORETA) Z Score Neurofeedback (LZNFB) compared to cognitive rehabilitation therapy combined with methadone maintenance treatment in reducing craving in patients with opioid use disorder.[66] Thirty male patients, 20 to 60 years old, with opioid use disorder, undergoing methadone maintenance treatment, were randomized to three groups: LZNFB (20 sessions) with methadone maintenance treatment (n=10), cognitive rehabilitation (15 sessions) with methadone maintenance treatment (n=10), and methadone maintenance treatment alone (n=10). At a one-month follow-up, multiple questionnaires were used to assess opioid cravings—The Leeds Dependence Questionnaire, Desire for Drug Questionnaire, the Obsessive-Compulsive Drug Use Scale question, and the recovery assessment scale, as well as the visual probe cognitive test. Based on questionnaire assessments, the LZNFB group and the cognitive rehabilitation group accomplished a greater reduction in opioid craving compared to the methadone maintenance treatment control group ($p<0.05$). The cognitive rehabilitation group experienced greater improvement in attentional bias towards opioid cues than the LZNFB group ($p=0.002$). Study limitations include small sample size, lack of blinding, and lack of sham or placebo groups to control for therapist intervention and neurofeedback technology.

Gabrielsen (2022) published the results of a RCT evaluating infralow neurofeedback (ILF-NF) in the treatment of substance use disorder.[67] Ninety-three patients age 19 to 66 years (mean

± SD 38 ± 11.7 years) with substance use disorder were recruited from an outpatient unit and randomized to receive 20 sessions (30 minutes each) of ILF-NF training combined with treatment as usual (TAU) or TAU alone. TAU consisted of cognitive behavioral techniques, psychosocial approaches, and motivational interviews. The primary study outcome was determined *a priori* to be quality of life as assessed by the QoL-5 instrument. Independent-sample t tests showed no significant difference between groups for the primary outcome measure (p=0.28).

TOURETTE SYNDROME

Systematic Reviews

In 2011, the working group of the European Society for the Study of Tourette Syndrome conducted a SR of behavioral and psychosocial interventions for Tourette syndrome and other tic disorders.[68] There were no randomized or comparative studies on neurofeedback for Tourette syndrome; the literature was limited to two case series.

Randomized Controlled Trials

Since the SR, no RCTs for neurofeedback for this indication have been published.

OTHER CONDITIONS

Literature searches have identified small studies (e.g., case reports, case series, comparative cohorts, RCTs) of neurofeedback for the following conditions:

- Aging-associated cognitive decline[69]
- Anxiety and panic disorders[70]
- Asperger syndrome[70]
- Childhood obesity[71]
- Cigarette cravings[72]
- Chronic pain[73]
- Depression (on its own, or in patients with multiple sclerosis or alcohol addiction)[70, 74, 75]
- Dissociative identity disorder[70]
- Fecal incontinence[76]
- Menopausal symptoms
- Parkinson's Disease[77-79]
- Primary headache[80]
- Schizophrenia[70, 81]
- Stress management and relaxation[82]
- Stroke[83, 84]
- Traumatic brain injury (TBI)[85]
- Tinnitus[86]
- Urinary incontinence[87]

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS (AAP)

The AAP's 2011 clinical practice guidelines on the diagnosis and treatment of ADHD did not include neurofeedback in the treatment recommendations.[88] EEG biofeedback was included

on the list of areas for future research. The AAP (2019) published an evidence-based guideline update to the 2011 guideline for the treatment of ADHD in children and adolescents.[89] The guideline states that EEG biofeedback is one of several nonmedication treatments that have either too little evidence to support their recommendation or have little or no benefit.

AMERICAN PSYCHIATRIC ASSOCIATION (APA)

Neurofeedback is not recommended in APA practice guidelines on treatment of substance use disorders (2007),[90] major depressive disorder (2010),[91] obsessive-compulsive disorder (2013),[92] Posttraumatic Stress Disorder (2009),[93] or panic disorder (2009).[94]

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Institute for Clinical Systems Improvement (ICSI) released a 2014 update of their clinical practice guideline for the diagnosis, evaluation and management of attention deficit hyperactivity disorder in children and adolescents.[95] The updated guideline does not mention neurofeedback as a treatment option.

INTERNATIONAL SOCIETY FOR NEUROFEEDBACK & RESEARCH (ISNR)

The ISNR 2012 guideline is related to standards for practice but does not address specific treatments, indications, or scientific evidence.[96]

SUMMARY

There is not enough research to show that neurofeedback improves health outcomes for people with any indication. In addition, no practice guidelines based on research recommend neurofeedback for any indication. Therefore, neurofeedback is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	90875	Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30 minutes
	90876	;45 minutes
	90901	Biofeedback training by any modality
HCPCS	None	

Date of Origin: *July 1998*

Regence

Medical Policy Manual Medicine, Policy No. 100

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

Effective: February 1, 2025

Next Review: October 2025
Last Review: December 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

Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogeneic) for tissue repair and/or regeneration. Progenitor cell therapy is being investigated for the treatment of damaged myocardium resulting from acute or chronic cardiac ischemia.

MEDICAL POLICY CRITERIA

I. Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic stem cells, is considered **investigational** as a treatment of damaged myocardium.

II. Infusion of growth factors (i.e., granulocyte colony stimulating factor [GCSF]) is considered **investigational** as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

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

CROSS REFERENCES

1. Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141

2. Orthopedic Applications of Stem Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow, Medicine, Policy No. 142

BACKGROUND

Ischemia is the most common cause of cardiovascular disease and myocardial damage in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are not able to reverse existing damage to heart muscle.[1, 2] Treatment with progenitor cells (i.e., stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium.

Various types of autologous cell transplantation have been researched as a technique to either stimulate regeneration of the myocardium or modify ventricular remodeling after infarct. The ideal donor cell is uncertain, and there are scientific as well as ethical concerns involved in choosing the ideal source of donor cells.[1] The range of potential sources of donor cells includes embryonic stem cells, adult stem cell, fetal myocytes, and adult blood progenitor cells. The potential sources of embryonic and adult donor cells include skeletal myoblasts, bone marrow cells, circulating blood-derived progenitor cells, endometrial mesenchymal stem cells (MSCs), adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow MSCs, all of which are able to differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit following treatment with progenitor cells is not entirely understood.[2, 3] Differentiation of progenitor cells into mature myocytes and engraftment of progenitor cells into areas of damaged myocardium has been suggested in animal studies using tagged progenitor cells.[3, 4] However, there is controversy concerning whether injected progenitor cells actually engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit.[2]

Other mechanisms of benefit have been hypothesized. Progenitor cells may improve perfusion to areas of ischemic myocardium.[5] Basic science research also suggests that injected stem cells secrete cytokines with antiapoptotic and pro-angiogenesis properties.[5, 6] Clinical benefit may result if these paracrine factors are successful at limiting cell death from ischemia or stimulating recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic process. Alternatively, paracrine factors might affect intrinsic repair mechanisms of the heart through neovascularization, cardiac metabolism and contractility, increase in cardiomyocyte proliferation, or activation of resident stem and progenitor cells. The relative importance of these proposed paracrine actions will depend on the age of the infarct, e.g., cytoprotective effects with acute ischemia versus cell proliferation with chronic ischemia. Investigation of the specific factors that are induced by administration of progenitor cells is ongoing.[3, 5, 7]

There is a variety of potential delivery mechanisms for donor cells, encompassing a wide range of invasiveness. Donor cells can be delivered via thoracotomy and direct injection into areas of damaged myocardium.[4, 8] Injection of progenitor cells into the coronary circulation can also be done using percutaneous, catheter-based techniques. Finally, progenitor cells can be delivered intravenously via a peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

Adverse effects of treatment with progenitor cells include the risk of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based, etc.) and the risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes.[1] This may create a substrate for malignant ventricular arrhythmias. There is also a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk of this occurring in humans is not known at present.[1]

REGULATORY STATUS

U.S. Food and Drug Administration (FDA) approval is not required in situations in which autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. However, there are several products that require FDA approval.

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), Ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMP™ (BioCardia) are being commercially developed, but none has been approved by the U.S. Food and Drug Administration (FDA) so far.

MyoCell® comprises patient autologous skeletal myoblasts that are expanded ex vivo and supplied as a cell suspension in a buffered salt solution for injection into the area of damaged myocardium. In 2017, U.S. Stem Cell reprioritized its efforts away from seeking RMAT designation for MyoCell®. The expanded cell product enriched for mesenchymal and macrophage lineages might enhance potency. Vericel has received RMAT designation for Ixmyelocel-T.

MultiStem® is an allogeneic bone marrow-derived adherent adult stem cell product that has received RMAT designation.

The CardiAMP™ Cell Therapy system consists of a proprietary assay to identify patients with a high probability to respond to autologous cell therapy, a proprietary cell processing system to isolate process and concentrate the stem cells from a bone marrow harvest at the point of care, and a proprietary delivery system to percutaneously inject the autologous cells into the myocardium. BioCardia has received an investigational device exemption from the FDA to perform a trial of CardiAMP™ and is designated as an FDA Breakthrough Device.

EVIDENCE SUMMARY

Autologous progenitor cell transplantation for the treatment of damaged myocardium is a rapidly evolving field, with many areas of substantial uncertainty.[1-3, 9]

- The mechanism of benefit is not well understood.
- Patient selection criteria are still evolving, and the current studies have been performed in highly selected populations.
- There is a lack of standardization in treatment protocols, with uncertainty in cell type and in the optimal methods for harvesting of donor cells, the timing of the transplantation, and the optimal delivery mode (directly into myocardium, intracoronary artery or sinus, or intravenously).
- Strategies to enhance cell engraftment and prolong cell survival are lacking.

The most clinically relevant outcome of any treatment of acute or chronic ischemic myocardial damage is improvement of symptoms, exercise tolerance, and quality of life, and reduction of

future myocardial damage and mortality. Evaluating the safety and efficacy of progenitor cell therapy requires randomized comparisons with conventional medical treatments. These comparisons are necessary to determine whether any benefits of progenitor cell therapy outweigh any risks and whether the therapy offers advantages over conventional medical treatment.

ACUTE ISCHEMIA

Systematic Reviews

Fisher (2016) published a trial sequential analysis of two Cochrane reviews to address limitations associated with meta-analyses. The trial sequential analysis was conducted on two clinical outcomes using cell therapy, all-cause mortality and hospitalization for heart failure as well as left ventricular ejection fraction. The results of this analysis suggested that there is evidence of reduced risk of mortality and hospitalization in heart failure, but insufficient to determine if there was a treatment effect in acute ischemia. The cell therapy did not improve left ventricular ejection fraction by more than a mean difference of 4% in patients.

A 2012 Cochrane review included 33 RCTs (39 comparisons with 1,765 participants) on bone marrow-derived stem-cell (BMC) therapy for acute MI (AMI).[10] Twenty-five trials compared stem/progenitor cell therapy with no intervention, and 14 trials compared the active intervention with placebo. There was a high degree of statistical and clinical heterogeneity in the included trials, including variability in the cell dose, delivery and composition. Overall, stem-cell therapy was found to improve left-ventricular ejection fraction (LVEF) in both the short-term (<12 months, weighted mean difference of 2.9 percentage points, 95% confidence interval [CI], 2.0 to 3.7, I^2=73%) and long-term (12 to 61 months, weighted mean difference of 3.8 percentage points, 95% CI 2.6 to 4.9, I^2=72%). Stem-cell treatment reduced left-ventricular end systolic and end-diastolic volumes at certain times and reduced infarct size in long-term follow-up. There were positive correlations between mononuclear cell dose infused and the effect on LVEF and between the timing of stem-cell treatment and the effect on LVEF. Although the quality of evidence on LVEF was rated as high, the clinical significance of the change in LVEF is unclear. The quality of evidence on health outcomes was rated as moderate. Stem/progenitor cell treatment was not associated with statistically significant changes in the incidence of mortality or morbidity (re-infarction, arrhythmias, hospital re-admission, restenosis, and target vessel revascularization), although the studies may have been underpowered to detect differences in clinical outcomes. Due to variability in outcomes measured, it was not possible to combine data on health-related quality of life or performance status.

Fisher (2015) published an updated Cochrane review assessing the safety and efficacy of stem-cell therapy for AMI.[11] Literature was searched through March 2015, and 41 RCTs with a total of 2,732 participants (1,564 cell therapy and 1,168 controls) were included.[11-19] There was a low degree of statistical heterogeneity and low risk of bias in the included trials, but substantial clinical heterogeneity within and between trials. At long-term follow-up (≥12 months) moderate quality evidence indicated that stem cell treatment was not associated with any changes in risk in all-cause mortality (6.3% vs 6.9%, relative risk [RR] 0.93, 95% CI 0.58 to 1.50), cardiovascular mortality (8.3% vs 7.2%, RR 1.04, 95% CI 0.54 to 1.99) or reinfarction/re-hospitalization (9.2% vs 14.0%, RR 0.63, 95% CI 0.36 to 1.10). Similar results were reported for short-term follow-up. Stem cell therapy had no effect on morbidity or quality of life/performance, and the differences in mean LVEF between treatment groups, while reaching statistical significance in the majority of trials, was too low to be clinically relevant. While there

remains insufficient evidence for a significant beneficial effect of stem cell therapy for AMI patients, the included RTCs may have been underpowered to detect differences in clinical outcomes.

Delewi (2014) published a systematic review of bone marrow cell therapy in patients with ST-elevation myocardial infarction (STEMI) that included 16 RCTs (n=1,641).[20] A meta-analysis of placebo-controlled RCTs that reported LVEF found statistically significant increases in LVEF with bone marrow stem-cell infusion compared with placebo (≤ six months, mean difference of 2.6 percentage points, 95% CI 1.8 to 3.3, p<0.001, I^2=84%). Statistically significant reductions in LV end diastolic volumes were reported. Based on these findings, the authors concluded that intracoronary bone marrow cell infusion "is associated with improvement of LV function and remodeling in patients after STEMI." Limitations of the meta-analysis included substantial statistical heterogeneity (I^2≥55%).

De Jong (2014) conducted a meta-analysis of major adverse cardiac and cerebrovascular events based on literature through August 2013.[21] The analysis included 22 RCTs (n=1,513), 13 of which (n=1,300) were also included in the Delewi (2014) meta-analysis. Analysis of placebo-controlled RCTs that reported LVEF found statistically significant increases in LVEF with bone marrow stem-cell infusion compared with placebo (≤18 months, mean difference of 2.1 percentage points, 95% CI 0.7 to 3.5, p<0.004, I^2=80%). With median follow-up of six months, there was no difference between bone marrow cell infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter defibrillator implantations. Infusion with bone marrow progenitor cells, but not bone marrow mononuclear cells, led to a statistically significant reduction in the rate of rehospitalization for heart failure (odds ratio vs placebo, 0.14, 95% CI 0.04 to 0.52, p=0.003). Based on these findings, the authors concluded that, although safe, intracoronary infusion of bone marrow stem cells does not improve clinical outcome and clinical efficacy "needs to be defined in clinical trials." Limitations of the meta-analysis included substantial statistical between-study heterogeneity (I^2≥55%).

Lipinski (2007) published a quantitative meta-analysis of studies that estimated the magnitude of benefit of progenitor cell treatment on LV function and infarct size.[22] This analysis included 10 controlled trials with a total of 698 patients. Results for the primary endpoint, change in LVEF, showed a statistically significant greater improvement of 3.0% (95% CI 1.9 to 4.1%, p<0.00001) for the progenitor cell group. There was also a statistically significant greater improvement in infarct size for the progenitor cell group with an incremental improvement of -5.6% over the control group (95% CI -8.7 to -2.5, p<0.001).

A 2008 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment systematically reviewed RCTs of progenitor cell therapy versus standard medical care for treatment of either acute or chronic myocardial ischemia.[23] The TEC Assessment focused on the impact of progenitor cell therapy on clinical outcomes, but also included data on physiologic outcomes such as change in LVEF. For acute ischemia, the TEC Assessment reviewed a total of 10 publications from six unique studies enrolling a total of 556 patients.[24-33] These trials had similar inclusion criteria, enrolling patients with acute ST-segment elevation MI treated successfully with percutaneous coronary intervention (PCI) and stenting, with evidence of residual myocardial dysfunction in the region of the acute infarct. Progenitor cell therapy was delivered via an additional PCI procedure within one week of the acute event.

The REPAIR-AMI trial was the largest trial in this review, and had the largest number of clinical outcomes reported.[26, 27] This was a double-blind trial that employed a sham placebo control infusion of the patients' own serum. This trial enrolled 204 patients with acute ST-segment elevation MI meeting strict inclusion criteria from 17 centers in Germany and Switzerland. At 12 months of follow-up, there were statistically significant decreases in the progenitor cell group for myocardial infarction (MI 0 vs 6, p<0.03) and revascularization (22 vs 37, p<0.03) as well as for the composite outcome of death, MI, and revascularization (24 vs 42, p<0.009). The other trials had very few clinical events, precluding meaningful analysis of clinical outcomes. The primary evidence from these other trials consists of physiologic outcomes measures such as change in LVEF and change in infarct size.

The primary endpoint in all six trials was change in LVEF. In each trial, there was a greater increase in the LVEF for the progenitor cell group compared with the control group. In four of the six studies, this difference reached statistical significance, while in two studies there was a nonsignificant increase in favor of the treatment group. The magnitude of the incremental improvement in LVEF was not large in most cases, with five of the six studies reporting an incremental change of 1.0% to 6.0%, and the final study reporting a larger incremental change of 18%.

At least four meta-analyses of BMC treatment for AMI were also found, each examining between six and 13 randomized, controlled trials, have been published since the 2008 TEC Assessment.[34-37] All four meta-analyses concluded that there was a modest improvement in LVEF for patients treated with progenitor cells. The mean estimated improvement in ejection fraction over control ranged from 2.9 to 6.1%. The studies also concluded that myocardial perfusion and/or infarct size was improved in the progenitor cell treatment group, although different outcome parameters were used. All four of the meta-analyses concluded that there were no demonstrable differences in clinical outcomes for patients treated with progenitor cells.

Gyöngyösi (2015) conducted an individual patient data meta-analysis of 12 RCTs (n=1,252) on autologous intracoronary cell therapy after AMI, including the REPAIR-AMI trial discussed above, using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study, NCT01098591).[38] All patients had STEMI treated with PCI. Mean (standard deviation [SD]) baseline LVEF was approximately 46% (12%). Most studies used bone marrow mononuclear cells and administered cell therapies within two weeks after AMI. Median follow-up duration was six months. Eight trials had low risk of bias, and four single-blind (assessor) trials had medium-low risk of bias. Adjusted (for cardiovascular risk factors) random effects meta-analyses showed no effect of cell therapy on the primary end point, MACCE (major adverse cardiac and cerebrovascular events, a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke) (186 events, 14.0% cell therapy vs 16.3% control, hazard ratio [HR], 0.86, 95% CI 0.63 to 1.18, I^2=0%); death (21 events, 1.4% cell therapy vs 2.1% control); or a composite of clinical hard end points (death, AMI recurrence, and stroke, 45 events; 2.9% cell therapy vs 4.7% control). Compared with controls, changes in LVEF (mean difference 0.96%, 95% CI −0.2 to 2.1), end-diastolic volume (mean difference, 1.2 mL, 95% CI -3.4 to 5.8), or end-systolic volume (mean difference 3.6 mL, 95% CI -3.4 to 4.1) were not observed. The study was limited by variation in the time from AMI to cell delivery (median, 6.5 days) and in imaging modality for assessing cardiac function (magnetic resonance imaging [MRI], single-proton emission computed tomography [SPECT], angiography, echocardiography).

Section Summary

Reported study outcomes have ranged from modest improvement to no improvement with cell therapy compared with placebo in patients with acute ischemia. The current evidence to date should be viewed as preliminary rather than definitive. Most studies reported secondary outcomes such as LVEF and revascularization; minimal data was included for the primary outcomes of recurrent MI or mortality rates. All of the trials had one or more methodologic limitations. The most common limitations were lack of double-blinding and failure to account for all randomized patients in the analysis. The REPAIR-AMI trial had the highest methodologic quality and was double-blinded. However, this trial excluded 17 of 204 randomized patients from the analysis, and thus was not considered to meet the criteria for a high-quality trial. While the evidence for a beneficial impact on physiologic outcomes, particularly LVEF, is fairly strong, the magnitude of effect does not appear to be large. As a result, it is not certain whether the improvement in LVEF translates to meaningful improvements in clinical outcomes, but further adequately powered trials are still needed to prove the efficacy of this intervention.

CHRONIC ISCHEMIC HEART DISEASE (IHD)

Systematic Reviews and Technology Assessments

Fisher (2016)[39] published an update to a 2014 Cochrane review with meta-analysis of autologous stem-cell therapy for chronic ischemic heart disease and congestive heart failure.[40] The review included 38 RCTs (n=1,907). The overall quality of the evidence was considered low because selected studies were small (only three included >100 participants) and the number of events was low, leading to a risk of small-study bias and spuriously inflated effect sizes. Results of the 2016 Cochrane review are shown in Table 1. While reviewers were unable to detect evidence of publication bias using funnel plots, they noted that, of 28 identified ongoing trials, 11 trials with 787 participants were recorded as having been completed or were due to have been completed in advance of the search date but had no publications. Therefore, publication bias cannot be ruled out. Similar results were reported in 2014 meta-analyses conducted by Xu (2014)[41] and by Xiao (2014)[42].

Table 1. Cochrane Review Results of Stem Cell Therapy for Chronic Ischemic Heart Disease[39]

Variables	Short-Term[a] Mortality	Long-Term[b] Mortality	Long-Term[b] Rehospita-lization	Long-Term[b] MACE	Short-Term[a] NYHA Class-ification	Short-Term[a] LVEF (%)[c]
N	1,637	1,010	495	201	658	352
PE (95% CI), p value	0.48 (0.26 to 0.87), 0.02	0.68 (0.25 to 0.58), <0.001	0.62 (0.36 to 1.04), 0.07	0.68 (0.41 to 1.12), 0.13	-0.42 (-0.84 to -0.00), 0.05	3.01 (-0.05 to 6.07), 0.054
I^2 (p)	0% (0.76)	0% (0.97)	0% (0.70)	0% (0.80)	97% (<0.001)	59% (0.01)

CI: confidence interval

Fisher (2016) also reported on the results of a sequential trial analysis using cumulative data obtained from two previous Cochrane reviews with updated results to March 2015.[43] The intent of their analysis was to obtain estimates of sample sizes required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. Twenty-two trials that included all-cause mortality were selected. Six trials reported no deaths, while the remaining 16 trials reported 25 (5.6%) deaths in 444 patients who received progenitor cells compared with 50 (15.9%) deaths in 315 patients who did not. Meta-analysis

of the pooled data revealed a significant reduction in mortality associated with cell therapy in patients with heart failure (RR=0.42, 95% CI 0.27 to 0.64, p<0.001).

The 2008 TEC Assessment, described above, included a total of six trials randomizing 231 patients for treatment of chronic ischemic heart disease. Three of these trials randomized a total of 125 patients to progenitor cell therapy versus standard medical care.[44-46] The other three trials randomized a total of 106 patients undergoing coronary artery bypass grafting (CABG) to CABG plus progenitor cell treatment versus CABG alone.[47-49] Four trials employed bone-marrow-derived progenitor cells as the donor cell source, one trial used circulating progenitor cells (CPC), and the final trial included both a CPC treatment group and a bone-marrow-derived treatment group.[44] The primary physiologic measurement reported in these trials was change in LVEF. In all six trials there was a greater improvement in LVEF for the treatment group compared with the control group, and in four of six trials, this difference reached statistical significance. For the three trials of progenitor cell treatment versus standard medical care, the range of incremental improvement in LVEF was 2.7% to 6.0%. For the trials of progenitor cell treatment plus CABG versus CABG alone, the range of improvement in LVEF was 2.5% to 10.1%. Only one trial reported comparative analysis of data on the change in size of ischemic myocardium. This trial reported that there was no difference in size of ischemic myocardium between treatment groups.[48]

There are limited data from this group of studies on clinical outcomes, with only two studies reporting any clinical outcomes.[44, 49] Both trials reported on change in New York Heart Association (NYHA) class between groups. Assmus also reported an improvement in mean NYHA class of 0.25 (0 to 4 scale) for the bone-marrow treatment group and an improvement of 0.23 for the CPC group, compared with a worsening of 0.18 for the standard medical therapy group (p<0.01).[44] Adverse cardiac events were reported to be extremely small in number with no differences between groups. Patel reported a greater improvement in mean NYHA class for patients in the CABG plus progenitor cell group compared to CABG alone (2.7 vs 0.7, p value not reported), but no statistical testing for this outcome was reported.[49]

Recent systematic reviews of smaller size have been published that include several new RCTs.[50-52] Xu (2014)[41] published a meta-analysis of 19 RCTs (n=886) using similar study inclusion criteria to the Cochrane review with additional RCTs. Statistically significant improvement of LVEF was detected, as was a significant decrease in all-cause death (RR= 0.49, 95% CI 0.29 to 0.84, p=0.01). Xiao (2014) [42] included 20 RCTs that assessed stem cell therapy safety and efficacy in two subgroups of CIHD patients: those with revascularization and without revascularization. Bone marrow cell (BMC) transplantation significantly improved LVEF in patients both with and without revascularization, and patients without revascularization also had other measures of cardiac function significantly improve after BMC transplantation. In both studies the increases in cardiac function, although statistically significant, are too low to be considered clinically relevant. Both studies concluded that additional research in larger studies are required to confirm the efficacy of efficacy of BMC transplantation in CIHD patients.

Randomized Controlled Trials

Qayyum (2023) published results of a phase 2, international, multicenter, placebo-controlled, double-blind RCT (SCIENCE).[53] The SCIENCE trial objective was to see if a single treatment with direct intramyocardial injections of allogeneic adipose tissue-derived mesenchymal stromal cells (ASCs) would be safe and effective at improving cardiac function in individuals

with chronic ischemic heart failure with reduced ejection fraction (HFrEF) compared to placebo. A total of 133 patients with symptomatic HFrEF (defined as LVEF <45%) on guideline-directed medical therapy were included. At baseline, mean age was 64 to 66 years, mean LVEF was 32%, and most patients were NYHA class II and male. Race and ethnicity of included patients were not disclosed. The primary outcome was change in left ventricular end-systolic volume at six-month follow-up, as measured by echocardiography. Quality of life endpoints and change in LVEF and NYHA class were secondary outcomes. Patients were randomized 2:1 to receive either intramyocardial injections of ASC or placebo. After six months, there were no differences in changes in left ventricular end-systolic volume from baseline between the two groups (-3.5 ± 2.8 mL in ASC vs. -3.9 ± 4.1 mL in placebo, p=0.945). There were also no significant differences at six months in changes associated with LVEF, six-minute walk test, NYHA functional class, or other quality of life or biomarker secondary outcomes between the groups. Over 12 months, there were no significant differences in occurrence of adverse events between the two groups. There were three deaths due to progression of HFrEF in the ASC group and two in the placebo group. The study was not powered to detect quality of life outcomes or changes in NYHA functional class or LVEF, limiting interpretation.

Bolli (2021) conducted a phase 2, double-blind, placebo-controlled RCT (CONCERT-HF) on behalf of the Cardiovascular Cell Therapy Research Network with funding from the National Heart, Lung, and Blood Institute.[54] This multicenter trial included 125 patients with ischemic heart failure and ejection fraction ≤40% and on guideline-directed therapy. Most patients were NYHA class II. At baseline, the mean age was about 62 years, mean LVEF was 28.6%, about 90% of patients were White, about 8% of patients were Black, and about 16% of patients were Hispanic. Patients were randomized to one of four treatment groups: autologous bone marrow-derived mesenchymal stromal cells, c-kit positive cardiac cells, a combination of both cell types, or placebo, all given by transendocardial injection. After 12 months, heart failure-related major adverse cardiac events (MACE) occurred in 24.1%, 6.5%, 9.1%, and 28.1% of patients who received mesenchymal stem cells, cardiac cells, combination cell therapy, and placebo, respectively (p=0.049). Other clinical event outcomes, including heart failure hospitalization, heart failure exacerbation, death, stroke, MI, and coronary artery revascularization, did not differ between groups. Quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire was improved at 12 months with combination cell therapy versus placebo (p=0.02); other secondary outcomes did not differ between groups at 12 months. The clinical applicability of this trial is limited by a small sample size and limited power to detect differences in clinical outcomes.

Bartunek (2017) reported on the results of a well-conducted double-blind trial in which 271 patients with NYHA class II or greater symptomatic heart failure (LVEF ≤35%) were randomized to bone marrow−derived mesenchymal cardiopoietic cells (n=120) or sham (n=151).[55] The primary outcome was Finkelstein–Schoenfeld hierarchical composite (all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, six-minute walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. Sixteen patients who died and three who withdrew consent after randomization were not included in analysis. In addition, 19 patients whose cell product did not meet release criteria were excluded from analysis in the cardiopoietic cell group. The probability that the treatment group had a better outcome on the composite primary outcome was 0.54 (a value >0.5 favors active treatment, 95% CI 0.47 to 0.61, p=0.27). Exploratory subgroup analysis reported treatment benefit in patients, with baseline left ventricular end-diastolic volumes of

200 to 370 mL (60% of patients) (0.61, 95% CI 0.52 to 0.70, p=0.015). There was no statistical difference in serious adverse events between treatment arms. One (0.9%) cardiopoietic cell patient and nine (5.4%) sham patients experienced aborted or sudden cardiac death.

Pokushalov (2010) reported on the results of an RCT of intramyocardial injections of autologous bone marrow mononuclear cells (n=55) compared with optimal medical management (n=54) in patients who had chronic, ischemic heart failure.[56] The trial appears to have been conducted in Russia; dates of study conduct were not reported. Power calculations were not reported, and it is not clear if the trial was registered. Comparative treatment effects were not calculated for many outcomes. The RCT reported statistically significantly improvements in mortality rates at 12 months for cell therapy (11%) vs medical therapy (39%) favoring medical therapy (p<0.001)

Nonrandomized Studies

The STAR-Heart trial evaluated stem cell therapy for chronic heart failure due to ischemic cardiomyopathy. This nonrandomized open-label study, reported by Strauer (2010), evaluated 391 patients with chronic heart failure.[57] In this trial, 191 patients received intracoronary BMC therapy, and 200 patients who did not accept the treatment agreed to undergo follow-up testing served as controls. Mean time between percutaneous coronary intervention for infarction and admission to the tertiary clinic was 8.5 years. For BMC therapy, mononuclear cells were isolated and identified (included CD34-positive cells, AC133-positive cells, CD45-/CD14-negative cells). Cells were infused directly into the infarct-related artery. At up to five years after intracoronary BMC therapy, there was a significant improvement in hemodynamics (LVEF, cardiac index), exercise capacity (NYHA classification), oxygen uptake, and left ventricular contractility compared with controls. There also was a significant decrease in long-term mortality in the BMC-treated patients (0.75% per year) compared with the control group (3.68% per year, p<0.01). However, the trial was limited by the potential for selection bias (patient self-selection into treatment groups). For example, there was a 7% difference in baseline ejection fraction rates between groups, suggesting that the groups were not comparable on important clinical characteristics at baseline. Additionally, lack of blinding raises the possibility of bias in patient-reported outcomes such as NYHA class.

Section Summary

For chronic ischemic heart disease, too few primary clinical outcome events (e.g., mortality rates) have been reported across studies to permit meaningful analysis. Other clinical outcomes such as NYHA class are confined to very small numbers of patients and lack sufficient methodologic rigor to permit conclusions. One well-conducted, phase 3 trial failed to demonstrate superiority for cell therapy for the primary outcome that included death, worsening heart failure, and other multiple events. The nonrandomized STAR-Heart trial showed a mortality benefit as well as a favorable hemodynamic effect but the lack of randomization limits interpretation due to concerns about selection bias and differences in known and unknown prognostic variables at baseline between arms. Overall, this evidence has suggested that progenitor cell treatment may be a promising intervention, but robust data on clinical outcomes are lacking. High-quality RCTs, powered to detect differences in clinical outcomes, are needed.

REFRACTORY ANGINA

Stem-cell therapy is also being investigated in patients with intractable angina who are not candidates for revascularization.

Systematic Reviews

A meta-analysis by Khan (2016) included six RCTs studying cell-based therapy in patients with refractory angina.[58] The pooled outcomes of these trials were indices of angina (anginal episodes, Canadian Cardiovascular Society angina class, exercise tolerance, and antianginal medications, myocardial perfusion, and clinical endpoints. The authors created a composite end point, major adverse cardiac events, by combining myocardial infarction, cardiac-related hospitalization, and mortality. The analysis indicated that cell therapy led to improvements in many outcomes, compared with placebo, including anginal episodes (mean difference [MD] -7.81, 95% CI -15.22 to -0.41) Canadian Cardiovascular Society class (MD -0.58, 95% CI -1.00 to -0.16), use of antianginal medications (standardized MD -0.59, 95% CI -1.03 to -0.14), myocardial perfusion (standardized MD -0.49, 95% CI -0.76 to -0.21), exercise tolerance (standardized MD 0.331, 95% CI 0.08 to 0.55), risk of major adverse cardiac events (odds ratio, 0.49, 95% CI 0.25 to 0.98), and arrhythmias (odds ratio 0.25, 95% CI 0.06 to 0.98). The authors suggest that these results require confirmation in larger, phase III RCTs.

The 2014 Cochrane review, described above, reported six studies that included patients with intractable or refractory angina.[40] Five studies measured angina frequency. Combined data showed a significant difference (p=0.0002) in the short-term (<12 months follow-up) in favor of the stem cell groups compared to standard treatment without stem cells. The impact of stem cell therapy on mortality in patients with intractable/refractory angina is unclear because participants included in the meta-analysis also had varying severity of IHD and heart failure. The authors ranked the level of evidence for this indication to be low quality and recommended further study in larger clinical trials to confirm present findings.

Li (2013) published a meta-analysis that included five RCTs (n=381) for stem cell therapy in patients with refractory angina.[59] Compared with controls, patients who received stem cells had a significant improvement in exercise tolerance (p=0.005), reduction in angina frequency (p=0.02), and lower risk of MI (p=0.04). No difference was found for risk of death (p=0.13). The authors concluded that the currently available findings require confirmation in larger studies with long-term follow-up.

Randomized Controlled Trials

Povsic (2016) reported on the industry-sponsored Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells (RENEW) trial.[60] This three-arm multicenter trial compared outcomes from the intramyocardial administration of autologous CD34-positive cells using exercise capacity at 3, 6, or 12 months. Patients underwent cell mobilization with G-CSF for four days followed by apheresis. The peripheral cell product was shipped to a central processing facility (Progenitor Cell Therapy) for selection of CD34-positivecells. The trial was terminated after enrollment of 112 of a planned 444 patients before data analysis due to strategic considerations. The progenitor cell group had greater exercise capacity than the standard therapy group but was no better than the double-blinded placebo group, consistent with a placebo effect. Additionally, with only 122 participants, the trial was not adequately powered to detect a between-group difference.

Section Summary

Evidence on stem cell therapy for refractory angina includes early-phase trials, as well as a phase 3 pivotal rial terminated early and insufficiently powered to evaluate clinical outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improves health outcomes in patients with refractory angina.

TREATMENT WITH GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

Systematic Review

Moazzami (2013) published a Cochrane review of G-CSF for AMI.[61] Literature was searched in November 2010, and seven small, placebo-controlled RCTs (n=354) were included. Overall risk of bias was considered low. All-cause mortality did not differ between groups (RR 0.6, 95% CI 0.2 to 2.8, p=0.55, I^2=0%). Similarly, change in LVEF, LV end systolic volume, and LV end diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. The study indicated a lack of evidence for benefit of G-CSF therapy in patients with AMI.

Randomized Controlled Trials

The following RCTs were published after the 2013 Cochrane summarized above:

Brenner (2016) evaluated G-CSF and Sitagliptin compared with placebo in 174 patients with AMI who had successful revascularization.[62] Both diabetic and nondiabetic patients were included. The primary endpoint of the trial was the hierarchically combined global left and right ventricular ejection fraction changes from baseline to six months follow-up, determined by MRI. There were no significant differences between groups for this endpoint, and they had a similar risk of major cardiac adverse events.

Achilli (2010, 2014) published six-month[63] and three-year[64] results of their multicenter, placebo-controlled RCT, STEM-AMI. Sixty consecutive patients with first anterior STEMI, who underwent primary PCI within 12 hours after symptom onset and had LVEF of 45% or less were enrolled. Patients were randomized 1:1 to G-CSF 5 mg/kg body weight or placebo. Standard STEMI care was provided to all patients. Among cardiac MRI outcomes (LVEF, LV end systolic volume, LV end diastolic volume) at six months and three years, only LV end diastolic volume at three years was statistically significantly improved in the G-CSF group compared with placebo. At three years, there was no statistical difference in clinical outcomes, including death, reinfarction, target vessel restenosis or revascularization, heart failure, and stroke. The study was likely underpowered to detect statistically significant differences in most of these parameters.

Hibbert (2014) randomized 86 patients with LVEF less than 45% after anterior-wall MI to receive either G-CSF or placebo.[65] Eighty patients completed six-month follow-up. While both groups had improved LV function, the improvement was lower in the G-CSF group than in the placebo group. Similar rates in both groups were reported for target vessel revascularization. Both groups had one or more major adverse cardiac events in eight (19%) patients. The authors cautioned that careful monitoring for safety is warranted in future studies of G-CSF in this population.

Section Summary

The small number of trials that use G-CSF as a treatment for acute ischemia generally did not report an improvement in physiologic or clinical outcomes. The 2013 Cochrane review of

seven placebo-controlled trials reported a lack of evidence for benefit. This evidence is not supportive of the use of G-CSF in the treatment of acute ischemia.

PRACTICE GUIDELINE SUMMARY

There are no clinical practice guidelines that address the use of progenitor cell therapy for the treatment of damaged myocardium due to ischemia.

SUMMARY

There is not enough research to determine whether progenitor cell therapy can improve health outcomes for patients with ischemic heart disease. No clinical guidelines based on research recommend progenitor cell therapy for patients with ischemic heart disease. Therefore, progenitor cell therapy is considered investigational for the treatment of ischemic heart disease.

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CODES

NOTE: There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. In some situations, the implantation may be an added component of a scheduled coronary artery bypass graft (CABG); in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

Codes	Number	Description
CPT	33999	Unlisted procedure, cardiac surgery
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic

Codes	Number	Description
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	None	

Date of Origin: *August 2004*

Regence

Medical Policy Manual Medicine, Policy No. 104

In Vivo Analysis of Colorectal Lesions

Effective: February 1, 2025

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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

Several adjunct techniques of in vivo analysis of polyps are being researched for the purpose of improving the analysis of lesions and detection of changes in the colon. Use of these devices is proposed to increase the rate of polyp detection and/or to distinguish premalignant from benign lesions for removal.

MEDICAL POLICY CRITERIA

In vivo analysis of colorectal lesions, including but not limited to polyps, is considered **investigational**.

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

CROSS REFERENCES

1. Confocal Laser Endomicroscopy, Medicine, Policy No. 151

BACKGROUND

During a colonoscopy or sigmoidoscopy as a screening test for colorectal cancer, the physician must often decide which polyp should be removed for histologic diagnosis. While

hyperplastic polyps are considered benign without malignant potential, adenomatous polyps are thought to represent one of the earliest stages in the progression to a malignancy. Identification of these premalignant lesions is considered one of the cornerstones of colorectal cancer prevention. The physician must thus balance the time and potential morbidity of removing all polyps, many of which will be benign, versus removal of those polyps most likely to be adenomatous.

Several techniques of in vivo analysis of polyps are being researched for the purpose of improving the analysis of lesions and detection of changes in walls of colon. These methods are intended to be used as an adjunct to colonoscopy. Some of these methods include autofluorescence, narrow band imaging (NBI), multi-band imaging, chromoendoscopy, third eye retroscope and fiberoptic analysis. It is proposed that these technologies may allow for in vivo analysis of the polyps, possibly avoiding unnecessary biopsies and increasing detection of difficult to visualize lesions (e.g., flat lesions).

The first system developed was based on the observation that benign and malignant tissues emit different patterns and wavelengths of fluorescence after exposure to a laser light. This system consists of an optical fiber, emitting a laser that is directed against three different regions of the same polyp. The subsequent florescent signal is collected, measured, and analyzed by a proprietary software system, which classifies a polyp as "suspicious" (i.e., adenomatous) or "not suspicious" (i.e., hyperplastic). There are several different types of spectroscopy-based in vivo techniques that rely on autofluorescence, emitting light at different frequencies in an attempt to distinguish between hyperplastic and adenomatous lesions.

Narrow band imaging (NBI) is another new technique that allows visualization of the mucosal surface and capillary vessels and thus may assist in the differentiation of abnormal from normal mucosa during colonoscopy. Two NBI systems are available. The NBI color chip system is used in the United States; in this system a single filter with a two-band pass characteristic is used to generate central wavelengths at 415 nm (blue) and 540 nm (green and red). The NBI red-green-blue sequential illumination system uses narrow spectra of red, green, and blue light and a video endoscopic system with a frame sequential lighting method. The light source unit consists of a xenon lamp and a rotation disk with three optical filters. The rotation disk and monochrome charge-coupled device are synchronized and sequentially generate images in three optical filter bands. By use of all three band images, a single color endoscopic image is synthesized by the video processor. NBI has limited penetration into the mucosal surface and has enhanced visualization of capillary vessels and their fine structure on the surface layer of colonic tissue.

Chromoendoscopy, also known as chromoscopy and chromocolonoscopy, refers to the application of topical stains or dyes during endoscopy to enhance tissue differentiation or characterization and facilitate identification of mucosal abnormalities. Chromoendoscopy may be particularly useful for detecting flat or depressed lesions. Standard colonoscopy uses white light to view the colon. In chromoendoscopy, stains are applied, resulting in color highlighting of areas of surface morphology of epithelial tissue. The dyes or stains are applied via a spray catheter that is inserted down the working channel of the endoscope. Chromoendoscopy can be used in the whole colon (pancolonic chromoendoscopy) on an untargeted basis or can be directed to a specific lesion or lesions (targeted chromoendoscopy). Chromoendoscopy differs from endoscopic tattooing in that the former uses transient stains, whereas tattooing involves the use of a long-lasting pigment for future localization of lesions.

Virtual chromoendoscopy (also called electronic chromoendoscopy) involves imaging enhancements with endoscopy systems that could be an alternative to dye spraying. One system is the Fujinon® Intelligent Color Enhancement (FICE®) feature (Fujinon Inc.). This technology uses postprocessing computer algorithms to modify the light reflected from the mucosa from conventional white light to various other wavelengths.

REGULATORY STATUS

Auto-fluorescence

In 2000, the Optical Biopsy™ System (SpectraScience™, Inc.) was approved by the Food and Drug Administration (FDA).The FDA-labeled indication for the Optical Biopsy™ System reads as follows:[1]

> "The SpectraScience™ Optical Biopsy™ System is indicated for use as an adjunct to lower gastrointestinal endoscopy. The device is intended for the evaluation of polyps less than 1 cm in diameter that the physician has not already elected to remove. The device is only to be used in deciding whether such polyps should be removed (which includes submission for histological examination)."

NBI

NBI received FDA clearance through the 510K process in 2005. This clearance (K051645) added NBI with the EVIS EXERA 160A System (Olympus Medical Systems Corp.) to existing endoscopic equipment. FDA indications are for endoscopic diagnosis, treatment, and video observation. In addition, in 2012, the EVIS EXERA III System, which has dual focus (DF) capabilities received FDA approval.[2]

Chromoendoscopy

In August of 2016, the Fuse Colonoscope with FuseBox Processor was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process.[3] This system is indicated for use within the lower digestive tract for adult patients. This system includes Lumos and is intended to be used as an optional adjunct following white light endoscopy and is not intended to replace histopathological sampling as a means of diagnosis.

In August 2014, the Fujifilm EPX-4440HD Digital Video Processor with FICE and Light Source was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. In October of 2015, the PMA was extended to include and additional digital video processor, EPX-4440. FDA documents state that FICE can be used to supplement white-light endoscopy but is not intended to replace histopathologic sampling as a means of diagnosis. In January 2017, the Fujifilm Processor VP-7000 and Light source BL-7000 was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process with the EPX-4440HD as a predicate device.[4] FDA documents state “BLI (Blue Light Imaging), LCI (Linked Color Imaging) and FICE (Flexible spectral-Imaging Color Enhancement) are adjunctive tools for gastrointestinal endoscopic examination which can be used to supplement Fujifilm white light endoscopy. BLI, LCI and FICE are not intended to replace histopathological sampling as a means of diagnosis.”

In November, 2019, the i-scan™ (Pentax), used for virtual chromoendoscopy, was cleared for marketing by FDA through the 510(k) process.[5] This is a digital image enhancement technology and is part of the Pentax EPK-i5010 and EPK-i7010 Video Processors. The i-scan

has several modes that digitally enhance images in real–time during endoscopy. FDA documents state that i-scan is intended as an adjunct following white-light endoscopy and is not intended to replace histopathologic analysis.

No dye or stain product has been specifically approved by FDA for use in chromoendoscopy.

EVIDENCE SUMMARY

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The comparator for the techniques discussed in this review is standard definition white light endoscopy (SD-WLE) or high-definition WLE (HD-WLE). The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

MULTIPLE TECHNIQUES

Systematic Reviews

Al-Mansour (2021) reported about the safety and accuracy of Confocal laser endomicroscopy (CLE) that allows real time *in vivo* histological examination of mucosal surfaces in the gastrointestinal tract.[6] The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Technology and Value Assessment Committee (TAVAC) performed a PubMed/Medline database search of clinical studies involving CLE in May of 2018. Case reports and small case series were excluded. It was concluded that the technology offers an excellent safety profile with rare adverse events related to the use of fluorescent agents. It has been shown to increase the detection of dysplastic Barrett's esophagus, gastric intraepithelial neoplasia/early gastric cancer, and dysplasia associated with inflammatory bowel disease when compared to standard screening protocols.

El-Dallal (2020) reported results of a meta-analysis comparing virtual chromoendoscopy, dye-spraying chromoendoscopy, and HD-WLE.[7] Eleven randomized controlled trials met inclusion criteria. The quality of evidence was moderate in the HD-WLE studies and low to moderate in the DCE studies. In the per-patient analysis of the 1,328 patients, there were no statistically significant differences between virtual chromoendoscopy and dye-spraying chromoendoscopy (risk ratio [RR] 0.77; 95% CI 0.55 to 1.08) or between virtual chromoendoscopy and HD-WLE (RR 0.72; 95% CI 0.45 to 1.15). In the per-dysplasia analysis, there were no statistically significant differences between virtual chromoendoscopy and dye-spraying chromoendoscopy (RR 0.72; 95% CI 0.47 to 1.11), but virtual chromoendoscopy was inferior to HD-WLE (RR 0.62; 95% CI 0.44 to 0.88).

Facciorusso (2019) performed a systematic review of RCTs comparing the efficacy of a variety of devices for the detection of adenomas.[8] A total of 74 two-arm trials assessing add-on devices, enhanced imaging techniques, new scopes, and low-cost optimization of existing resources were included. Moderate increases in adenoma detection rate were found for low-cost optimization of existing resources (odds ratio [OR], 1.29; 95% confidence interval [CI] 1.17 to 1.43), enhanced imaging techniques (OR,1.21; 95% CI 1.09 to 1.35), and add-on devices

(OR,1.18; 95% CI 1.07 to 1.29). Of those, no specific technology was superior to others for detection of advanced adenomas, polyp detection rate, or mean number of adenomas per patient, indicating that low-cost optimization of existing resources was as effective as enhanced endoscopic imaging.

Bessissow (2018) performed a systematic review and meta-analysis of RCTs that compared dysplasia detection techniques in patients with ulcerative colitis.[9] Eight parallel group RCTs including 924 patients met inclusion criteria. Patients were adults with long-standing ulcerative colitis (UC) undergoing surveillance colonoscopy with SD-WLE, HD-WLE, narrow band imaging (NBI), or dye-based chromoendoscopy. The evidence was rated as low- to very low-quality using GRADE. The meta-analysis supported chromoendoscopy over SD-WLE (odds ratio [OR], 2.37; 95% credible interval [CrI], 0.81 to 6.94) for any dysplasia detection with low-quality evidence, whereas very low-quality evidence supports using HD-WLE or NBI over SD-WLE (HD-WLE [vs SD-WLE]: OR, 1.21; 95% CrI, 0.30 to 4.85; NBI: OR, 1.68; 95% CrI, 0.54 to 5.22).

Lord (2018) performed a systematic review of the diagnostic accuracy of several techniques of colonic lesion characterization.[10] A total of 22 studies assessing techniques for in-vivo optical characterization of lesions in patients with colonic IBD during colonoscopy, including 1,491 patients, met inclusion criteria. Techniques examined were virtual chromoendoscopy (VCE), dye-based chromoendoscopy (DBC), magnification endoscopy and confocal laser endomicroscopy (CLE). The quality of included studies was rated and there was mixed quality for all three domains of risk of bias (patient selection, index test, and reference standard). Pooled sensitivities of CLE, magnification endoscopy, DBC, and VCE were 91% (95% CI 94 to 98%), 90% (95% CI 77 to 96%), 67% (95% CI 44 to 84%) and 86% (95% CI 62 to 95%), respectively. Pooled specificities of magnification endoscopy, VCE, and DBC were 87% (95% CI 81 to 91%), 87% (95% CI 72 to 95%), and 86% (95% CI 72 to 94%), respectively, and the area under the SROC curve for CLE was 0.98 (95% CI 0.97-0.99). The authors concluded that real-time CLE is a highly accurate technology while acknowledging that this study is limited by the fact that most CLE studies were performed by single expert users within tertiary centers.

In 2013, Wanders assessed the sensitivity, specificity, and real-time negative predictive value or NBI, image-enhanced endoscopy (i-scan), Fujinon intelligent chromoendoscopy (FICE), CLE, and autofluorescence imaging for differentiating neoplastic from non-neoplastic colon lesions.[11] A total of 91 studies were included in the analysis (NBI=56, i-scan=10, FICE=14, CLE=11 and autofluorescence imaging=11). The authors reported the following for each modality:

- “For NBI, overall sensitivity was 91.0% (95% CI 88.6 to 93.0), specificity 85.6% (81.3 to 89.0), and real-time negative predictive value 82.5% (75.4 to 87.9).
- For i-scan, overall sensitivity was 89.3% (83.3 to 93.3), specificity 88.2% (80.3 to 93.2), and real-time negative predictive value 86.5% (78.0 to 92.1).
- For FICE, overall sensitivity was 91.8% (87.1 to 94.9), specificity 83.5% (77.2 to 88.3), and real-time negative predictive value 83.7% (77.5 to 88.4).
- For autofluorescence imaging, overall sensitivity was 86.7% (79.5 to 91.6), specificity 65.9% (50.9 to 78.2), and real-time negative predictive value 81.5% (54.0 to 94.3).
- For CLE, overall sensitivity was 93.3% (88.4 to 96.2), specificity 89.9% (81.8 to 94.6), and real-time negative predictive value 94.8% (86.6 to 98.1).”

The authors did not recommend autofluorescence imaging as a reliable optical diagnostic

option due to low specificity rates. This study did not assess whether any of these optical imaging modalities improved patient management or overall health outcomes.

Randomized Controlled Trials

Iacucci (2018) performed a randomized non-inferiority trial to determine detection rates of neoplastic lesions in IBD patients with longstanding colitis.[12] A total of 270 patients with inactive disease were enrolled and divided evenly to be assessed by high definition (HD), dye spraying chromoendoscopy (DCE), or VCE using i-scan image enhanced colonoscopy. Neoplastic lesions were classified by the Paris classification and Kudo pit pattern followed by histological classification using the Vienna classification. VCE was determined to have non-inferior neoplastic lesion detection rates compared to DCE. HD rates of detection of all neoplastic lesions were non-inferior to DCE and VCE. Kudo pit pattern and location at the right colon were found to predict neoplastic lesions. The authors concluded that HD-WLE alone was sufficient for detection of dysplasia, adenocarcinoma, or all neoplastic lesions.

AUTO-FLUORESCENCE IMAGING

Nonrandomized Studies

In 2013, Inomata conducted a prospective nonrandomized trial to evaluate colorectal lesions using a new auto-fluorescence imaging (AFI) system.[13] A total of 88 patients with 163 lesions greater than 5 mm were evaluated using the novel AFI system which assessed the green/red (G/R) ratio for each lesion using a computer-assisted color analysis system that permits real-time color analysis during endoscopic procedures. Authors reported significant differences in the G/R ratios of hyperplastic polyps, adenoma/intramucosal cancer/submucosal (SM) superficial cancer, and SM deep cancer ($p<0.0001$). The mean ± SD G/R ratios were 0.984 ± 0.118 in hyperplastic polyps and 0.827 ± 0.081 in neoplastic lesions. When a cut-off value of >0.89 was applied to non-neoplastic lesions, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 83.9%, 82.6%, 53.1%, 95.6% and 82.8%, respectively. When a cut-off value of <0.77 was applied to identify SM deep cancers, the sensitivity, specificity, PPV, NPV, and accuracy were 80.0%, 84.4%, 29.6%, 98.1% and 84.1%, respectively. Additional studies are needed to validate these cut-off values and to assess the impact of AFI upon improved health outcomes.

The FDA approval for the SpectraScience™ Optical Biopsy™ System was based on a prospective, nonrandomized phase II study involving 101 subjects from five sites. The data from this trial have not been published in a peer-reviewed journal but are available as an FDA summary of safety and effectiveness.[1] Patients who participated in the study had undergone a prior lower GI endoscopic procedure with at least one polyp identified. They were then referred for an additional colonoscopy exam, in which fiberoptic analysis of the polyps was performed. At the time of the colonoscopy, the physicians documented whether or not the polyp was considered hyperplastic or adenomatous, and whether or not they would remove the polyp. The fiberoptic probe was then applied to three different portions of the polyp and a segment of normal adjacent mucosa. The physician did not know the results of the analysis and thus the test did not affect patient treatment. The effectiveness of the analysis was then calculated as its ability to correctly identify adenomatous polyps (sensitivity) and to correctly identify hyperplastic polyps (specificity), either alone or in conjunction with the physician assessment. The sensitivity and specificity of the physician assessment alone was 82.7% and 50%, respectively, compared to a combined sensitivity and specificity of 96.3% and 33%, respectively. In other words, fiberoptic analysis identified additional adenomatous polyps that

the physician had classified as hyperplastic and presumably would not have removed based on visual assessment alone. This increase in sensitivity comes at the price of a decrease in specificity, as more hyperplastic polyps will undergo biopsy. However, according to the FDA, the risk of taking biopsies of additional hyperplastic polyps is minimal.

The clinical significance of these results and their effect on patient management is difficult to interpret from the data presented. It is not clear how the physician decided to select additional polyps for fiberoptic analysis (it is not entirely clear whether all polyps were analyzed and then underwent biopsy), or whether the same results could be obtained by simply randomly taking a biopsy of a subset of polyps that were considered hyperplastic on visual assessment. While adenomatous polyps are considered premalignant lesions, the evolution to cancer is a slow process requiring seven to eight years, and thus the immediate removal of all adenomatous polyps is not required. In addition, the finding of an adenomatous polyp serves as a marker that the patient should undergo more frequent endoscopic exams. It is well known that the current practice of visual inspection of polyps will certainly miss some adenomatous polyps, but this lack of sensitivity is considered acceptable if at least one adenomatous polyp is identified and the patient undergoes more frequent screening.

Few studies have been published on the SpectraScience™ Optical Biopsy™ System since 2002. A feasibility study of fiberoptic analysis of normal, adenomatous, and cancerous tissue in 11 patients was published by Mayinger in 2003.[14] No additional literature on the Optical Biopsy™ System was found, but a report in 2006 detailed the results of spectral scattering to different colonic lesions in a small series of 45 patients.[15]

NARROW BAND IMAGING (NBI)

The following evidence review for the diagnostic utility of NBI will focus on RCTs comparing NBI with white light and standard colonoscopy techniques.

Systematic Reviews

Feuerstein (2019) performed a systematic review and meta-analysis of RCTs and non-RCTs that assessed the efficacy of NBI versus white light endoscopy.[16] Six RCTs and four non-RCTs met inclusion criteria. The reported detection rates were 17% and 11%, respectively, for chromoendoscopy and white light endoscopy, respectively (relative risk 1.50; 95% CI, 1.08 to 2.10). The quality of evidence from RCTs was moderate. In data from non-RCTs, chromoendoscopy was more effective than white light endoscopy (16% versus 6%; RR, 3.41; 95% CI 2.13 to 5.47). The quality of evidence from non-RCTs was very low.

Atkinson (2019) performed a systematic review and meta-analysis of RCTs that assessed the adenoma detection rate in NBI versus white light endoscopy.[17] Studies of patients with inflammatory bowel disease or with familial or genetic syndromes were excluded. A total of 11 trials met inclusion criteria and data from 4491 patients were analyzed. A risk of bias assessment was performed, and little evidence of publication bias was found. The detection rate was similar overall, with an unadjusted OR for detection of adenoma by white light endoscopy vs NBI of 1.14 (95% CI 1.01 to 1.29; p=0.04). However, in cases when bowel preparation was considered best, NBI outperformed WLE (adequate preparation OR, 1.07, 95% CI 0.92 to 1.24, p=0.38; vs best preparation OR, 1.30 95% CI 1.04 to 1.62, p=0.02). Additionally, second-generation, but not first-generation, NBI had a better detection rate than white light endoscopy (second-generation NBI OR, 1.28; 95% CI 1.05 to 1.56, p=0.02).

Sabbagh (2011) conducted a meta-analysis of studies (regardless of indication) evaluating NBI compared to colonoscopy and did not find any significant differences in the mean number of polyps (five RCT, 2479 participants), the mean number of adenomas (eight RCTs, 3517 participants), and the rate of patients with at least one adenoma (eight RCTs, 3512 participants).[18] However, individual studies included in the analysis were noted to have heterogeneous populations and indications, as well as diverse findings. Overall, the authors concluded that NBI did not improve detection of colorectal polyps when compared with conventional colonoscopy.

Additional reviews assessing the ability of NBI to differentiate between neoplastic and non-neoplastic polyps have been published; however, these studies are limited due to their inclusion of nonrandomized studies and lack of analysis regarding the impact of NBI upon patient management of overall health outcomes.[19]

Randomized Controlled Trials

Data from several randomized trials of NBI versus white-light colonoscopy (WLE) failed to show any advantage in total detection rate for NBI.[18, 20-24] Published randomized trials differ from the conventional approach to the assessment of diagnostic tests. In these trials patients were randomized to one test or the other (i.e., they received only one test). In general, when comparing diagnostic tests, each patient would receive both tests and the test results would be compared, which more recent trials have done.

Jung (2021) reported results of a randomized study comparing NBI and WLE to detect remnant tissue following removal of suspicious sessile-serrated adenoma.[25] A total of 145 lesions were removed from 138 patients. There were no statistically significant differences in histologic diagnostic rate (89.9% (62/69) vs. 85.5% (65/76); p>0.05), detection of remnant tissue (12.9% (8/62) vs. 15.4% (10/65); p>0.05), the proportion of SSA in remnant tissue (11.3% (7/62) vs. 12.3% (8/65); p>0.05), or the proportion of incomplete resection (6.5 (4/62) vs. 10.8 (7/65); p>0.05) between the NBI and WLE inspection groups, respectively.

Riu Pons (2020) conducted a randomized cross-over trial to compare NBI with HD-WLE in 41 patients with prior detection of at least one serrated polyp ≥10 mm or ≥ 3 serrated polyps larger than 5 mm, both proximal to the sigmoid colon.[26] All patients received tandem same-day colonoscopies with both techniques, performed by one of five experienced endoscopists, with the order being randomized 1:1 to NBI-HD-WLE or HD-WLE-NBI. All tandem colonoscopies were performed by the same endoscopist. No differences were reported in serrated lesion detection rate (47.4% for NBI versus 51.9% for HD-WLE; OR 0.84, 95% CI 0.37 to 1.91) or polyp miss rate (21.3% for NBI versus 26.1% for HD-WLE; OR 0.77, 95% CI 0.43 to 1.38).

Kim (2019) randomized 117 patients to NBI using the new 290 system (290-NBI) or HDWL colonoscopy.[27] All patients were then inspected with the technology not used initially, such that each patient was inspected with both NBI and HDWL with the order randomized. While the adenoma or polyp detection rates were not different between the two groups (polyp miss rates for 290-NBI and HDWL were 20.6% and 33.9%, respectively; p=0.068), the non-adenomatous polyp miss rate for 290-NBI was significantly lower than that of HDWL (11.5% vs. 52.2%, p=0.002). In addition, for polyps on the left side of the colon, flat-type polyps, and non-adenomatous polyps miss rates were significantly lower for 290-NBI than HDWL.

In a 2017 RCT, Min reported on 152 patients (142 were included in the analysis) that underwent crossover colonoscopies with white light endoscopy and linked color imaging (LCI), which uses narrow-band short-wavelength light and WL, randomized for order.[28] The sensitivities in the white light and LCI groups were significantly different, at 73% and 91%, respectively. Negative predictive value was not reported.

In a 2016 RCT, Klare randomized 380 patients to the NBI arm or the high-definition white light arm.[29] Accuracy was 73.7% and 79.2%, sensitivity was 82.4% and 79.8%, and negative predictive value was 75.5% and 73.4% in the NBI and white light arms, respectively. These values were not significantly different between arms.

In a randomized controlled trial reported by Gross (2011), 100 patients undergoing routine screening and surveillance were randomized to receive tandem colonoscopies with standard definition white light (SDWL) and image-enhanced (HD-NBI) colonoscopy.[30] The main outcome measurement was the per-polyp false-negative ("miss") rate. Secondary outcomes were adenoma miss rate, and per-patient polyp and adenoma miss rates. Polyp and adenoma miss rates for SDWL colonoscopy were 57 % (60/105) and 49 % (19/39); those for image-enhanced colonoscopy were 31 % (22/72) and 27 % (9/33) (p=0.005 and p=0.036 for polyps and adenomas, respectively). Image-enhanced and SDWL approaches had similar per-patient miss rates for polyps (6/35 vs. 9/32, p=0.27) and adenomas (4/22 vs. 8/20, p=0.11). The authors concluded that utilization of multiple recent improvements in image-enhanced colonoscopy was associated with a reduced miss rate for all polyps and for adenomatous polyps. It is not known which individual feature or combination of image-enhancement features led to the improvement.

Kakol (2013) evaluated the usefulness of NBI for detection of missed polyps after colonoscopy comparing white light (WL) to NBI.[31] After initial colonoscopy 253 patients were randomized to a second colonoscopy with either NBI or WL. Authors found no significant difference between missed polyps or adenomas between groups.

In 2014, Wallace published results an RCT which compared NBI to standard colonoscopy and found no differences between groups.[32] A total of 522 patients were randomized and 927 total polyps were analyzed. No differences were observed in adenoma detection rate or diagnostic accuracy, regardless of polyp size.

Several randomized trials addressed both total detection rate and differentiation of neoplastic from nonneoplastic lesions.

Pohl conducted a randomized multicenter trial in 2009 of virtual chromoendoscopy with the “Fujinon intelligent colour enhancement” system (FICE or NBI) versus standard colonoscopy with targeted indigocarmine chromoscopy.[33] This German trial included 764 patients in the final analysis and reported that FICE/NBI was not superior to control for overall adenoma detection rates; it was comparable on the differentiation of neoplastic and non-neoplastic lesions. The sensitivity of FICE/NBI was 92.7% versus 90.4% for the control.

Additional RCTs were identified[34-36]; however, these studies contained several methodological flaws in that they only reported on the accuracy of the NBI system in the in vivo evaluation of colonic polyps. In addition, none of the studies evaluated the impact of this technology on outcomes including whether or not there would be an improvement in the selection of polyps for removal during colonoscopy. Furthermore, subsequent RCTs[37] demonstrate no differences in polyp detection rate of NBI compared to WL.

CHROMOENDOSCOPY

Systematic Reviews

Antonelli (2022) conducted a meta-analysis to evaluate the efficacy of dye-based chromoendoscopy in detecting colorectal neoplasia.[38] The analysis included 10 RCTs of individuals at average or increased risk of colorectal cancer (CC) undergoing conventional (standard or high-definition white light) colonoscopy, or colonoscopy with dye-based chromoendoscopy. Patients with IBD or genetic/familial syndromes were excluded. In patients at average or increased risk of CC, the meta-analysis showed that dye-based chromoendoscopy increased adenoma detection rate by 20%, and adenomas per colonoscopy by 50%, corresponding to a number needed to treat of 12 to detect 1 additional patient with adenoma. Limitations of the meta-analysis included unclear indication of colonoscopy in the studies and some heterogeneity in mean adenomas per patient.

Azizi (2018) performed a systematic review comparing white light endoscopy and chromoendoscopy for identifying dysplastic or cancerous lesions in patients with ulcerative colitis without primary sclerosing (PSC) or Crohn's disease (CD).[39] Studies were included if they reported on colonoscopy detection rates of dysplasia and cancers in UC without involvement of PSC or CD. Ten studies met inclusion criteria; most were of moderate quality. Publication bias was not assessed due to the low number of publications per incidence outcome. A meta-analysis of the five studies reporting overall pick-up rate of dysplastic/cancerous lesions on WLE random biopsies calculated showed a pooled rate of 5.6%. Only one study reported on the use of chromoendoscopy for ulcerative colitis patients without PSC. The reported pick-up rate of dysplastic lesions in this study was 7%.

In 2016, Brown updated their 2010 Cochrane review that compared chromoendoscopy and conventional colonoscopy for the detection of colorectal lesions in individuals at increased risk of colorectal neoplasia due to family history, previous polyp detection, or previous CRC resection.[40, 41] The review excluded studies of individuals with IBD or a known polyposis syndrome. Seven RCTs (2,727 participants) were included, five of which were used for a meta-analysis. All of these studies were published prior to 2012. The review found that chromoscopy was likely to yield more people with at least one neoplastic lesion (odds ratio (OR) 1.53, 95% CI 1.31 to 1.79; seven trials; 2,727 participants), and significantly more people with three or more neoplastic lesions were also detected, but only when studies that used high-definition colonoscopy in the control group were excluded (OR 4.63, 95% CI 1.99 to 10.80; two trials; 519 participants). None of the included studies reported any adverse events related to the use of the contrast dye. However, all the trials had some methodological drawbacks, and all were graded as low quality. In addition, some of the included studies were underpowered and significant heterogeneity was present between the included studies (variability of the colonoscopes used in the studies and differences in dye-spraying technique). There are also differences in the study inclusion criteria between the included studies).

Randomized Controlled Trials

The following randomized controlled trials were not included in the above systematic reviews.

Paiva (2023) compared chromoendoscopy to standard colonoscopy during a second sequential colonoscopy in 203 patients.[42] Both groups had routine colonoscopy and were then randomized to have either second procedure with chromoendoscopy or second procedure without chromoendoscopy. The most common reason for colonoscopy was screening (43.8%)

and the average age of subjects was 59.3 years. Prior to randomization, the difference between the groups in the number of patients who had polyps detected at first routine colonoscopy approached statistical significance (p=0.052); however, the difference in the number of polyps found at first procedure was not statistically significant (p=0.097). The second procedure revealed new polyps in both groups; and the chromoendoscopy group had more polyps than the standard colonoscopy group (35/102 vs. 14/1011; p=0.001). No high-grade adenomas or malignancy was found in either group at second colonoscopy. The rates of hyperplastic polyps and low-grade adenomas found in the second procedure were similar (p=0.294). While the study found chromoendoscopy led to the detection of more polyps, chromoendoscopy did not lead to a higher rate of clinically relevant polyp detection than conventional colonoscopy.

Wan (2021) conducted a prospective, multicenter randomized controlled study on patients with longstanding (at least six years) ulcerative colitis.[43] The study compared chromoendoscopy with targeted biopsies to white-light endoscopy with targeted biopsies and random biopsies. In the full-analysis data set, a total of 122 patients with 447 colonoscopies were analyzed, and the randomized groups were as follows: chromoendoscopy (n=39), white-light endoscopy-targeted (n=43), and white-light endoscopy-random (n=40). The primary outcome of the study was the number of colonoscopies that diagnosed dysplasia in each group. The median follow-up period during the study was 55 months; white-light endoscopy-random and chromoendoscopy treated patients had more colonoscopies that diagnosed dysplasia than white-light endoscopy-targeted treated patients (8.0% vs. 1.9%, p=.013; 9.3% vs. 1.9%, p=0.004, respectively). There was no significant difference found between the white-light endoscopy-random and chromoendoscopy groups. In a sub-group analysis in the second half of the follow-up period (37 to 69 months), chromoendoscopy had more colonoscopies that diagnosed dysplasia than white-light endoscopy-targeted (13.3% vs. 1.6%, p=0.015) and had results that indicated a trend for increasing dysplasia detection rates compared to white-light endoscopy-random (13.3% vs. 4.9%, p=0.107).

Alexandersson (2020) conducted a single-center, prospective study on 305 patients with longstanding (at least eight years) ulcerative colitis or Crohn colitis.[44] The study compared high-definition chromoendoscopy with high-definition white-light endoscopy. Patients were randomized into each group: chromoendoscopy (n=152) and white-light endoscopy (n=153). The primary outcome was the number of patients with dysplastic lesions. Dysplastic lesions were detected in 17 patients in the chromoendoscopy group (11%) and in seven patients in the white-light endoscopy group (5%), which was statistically significant (p=0.032). The total number of macroscopic lesions detected in the chromoendoscopy group versus the white-light endoscopy group (n= 89 vs. 41, respectively) was statistically significant (p<0.001), and the total number of macroscopic lesions containing dysplasia was higher in the chromoendoscopy group (n=24; p=0.029). The study found that chromoendoscopy was superior to white-light endoscopy in the detection of dysplastic lesions during colonoscopy; however, the study was limited to a single-center institution in Sweden and the expertise of the endoscopists was not detailed.

Yang (2019) performed a randomized controlled trial comparing HD-WLE with random biopsy versus high-definition chromoendoscopy with targeted biopsy in 210 patients with long-standing ulcerative colitis.[45] The difference in detection rates of colitis-associated dysplasia were not statistically significant between groups (20.6% for chromoendoscopy vs. 12.0% for HD-WLE; p=0.093). The median length of colonoscopy withdrawal was not significantly different between groups (17.6 vs 16.5 minutes; p=0.212) but the difference in total number of

biopsies was statistically significant, with 34 in the HD-WLE group and nine in the chromoendoscopy group (p<0.001).

Haanstra (2019) reported results of a multicenter RCT of patients with Lynch syndrome who were undergoing regular surveillance by colonoscopy.[46] A total of 246 patients were randomly assigned (1:1) to conventional WLE (n=123) or colonoscopy with CE in the proximal colon (n=123). Patients were stratified for previous colorectal adenomas and enrolling center. The primary outcome was the proportion of patients with the detection of at least one neoplastic lesion at baseline and after two years. Detection rates were not significantly different between groups at either baseline (27% for WLE versus 30% for CE; OR, 1.23; 95% CI 0.69 to 2.2; p=0.56) or two years (26% for the original WLE group versus 28% for the CE group (OR, 1.1; p=0.81).

Rondonotti (2019) compared blue-light imaging (BLI) chromoendoscopy with HDWL endoscopy for the characterization of polyps in patients undergoing colonoscopy.[47] A total of 358 consecutive patients undergoing outpatient colonoscopy who had at least one polyp less than 10mm were randomized to BLI or HDWL for polyp characterization. The number of polyps characterized with high confidence was not significantly different between groups (p=0.887), though the overall accuracy was, in favor of BLI (92% versus 84%, p=0.011).

Vleugels (2018) randomized patients undergoing dysplasia surveillance for longstanding ulcerative colitis at five centers in the Netherlands and the UK to receive autofluorescence imaging or chromoendoscopy.[48] Patients were eligible if they were age 18 years or older and were undergoing dysplasia surveillance after a diagnosis of extensive colitis at least eight years before the study start or left-sided colitis at least 15 years before the study start. Each group contained 105 patients. Primary outcomes were the proportion of patients in whom at least one dysplastic lesion was detected and the mean number of dysplastic lesions per patient. Dysplasia was detected in 12% and 19% of patients in the autofluorescence and chromoendoscopy groups, respectively. The mean number of detected dysplastic lesions per patient was 0.13 (SD 0.37) and 0.37 (SD 1.02) for autofluorescence and chromoendoscopy, respectively. Two and three adverse events were reported in the autofluorescence and chromoendoscopy groups, respectively. Autofluorescence imaging did not meet criteria for proceeding to a large non-inferiority trial.

VIRTUAL CHROMOENDOSCOPY

Systematic Reviews

Aziz (2019) performed a systematic review of RCTs comparing “distal attachments” (endocap, endocuff, and endoring) or “electronic chromoendoscopy” (narrow-band imaging, iScan, blue-light imaging, autofluorescence imaging, and linked-color imaging) with high definition white light endoscopy for the detection of serrated adenomas.[49] A total of 17 studies including 13,631 patients met inclusion criteria. There was no statistically significant improvement in serrated adenoma detection rate identified using distal attachments (RR 1.21; p=0.45) or electronic chromoendoscopy (RR 1.29; p=0.09).

A meta-analysis by Omata published in 2014 compared the rate of polyp detection by virtual chromoendoscopy (i.e., FICE or i-scan) with white-light colonoscopy.[50] The review included patients of all risk levels and was limited to RCTs. Five trials on FICE/i-scan met eligibility criteria and the analysis did not find a significantly higher detection rate with virtual chromoendoscopy. The pooled relative risk of adenoma/neoplasia detected by virtual

chromoendoscopy versus conventional chromoendoscopy was 1.09 (95% CI 0.97 to 1.23; p>0.05).

Randomized Controlled Trials

Kandiah (2021) published a multicenter RCT comparing the performance of high-definition white light versus high-definition virtual chromoendoscopy in patients in the United Kingdom with longstanding (at least 8 years) ulcerative or Crohn colitis.[51] Patients were randomized, prior to starting surveillance colonoscopy, to either white light (n=92) or virtual chromoendoscopy (n=92) for a total of 184 patients included in the final analysis. The primary outcome was the difference in neoplasia detection rate between the two arms. Twenty-five neoplastic lesions were found in 14 patients in the virtual chromoendoscopy arm; 27 lesions were found in 22 patients in the white light arm. Compared to the virtual chromoendoscopy arm, neoplasia detection rate was higher in the white light arm (23.4% vs. 14.9%), but this was not statistically significant (p=0.14). The mean number of biopsies taken per patient was 35.9 in each arm of the study, and the difference in the mean number of neoplasia per patient was not statistically significant between the two arms (p=0.75).

Kidambi (2018) randomized 740 patients undergoing screening and surveillance for colorectal neoplasia to receive colonoscopies with i-scan or with standard high-definition white-light.[52] Endoscopists were permitted to switch between i-scan and high-definition white-light imaging to confirm polyps. Polyps were collected and analyzed by histology. The primary outcome was adenoma detection rate (ADR, proportion of subjects with at least one adenoma of any size). Intention to treat and per-protocol analyses were performed. ADR was significantly higher in the i-scan group for both the intent to treat and per-protocol analyses, with values of 47.2% and 47.6% in the i-scan group and 37.7% and 37.2% in the standard group, respectively. However, there was inconsistency across endoscopists. Secondary analyses showed that increased ADR was associated with improved detection of diminutive flat adenomas in the right colon. The groups had significantly different rates of neoplasia detection (i-scan, 56.4%; standard, 46.1%; p=0.005), but not detection of sessile serrated polyps.

Nonrandomized Studies

In 2016, Albrecht assessed the sensitivity, specificity, and positive and negative predictive values of i-scan. A total of 298 images of colonic lesions were assessed by endoscopists after undergoing a dedicated training. The sensitivity was 94.2% and the specificity was 90.9%. The positive predictive value was 87.5% and the negative predictive value was 95.9%. The intraobserver agreement was 0.9301.

In 2014, a large study using modified back-to-back designs in patients undergoing screening colonoscopy was conducted by Chung in South Korea, and included 1650 adults at average risk of CRC, who were randomly divided across three groups.[53] During the colonoscopy, the endoscope was fully inserted and each of three colonic segments (ascending, transverse, descending) was inspected twice during withdrawal. Participants received first withdrawal with narrow-band imaging (NBI), virtual chromoendoscopy using FICE, or white-light colonoscopy (n=550 each group). White light was used in all groups for the second inspection. Ninety-one patients (5.5%) were excluded from analysis due to inadequate bowel preparation. For the primary outcome of adenoma detection rate, no statistically significant difference was found among the three groups. The percentage of patients with at least one adenoma was 24.5% in the NBI group, 23.6% in the FICE group, and 25.3% in the white-light group (p=0.75). Moreover, the mean number of adenomas per patient was 0.35 in the NBI group, 0.36 in the

FICE group, and 0.37 in the white-light group (p=0.59). The adenoma miss rate, defined as an adenoma identified only during the second inspection, was 22.9% in the NBI group, 26.0% in the FICE group, and 20.8% in the white-light–only group; a difference that was not statistically significant (p=0.30). The mean size of the missed adenomas was 3.6 mm, which was smaller than the mean size of adenomas found during the first withdrawal, which was 4.4 mm.

A study using a modified back-to-back colonoscopy design was published in 2012 by Kiriyama in Japan.[54] The study included 102 consecutive patients with increased risk of colon cancer who received virtual chromoendoscopy using FICE and white-light colonoscopy in random order. Patients were eligible for study inclusion if they had been referred for a colonoscopy following sigmoidoscopy or for postoperative surveillance after anterior resection. Those with known IBD, bleeding, and polyposis syndrome were excluded; the right-sided colon was examined in the remaining patients. All lesions identified on either examination were removed, and specimens were sent for evaluation. Two patients were excluded from the analysis because insertion was not possible, leaving 100 patients in the analysis. A total of 110 lesions were detected. Of these, 65 lesions were detected using FICE and 45 with white light; the difference in the number of detected lesions did not differ significantly between groups. Most of the lesions detected were neoplastic; of these, 59 (91%) were found using FICE and 38 (84%) were found with white-light colonoscopy. The miss rate was defined as the proportion of total lesions in that grouping that were detected on the second examination. The miss rate for all polyps with FICE (12/39 lesions [31%]) was significantly less than that with white light (28/61 lesions [46%]) (p=0.03). Twenty-six of 59 (44%) neoplastic lesions detected by FICE and 14 of 38 (37%) of neoplastic lesions detected by white-light colonoscopy were at least 5 mm in size. For neoplastic lesions larger than 5 mm, there was no statistically significant difference between the FICE and white-light examinations in terms of the number of lesions detected.

In 2010, Cha evaluated South Korean patients at increased risk of CRC due to a personal history of polyps or gastrointestinal symptoms.[55] A total of 135 patients underwent colonoscopy, and seven were excluded due to poor bowel preparation or diagnosis of colon cancer or intestinal disease. Thus, 128 patients were randomized to white-light colonoscopy (n=65) or virtual chromoendoscopy with FICE (n=63). The overall percentage of adenomas and the overall number of polyps did not differ significantly between groups. A total of 31 patients (49.2%) in the FICE group and 23 (35.4%) in the white-light group were found to have one or more adenomas (p=0.12). The mean number of adenomas identified per patient was also similar between groups: 1.39 in the FICE group and 1.96 in the white-light group (p=0.46). The number of adenomas less than 5 mm in size (the primary study outcome) differed significantly between groups. A total of 28 (44.4%) of patients in the FICE group and 14 (21.5%) in the white-light group (p=0.006) were found to have adenomas between 0 and 5 mm. All adenomas identified were low grade and no complications were reported in either group.

A 2010 study by Chung included 359 asymptomatic patients receiving screening colonoscopies.[56] All received back-to-back examinations with white-light colonoscopy or FICE in random order (n=181 received white light first, n=178 received FICE first). In the initial colonoscopy, a total of 60 (33.7%) of patients in the FICE group and 55 (30.4%) in the white-light group were found to have at least one adenoma; the difference between groups was not statistically significant (p=0.74). The adenoma miss rate was 6.6% in the FICE group and 8.3% in the white-light group; the difference in miss rates was not statistically significant (p=0.59). All of the missed adenomas were low grade and nonpedunculated. All but one (which was 6 mm) were 5 mm or less in size. In both Chung studies, virtual chromoendoscopy was not found to

improve the rate of adenoma detection compared with white-light endoscopy and did not identify more large adenomas.

A 2009 industry-supported multicenter RCT by Pohl in Germany compared FICE and targeted standard chromoendoscopy using indigo carmine stain.[57] The study enrolled 871 patients presenting for screening (57%) or diagnostic (43%) colonoscopy. All patients were examined using high-resolution zoom endoscopes. Patients in the group receiving standard chromoendoscopy underwent withdrawal using white-light colonoscopy. Indigo carmine was applied using a spray catheter through the working channel of the colonoscope for further assessment of any lesions that were identified. In the FICE group, withdrawal was performed using FICE at the preset for examining colorectal mucosa. Data were available for analysis on a total of 764 patients (368 in the FICE group, 396 in the standard chromoendoscopy group); 107 patients were excluded for poor bowel preparation, incomplete colonoscopy, or incomplete documentation. A total of 131 (35.6%) patients in the FICE group and 140 (35.4%) patients in the standard chromoendoscopy group had at least one adenoma; the difference between groups was not statistically significant (p=1.0). The number of small adenomas (here defined as no more than 10 mm) did not differ significantly between groups (p=0.41). The proportion of large adenomas greater than 10 mm identified in the two groups was not reported. The proportion of patients with carcinoma was small in both groups and did not differ significantly; 12 (3.3%) in the FICE group and 12 (3.0%) in the standard chromoendoscopy group (p=0.85).

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening (v1.2024) recommend surveillance for individuals with a personal history of ulcerative colitis or Crohn's colitis eight years after onset of symptoms using colonoscopy with high-definition white light endoscopy (HD-WLE) or chromoendoscopy with targeted biopsies.[58] Non-targeted (random) biopsies should be considered in addition to chromoendoscopy in patients with a history of dysplasia or primary sclerosing cholangitis. For people with confirmed invisible dysplasia chromoendoscopy is recommended if not already performed. For people with traversable colon stricture, the recommendation is to consider chromoendoscopy if not already performed.

U.S. MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER

The Task Force, comprised of representatives of the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy, published recommendations for endoscopic removal of colorectal lesions in 2020.[59] The recommendations are:

Lesion assessment and description: "We suggest proficiency in the use of electronic (e.g., NBI, i-scan, Fuji Intelligent Chromoendoscopy, or blue light imaging) or dye histology (Conditional recommendation, moderate-quality evidence)."

Surveillance: To assess for local recurrence, we suggest careful examination of the post-mucosectomy scar site using enhanced imaging, such as dye-based (chromoendoscopy) or electronic-based methods, as well as obtaining targeted biopsies of the site. Post-resection scar sites that show both normal macroscopic and microscopic (biopsy) findings have the highest predictive value for long-term eradication (Conditional recommendation, moderate-

quality evidence).

This consensus-based guideline on colonoscopy surveillance after screening and polypectomy, published in 2012, stated that chromoendoscopy and narrow-band imaging may enable endoscopists to accurately determine if lesions are neoplastic, and if there is a need to remove them and send specimens to pathology. The guideline noted that, at this point, these technologies have not been studied in surveillance cohorts and therefore do not have an impact on surveillance interval.[60] The task force published evidence based recommendations for colorectal cancer screening in 2017.[61] These recommendations do not include in vivo analysis of colorectal polyps.

AMERICAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY AND AMERICAN GASTROENTEROLOGICAL ASSOCIATION

The American Gastroenterological Association (AGA) published a clinical practice update on appropriate and tailored polypectomy, based on expert review.[62] The document is focused on polyps smaller than two centimeters in size. The Best Practice Advice includes:

A structured assessment using high-definition white light and/or electronic chromoendoscopy and with photodocumentation should be conducted for all polyps found during routine colonoscopy.

In 2021, the American Gastroenterological Association (AGA) published a clinical practice update on the surveillance and management of colorectal dysplasia in patients with inflammatory bowel disease (IBD).[63] This was an expert review that underwent internal peer review by the AGA Clinical Practice Updates Committee and external peer review through standard procedures undertaken by the publishing journal (Gastroenterology).

Best Practice Statement:

- “Dye spray chromoendoscopy, performed by appropriately trained endoscopists, should be considered in all persons with colonic inflammatory bowel disease undergoing surveillance colonoscopy, particularly if a standard definition endoscope is used or if there is a history of dysplasia.”
- “Virtual chromoendoscopy is a suitable alternative to dye spray chromoendoscopy for dysplasia detection in persons with colonic inflammatory bowel disease when using high-definition endoscopy.”
- “Extensive nontargeted biopsies (roughly 4 adequately spaced biopsies every 10 cm) should be taken from flat colorectal mucosa in areas previously affected by colitis when white light endoscopy is used without dye spray chromoendoscopy or virtual chromoendoscopy. Additional biopsies should be taken from areas of prior dysplasia or poor mucosal visibility. Nontargeted biopsies are not routinely required if dye spray chromoendoscopy or virtual chromoendoscopy is performed using a high-definition endoscope, but should be considered if there is a history of dysplasia or primary sclerosing cholangitis.”
- “A finding of invisible dysplasia should prompt repeat examination by an experienced endoscopist using high-definition dye spray chromoendoscopy under optimized viewing conditions, with extensive nontargeted biopsies in the area of prior dysplasia if no lesion is seen. A finding of unresectable visible dysplasia or of invisible multifocal or high-grade dysplasia on histology should prompt colectomy. For visible lesions that can be

resected or if histologic dysplasia is not confirmed on a high-quality dye spray chromoendoscopy examination, continued endoscopic surveillance at frequent intervals is appropriate."

- "Targeted biopsies of representative or concerning pseudopolyps is appropriate during colonoscopy. Removal and sampling of all lesions is neither required nor practical. Surgery should be a last resort to manage colorectal cancer risk in the setting of severe pseudopolyposis. Dye spray chromoendoscopy should not be used to detect flat or subtle. lesions within a field of pseudopolyps."

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA) published a SCENIC consensus statement on the surveillance and management of dysplasia in patients with inflammatory bowel disease (IBD).[64] This statement, developed by an international multidisciplinary group representing a variety of stakeholders, incorporated systematic reviews of the literature. Table 1 summarizes relevant recommendations.

Table 1. Recommendations on Surveillance and Management of Dysplasia in Patients With Inflammatory Bowel Disease

Recommendation	LOA	SOR	QOE
"When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition."	80%	Strong	Low
"When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy."	85%	Strong	Moderate
"When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy."	84%	Conditional	Low

LOA: level of agreement; QOE: quality of evidence; SOR: strength of recommendation.

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2018, the American College of Gastroenterology (ACG) published an evidence based clinical guideline on the management of Crohn's Disease in adults.[65] The guideline makes the following statements regarding adjunct colonoscopy technologies:

- In patients at particularly high risk for colorectal neoplasia (e.g., personal history of dysplasia, primary sclerosing cholangitis), chromoendoscopy should be used during colonoscopy, as it may increase the diagnostic yield for detection of colorectal dysplasia, especially compared with standard-definition white light endoscopy (conditional recommendation, low level of evidence).
- For patients undergoing surveillance colonoscopy there is insufficient evidence to recommend universal chromoendoscopy for IBD colorectal neoplasia surveillance if the endoscopist has access to high-definition white light endoscopy (conditional recommendation, moderate level of evidence)
- Narrow-band imaging should not be used during colorectal neoplasia surveillance examinations for Crohn's disease (conditional recommendation, very low level of evidence)

In 2019, the ACG published evidence-based clinical guidelines on the management of Ulcerative Colitis in adults.[66] The guidelines make the following statements regarding adjunct

colonoscopy technologies:

- When using standard-definition colonoscopes in patients with UC undergoing surveillance, we recommend dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (strong recommendation, low quality of evidence).
- When using high-definition colonoscopes in patients with UC undergoing surveillance, we suggest white-light endoscopy with narrow-band imaging or dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (conditional recommendation, low quality of evidence).

SUMMARY

More research is needed to know whether in vivo assessment of colorectal lesions (including polyps) using various imaging systems as adjuncts to colonoscopy improves health outcomes. There is not enough research to show whether there would be an improvement in the selection of polyps for removal during colonoscopy. Therefore, in vivo analysis of colorectal lesions using any system is considered investigational.

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CODES

Codes	Number	Description
CPT	44799	Unlisted procedure, small intestine
	45399	Unlisted procedure, colon
	88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session
HCPCS	None	

Date of Origin: *June 2002*

Regence

Medical Policy Manual Medicine, Policy No. 105

Low-Level Laser Therapy

Effective: September 1, 2024

Next Review: June 2025
Last Review: July 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

Low-level laser therapy (LLLT) uses red-beam or near-infrared lasers at much lower intensity than surgical lasers. It is proposed as a treatment for a variety of conditions.

MEDICAL POLICY CRITERIA

I. Low-level laser therapy may be considered **medically necessary** for prevention of oral mucositis in patients undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy and/or radiotherapy, and/or hematopoietic cell transplantation.

II. Low-level laser treatment and laser acupuncture are considered **investigational** for all other 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

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 and indication
- Documentation of need for prevention of oral mucositis in cancer patients with high risk of developing oral mucositis including cancer treatment causing this risk

CROSS REFERENCES

None

BACKGROUND

Low-level laser therapy (LLLT), also called photobiomodulation (PBM), refers to the use of red-beam or near-infrared lasers with a wavelength between 600 and 1000 nm and power from 5 to 500 milliwatts. This contrasts with surgical lasers that typically use 300 watts. Low-level laser energy that is applied to acupuncture points on the body may be referred to as “laser acupuncture.”

When applied to the skin, low level lasers produce no sensation and do not burn the skin. Because of the low absorption by human skin, it is hypothesized that the laser light can penetrate deeply into the tissues where it has a photobiostimulative effect. The exact mechanism of its effect is unknown; hypotheses have included improved cellular repair and stimulation of the immune, lymphatic, and vascular systems.

LLLT has been proposed as a treatment of carpal tunnel syndrome, painful musculoskeletal disorders such as temporomandibular joint disfunction and low back pain, soft tissue injuries, tendinopathies, and osteoarthritis. LLLT has been used outside the U.S. to treat oral mucositis associated with radiation and chemotherapy, stimulate healing of chronic wounds, treat nerve injuries, and as an adjunct to antituberculosis drug treatment.

REGULATORY STATUS

A number of low-level lasers have received US Food and Drug Administration (FDA) 510(k) clearance, including:

- Super Pulsed Laser (Multi Radiance Medical)
- MicroLight ML830® (MicroLight Corporation of America)
- GRT LITE™ PRO-8A (GRT Solutions, Inc.)
- LightStream™ Low Level Laser (RJ Laser Canada Corp.)
- TouchOne™ (OTC)
- FX-635 (Erchonia Corporation)

EVIDENCE SUMMARY

The principal outcomes associated with treatment of musculoskeletal conditions, including carpal tunnel syndrome, are relief of pain and/or functional status. Relief of pain is a subjective outcome typically associated with a placebo effect. Therefore, blinded and randomized controlled trials (RCTs) are required to control for the placebo effect and determine its magnitude and whether any treatment effect provides a significant advantage over the placebo. The technology must also be evaluated in general groups of patients: (1) in patients with mild-to-moderate symptoms, low-level laser therapy (LLLT) may be compared with other

forms of conservative therapy such as splinting, rest, nonsteroidal anti-inflammatory drugs (NSAIDs), or steroid injection; and (2) in patients who have exhausted conservative therapy.

The focus of this policy is on peer-reviewed publications of RCTs, which follow patients (with the exception of those undergoing preventive treatment for oral mucositis) for at least two weeks beyond the end of the treatment period.[1]

LOW-LEVEL LASER TREATMENT

ACHILLES TENDINOPATHY

Systematic Review

A systematic review with meta-analysis on LLLT for Achilles tendinopathy was published by Martimbianco (2020).[2] Four trials (N=119) were included in the analysis, two of the studies were conducted in Norway, the other two in New Zealand. One of the trials compared LLLT to sham, the other three evaluated the addition of LLLT to eccentric exercises, and treatment duration ranged from one session to eight weeks of treatment. High risk of attrition bias was found in three trials and three trials did not report prospectively published protocols. LLLT associated with eccentric exercises when compared to eccentric exercises and sham had very low to low certainty of evidence in pain and function assessment. While one trial reported favorable outcomes with LLLT laser therapy at two months (mean difference (MD) -2.55, 95% confidence interval (95% CI) -3.87 to -1.23), the CIs did not include important differences between groups at three and 13 months. Functional outcomes were not significantly improved in the LLLT groups for any timepoint evaluated. Adverse event reporting was poor across trials. Sub-group and sensitivity analyses were not possible due to insufficient data. The authors conclude “there were insufficient data to support clinical effects of low-level laser therapy for Achilles tendinopathy.”

Section Summary

There is not enough research to show that LLLT improves health outcomes for people with Achilles tendinopathy.

BELL’S PALSY

Systematic Review

Javaherian (2020) published a SR of randomized controlled trials (RCTs) that compared the efficacy of the LLLT with placebo laser, exercise, massage, or no intervention in patients with Bell's palsy (BP).[3] Four studies (N=171) were included in the review, and the patients of all trials were in the sub-acute (less than one week) stage. Studies by Ordahan (2017) and Alayat (2013) summarized below were included in the review, the other two were published in Spanish. The only common outcome measure was the facial disability index (FDI), which was reported in only two studies. Significant differences between the groups after six weeks of laser application (830 nm, 100 mW) was found in two studies, and the other two studies did not identify any effectiveness following LLLT treatment with 670 and 830 nm wavelengths. Meta-analysis was not possible due to data limitations. No data on adverse effects during treatment and/or follow-up sessions were reported.

Randomized Controlled Trials

LLLT as an addition to facial exercise was evaluated in a study by Ordahan (2017).[4] There were 46 patients (40 women) randomized to a facial exercise intervention alone or the exercise intervention plus LLLT. LLLT was performed three times a week for six weeks. Facial exercises were performed five times a week for the six weeks. The main outcome measured was the facial disability index (FDI) questionnaire. FDI scores showed significant improvement in the exercise only group at week six, and in the exercise plus LLLT group at weeks three and six. The improvements in the FDI were greater with the LLLT plus exercise group than in the exercise only group. However, the lack of blinding and of long-term follow-up, and use of combination therapy make it difficult to draw conclusions from this study.

Alayat (2013) reported on a randomized double-blind placebo-controlled trial of laser therapy for the treatment of 48 patients with Bell's palsy.[5] Facial exercises and massage were given to all patients. Patients were randomized to one of three groups: high intensity laser therapy, low level laser therapy or exercise only. Each group included 17 patients that were blinded to treatment. Laser treatment was given three times per week to eight points of the affected side for six weeks. At three and six weeks after treatment, outcomes were assessed using the facial disability scale (FDI) and the House-Brackmann scale (HBS). The authors reported that significant improvements in recovery were seen in both laser therapy groups over exercise alone with the most improvement seen with high intensity laser.

Section Summary

The current evidence is limited to two small RCTs published in English that do not report long-term health outcomes and do not establish the clinical utility of LLLT for the treatment of Bell’s palsy.

CARPAL TUNNEL SYNDROME

Systematic Reviews and Technology Assessments

Evidence for the use of LLLT in carpel tunnel syndrome (CTS) was evaluated in a 2010 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) Assessment, which concluded that the existing randomized clinical trials were insufficient to determine the effect of low-level laser therapy on CTS.[1]

For inclusion in the assessment, studies had to meet the following: published in a peer-reviewed journal; randomized and sham-controlled; if adjunctive therapies were used, they had to be applied to both groups of patients; and outcomes had to be measured at least two weeks beyond the end of the treatment period. Only four studies met the above inclusion criteria, and findings from these studies were inconsistent. No one study was so methodologically sound that its results were considered definitive. Overall, the available studies were small and most did not follow patients for sufficient periods of time beyond the treatment period to determine the durability of the treatment effects.

A systematic review by Bekhet (2017) included eight RCTs that compared functional and electromyographic outcomes of LLLT with those of placebo.[6] A random effects model meta-analysis found that there were no significant differences between groups for all primary outcomes: visual analogue scale (VAS), symptom severity scale (SSS), and functional status scale (FSS) scores. Grip strength was the only measure that was improved with LLLT compared to placebo. Another 2017 systematic review included nine RCTs, but did not perform a meta-analysis due to study heterogeneity.[7] The authors similarly concluded that

there was no strong evidence of LLLT efficacy on pain and function outcomes in carpal tunnel syndrome.

A 2017 Cochrane report assessed the benefits and harms of LLLT compared with placebo and compared with other non-surgical interventions in the management of CTS.[8] Twenty-two RCTs (N=1153) were evaluated. Risk of bias varied across the studies but was high or unclear in most assessed domains in most studies. At short-term follow-up (less than three months), there was very low-quality evidence for any effect over placebo of LLLT on CTS for the primary outcome of Symptom Severity Score (scale 1 to 5, higher score represents worsening; MD -0.36, 95% CI -0.78 to 0.06) or Functional Status Scale (scale 1 to 5, higher score represents worsened disability; MD -0.56, 95% CI -1.03 to -0.09). The authors concluded the quality of evidence was very low and found no data to support a clinical effect of LLLT in treating CTS.

Li (2016) published a systematic review (SR) that included seven RCTs of this topic, with similar results to those of the Bekhet (2017) review.[9] Meta-analyses were conducted for the outcomes hand grip strength, pain measured by a VAS, SSS, and FSS. Short-term follow-up was defined as less than six weeks after treatment and long-term follow-up as at least 12 weeks after treatment. For six of the eight meta-analyses, there were not statistically significant between-group differences in outcomes. These include short-term assessment of hand grip, short-term assessment of pain by VAS, and short- and long-term assessment of SSS and FSS. Meta-analyses found stronger hand grip (three studies) and greater improvement in VAS score (two studies) at the long-term follow-up in the LLLT group compared with the control. Most data for these two positive analyses were provided by a single RCT. Reviewers concluded that additional high-quality trials with similar LLLT protocols are needed to confirm that the intervention significantly improves health outcomes.

Randomized Controlled Trials

RCTs not addressed in the 2016 Cochrane SR are discussed below.

Badıl Güloğlu (2022) published the results of a RCT comparing LLLT and corticosteroid injection in 87 patients (143 wrists) with moderate carpal tunnel syndrome (CTS).[10] Outcomes were assessed at baseline and one- and six-months post-treatment. Outcome measures were numbness and pain, QuickDASH questionnaire, grasping tests, Tinel and Phalen tests, electrophysiological tests and MRI evaluations. Six-month outcome data were available for 80 patients (133 wrists). Corticosteroid injection and LLLT groups showed statistically significant difference at one-month post-treatment in favor of the corticosteroid group and no significant group difference at the six-month timepoint was found.

Barbosa (2015) evaluated the efficacy of orthoses and patient education with or without the addition of LLLT in patients with mild and moderate carpal tunnel syndrome.[11] Laser treatment was provided twice a week for six weeks. Forty-eight patients were randomized and 30 (63%) completed the study protocol. Compared with baseline, outcomes, including scores on the Boston Carpal Tunnel Questionnaire and its domains, did not differ significantly between groups after treatment.

Section Summary

The evidence for LLLT for the treatment of CTS includes several SRs, a technology assessment, and RCTs, and generally does not demonstrate that LLLT is an effective treatment for CTS.

CHRONIC NECK PAIN

Systematic Reviews

In a 2013 SR and meta-regression, Gross (2013) evaluated 17 trials on LLLT for neck pain.[12] Ten of these trials were found to demonstrate high risk of bias. Two trials consisting of 109 subjects were considered to be of moderate quality and found LLLT produced better outcomes than placebo for chronic neck pain treatment. Evidence showed improved outcomes with LLLT compared to placebo for acute neck pain, acute radiculopathy and cervical osteoarthritis but was considered to be low quality. There was conflicting evidence on chronic myofascial neck pain.

A SR by Kadhim-Saleh (2013) analyzed eight RCTs (n=443 patients) to determine the efficacy of LLLT in reducing acute and chronic neck pain as measured by VAS.[13] Authors concluded the evidence was inconclusive and the benefit seen in the use of LLLT did not constitute the threshold of minimally important clinical difference.

The 2010 BCBSA TEC Assessment also determined that the evidence was insufficient to allow conclusions regarding the effect of LLLT on chronic neck pain.[1] The six trials that met the assessment inclusion criteria reported variable results, and no single study was methodologically sound. It was not possible to explain the differences in results due to the numerous differences in patient selection, treatment regimens, and trial co-interventions.

Randomized Controlled Trials

Subsequent to the publication of the 2010 technology assessment, an additional RCT was published.[14] However, interpretation of results from this trial is limited by lack of study of treatment durability (follow-up for at least two weeks beyond end of the treatment period).

Section Summary

The current evidence on the use of LLLT for the treatment of chronic neck pain has methodological limitations and the conclusions of the reports are conflicting. Therefore, it cannot be determined if LLLT improves health outcomes.

ELBOW PAIN

Systematic Reviews

A single SR has been identified on the use of LLLT in elbow pain.[15] Published in 2008, the review grouped placebo-controlled randomized clinical trials by application technique and laser wave length and reported on the 7 of 13 included trials with a common, narrowly defined regimen where lasers of 904 nm wavelength with low output (5-50 MW) were used to irradiate the tendon insertion at 2–6 points on the lateral elbow. Positive results in these trials were consistent with outcomes of pain and function, and significance persisted for at least 3–8 weeks after the end of treatment. However, among the articles included in this review, there were considerable differences in treatment protocol and type of patient treated, indicating that

these results may not be generalizable to all patients with elbow pain. The authors noted that the conclusions of their review differed from conclusions of prior reviews of this topic.

Section Summary

The current evidence on LLLT for the treatment of elbow pain is insufficient due to the variability across studies in the patient population and treatment protocols used. Based on this evidence, it cannot be determined if health outcomes are improved on the use of LLLT for the treatment of elbow pain.

FIBROMYALGIA

Systematic Reviews

A SR with meta-analysis by Yeh (2019) included nine RCTs with 325 patients with fibromyalgia undergoing LLLT or placebo laser treatment with or without an exercise program.[16] Primary outcomes evaluated were the total scores on the Fibromyalgia Impact Questionnaire (FIQ), pain severity, and number of tender points. Secondary outcomes were changes in fatigue, stiffness, anxiety, and depression. Significantly greater improvement in FIQ scores (SMD: 1.16; 95% CI, 0.64-1.69), pain severity (SMD: 1.18; 95% CI, 0.82-1.54), number of tender points (SMD: 1.01; 95% CI, 0.49-1.52), fatigue (SMD: 1.4; 95% CI, 0.96-1.84), stiffness (SMD: 0.92; 95% CI, 0.36-1.48), depression (SMD: 1.46; 95% CI, 0.93-2.00), and anxiety (SMD: 1.46; 95% CI, 0.45-2.47) were found in patients receiving LLLT compared to those receiving placebo laser. The methodological quality of the included RCTs was considered to be low-to-middle, as there was no clear allocation process and only patients were blinded in most studies. Considerable heterogeneity in study protocols such as differences in laser types, energy sources, exposure times, and associated medication status were noted.

Honda (2018) published a SR with meta-analysis of RCTs evaluating pain relief modalities for fibromyalgia. Eleven studies with a total of 498 patients (range, 20-80) were included.[17] Compared with control, LLLT was not associated with a reduction of VAS-measured pain (MD -4.0; 95% CI -23.4 to 15.4; p=0.69). A significant reduction in tender points (MD -2.21; 95% CI -3.51 to -0.92; I2=42%; p=0.0008) and in Fibromyalgia Impact Questionnaire score (MD -4.35; 95% CI -6.69 to -2.01; I2= 62%; p=0.03) were found for LLLT compared with control groups. The analysis was limited by including only English language studies and studies with a pure control group or placebo group (ie, no other intervention) as well as by the high heterogeneity score for included studies.

Section Summary

LLLT for treatment of fibromyalgia has been evaluated in several small RCTs and in two SRs. Although significant improvements in outcomes including disease severity and pain were found in one SR, another SR found no significant reduction in pain between LLLT and control groups. Studies are limited by small sample sizes and heterogeneity of study protocols. Additional RCTs with sufficient numbers of patients are needed.

LOW BACK PAIN

Systematic Reviews

Chen (2022) published a systematic review with meta-analysis of RCTs on LLLT for treating nonspecific chronic low back pain compared to placebo.[18] Eleven trials were included that

compared LLLT to placebo (N=836 patients); seven of these trials assessed LLLT alone compared to placebo and four trials assessed LLLT plus acupuncture compared to placebo. For the overall risk of bias in LLLT trials, eight were identified as low risk, two as having some concerns, and one as high risk. The primary outcomes of interest were changes from baseline in pain scores, measured by visual analogue scale (VAS), and disability measured by the ODI score. In pooled analyses, reviewers found a significant reduction in pain scores with all LLLT interventions compared to placebo posttreatment (SMD, -0.22; 95% CI, -0.38 to -0.05) and in disability scores for trials comparing LLLT therapy alone to placebo (SMD, -0.50; 95% CI, -0.79 to -0.21). In trials comparing LLLT plus acupuncture to placebo, there was no significant difference in disability scores posttreatment (SMD, 0.10; 95% CI, -0.15 to 0.35).

Glazov (2016) published a SR with meta-analysis of blinded sham-controlled trials evaluating LLLT for treatment of chronic low-back pain.[19] Fifteen RCTs (total n=1039 patients) met reviewers' eligibility criteria. Reviewers found that 3 of the 15 trials were at higher risk of bias (using a modified Cochrane tool), mainly due to lack of blinding. The primary outcomes of interest to reviewers were pain measured by a VAS or a numeric rating scale, and a global assessment measure evaluating overall improvement and/or satisfaction with the intervention. Outcomes were reported immediately posttreatment (<1 week) and at short-term (1 to 12 weeks) follow-up. Longer term outcomes at 6 and 12 months were considered secondary measures. For the pain outcome, meta-analysis of 10 trials found significantly greater reduction in pain scores in the LLLT group at immediate follow-up (weighted mean difference [WMD] = -0.79 cm, 95% confidence interval [CI] -1.22 to 0.36 cm). In a meta-analysis of six trials, there was no significant difference in pain reduction at short-term follow-up. However, in subgroup analyses, there was significantly greater pain reduction with LLLT in trials that used a higher dose (>3 J/point), but not a lower dose, and in trials that included patients with a short duration of back pain (5 to 27 months) but not long duration (49 months to 13 years). The decisions regarding the cutoff to use for laser dose and duration of back pain was made post hoc and considered review findings. Findings were similar for the global assessment outcome. Meta-analyses found significantly higher global assessment scores at immediate follow-up (five trials) but not short-term follow-up (three trials). Only two trials reported pain or global assessment at six months and 12 months, and neither found statistically significant differences between the LLLT and sham groups.

Huang (2015) published a SR of RCTs on LLLT for treatment of nonspecific chronic low back pain.[20] The review included trials comparing LLLT and placebo that reported pain and/or functional outcomes and reported a PEDro quality score. Seven trials (total n = 394 patients: 202 assigned to LLLT, 192 assigned to placebo) were included. Six of the seven trials were considered high quality (i.e., a PEDro score ≥7; maximum score, 11 points). Primary outcomes of interest were posttreatment pain measured by VAS score and disability measured by the Oswestry Disability Index (ODI) score. Range of motion and change in pain scores were secondary outcomes. In pooled analyses of study data, the authors found a statistically significant benefit of LLLT on pain outcomes, but not disability or ROM. For the primary outcome (posttreatment pain scores) in a meta-analysis of all seven trials, mean VAS scores were significantly lower in the LLLT group than in the placebo group (WMD = -13.57, 95% CI -17.42 to -9.72). In a meta-analysis of four studies reporting the other primary outcome (ODI score), there was no statistically significant differences between the LLLT and the placebo groups (WMD = -2.89, 95% CI -7.88 to 2.29).

An update of the Cochrane Database SR of LLLT for nonspecific low back pain was conducted in 2008.[21] The authors stated that “based on the heterogeneity of the populations, interventions, and comparison groups, we conclude that there are insufficient data to draw firm conclusions on the clinical effect of LLLT groups for low-back pain.”

A SR by Chou (2007) assessed benefits and harms of nonpharmacological therapies including LLLT for acute and chronic low back pain.[22] The reviewers did not find good evidence of efficacy for LLLT for either indication.

Randomized Controlled Trials

Since publication of the Glazov (2016) SR described above, additional RCTs have been published.

Taradaj (2019) published a RCT evaluating LLLT for the treatment of nonspecific lumbar pain (NSLP).[23] Sixty-eight patients were were randomly assigned to four groups: high-intensity laser therapy for 10 minutes (HILT), sham (HILT placebo), low-level laser therapy for eight minutes (LLLT), and sham (LLLT placebo). Postural stability measurements were taken pre- and post-laser sessions (three weeks) and at follow-up time points (one and three months). The authors concluded that neither LLLT nor HILT lead to a significant improvement in postural sway in patients with NSLP compared with standard stabilization training based on short- and long-term observations.

Koldaş Doğan (2017) reported a RCT that compared two different LLLT regimens for chronic low back pain.[24] Forty-nine patients were randomized to receive either hot-pack plus LLLT 1 (1850 nm Gallium-Aluminum-Arsenide [Ga-Al-As] laser) or hot-pack plus LLLT 2 (650 nm Helium-Neon [He-Ne], 785 ve 980 nm Gal-Al-As combined plaque laser), with a total of 15 sessions per treatment. Both groups reported improvements in pain and function, and neither regimen was superior for pain treatment. However, there was no non-LLLT control group for comparison in the study.

Section Summary

The literature on LLLT for low back pain consists of RCTs and several SRs of RCTs. Meta-analyses found that LLLT resulted in significantly greater reductions in pain scores and global assessment scores than a placebo control in the immediate posttreatment setting. Meta-analyses also found that other outcomes (eg, disability index, ROM) were significantly better immediately after treatment with active versus placebo LLLT, though not at longer-term follow-up.

LYMPHEDEMA

Systematic Reviews

Chiu (2023) published a systematic review and meta-analysis on LLLT on the treatment of breast cancer-related lymphedema.[25] The systematic review included 11 RCTs published between 2003 and 2021. There were positive effects in the LLLT group compared to the control group in post-treatment QOL (3 studies; n=73; SMD, 0.47; 95% CI, 0.00 to 0.94; I^2=0%; p=.05), reduction in swell at post-treatment (6 studies; n=204; SMD, -0.41; 95% CI, -1.01 to 0.18; I^2=76%; p=.18), and reduction in swelling at one to three months post-treatment (5 studies; n=193; SMD, -1.06; 95% CI, -2.11 to -0.02; I^2=90%; p=.05). Overall, limitations

included a high heterogeneity among studies and varying follow-up periods among studies. The authors note larger studies with long-term follow-up are needed.

A 2019 SR with meta-analysis was published by Chen evaluating effectiveness of LLLT for the treatment of breast cancer–related lymphedema.[26] The SR included nine RCTs. Six studies (N=316) were included in the meta-analysis. The primary outcome was the arm circumference or volume, and secondary outcomes were grip strength and pain scores. No significant difference in the reduction of the arm circumference or arm volume was found between LLLT and control groups after treatment, or at one-month, or at three-month follow-up. In addition, no significant differences in the change in grip strength or pain scores at any timepoint were identified between groups.

Smoot (2015) published a SR of studies on the effect of LLLT on symptoms in women with breast cancer–related lymphedema.[27] The authors identified nine studies, seven RCTs and two single-group studies. Three studies had a sham control group, one used a waitlist control, and three compared LLLT to an alternative intervention (e.g., intermittent compression). Only three studies had blinded outcome assessment and, in three studies, participants were blinded. A pooled analysis of four studies found significantly greater reduction in upper-extremity volume with LLLT than with the control condition (effect size [ES], -0.62, 95% CI -0.97 to -0.28). Only two studies were suitable for a pooled analysis of the effect of LLLT on pain. This analysis did not find a significant difference in pain between LLLT and control (ES = -1.21, 95% CI -4.51 to 2.10).

Randomized Controlled Trials

Kozanoglu (2022) published a RCT evaluating the long-term effectiveness of combined intermittent pneumatic compression (IPC) therapy plus LLLT compared to IPC therapy alone in patients with postmastectomy upper limb lymphedema (PML).[28] Group 1 received combined treatment with IPC plus LLLT (n = 21) and group 2 received only IPC (n = 21) for five sessions per week for four weeks. Clinical outcomes were assessed pre- and post-treatment at 3, 6, and 12-months. Statistically significant improvements in the circumference difference and grip strength were observed in both groups (for circumference, p=0.018 and p=0.032, respectively; for grip strength, p=0.001 and p=0.046, respectively). Visual analog scale values for arm pain and shoulder pain during motion decreased only in the combined treatment group (group 1).

A randomized double-blind sham-controlled trial of LLLT in 50 patients with post-mastectomy lymphedema was published by Omar (2010).[29] The average length of time that patients had swelling was 14 months (range, 12 to 36 months). Patients were treated with active or sham laser three times a week for 12 weeks over the axillary and arm areas. In addition, all participants were instructed to perform daily arm exercises and to wear a pressure garment. Limb circumference, shoulder mobility, and grip strength were measured before treatment and at 4, 8, and 12 weeks. Limb circumference declined over time in both groups, with significantly greater reduction in the active laser group. Shoulder flexion and abduction were significantly better in the active laser group at 8 and 12 weeks. Grip strength was significantly better in the active laser group after 12 weeks (26.2 kg vs 22.4 kg). The durability of these effects was not assessed.

Section Summary

There is insufficient evidence in the available literature to determine if the use of LLLT for the treatment of lymphedema improves health outcomes.

MEDIAL TIBIAL STRESS SYNDROME

Systematic Reviews

In a SR by Winters (2013) of treatments for medial tibial stress syndrome, LLLT was not found to be effective.[30] All studies included in the SR were considered to have methodological bias.

Section Summary

The evidence is insufficient due to the methodological limitations identified in the available literature; therefore, it cannot be determined if the use of LLLT for the treatment of medial tibial stress syndrome improves health outcomes.

MENISCAL KNEE PAIN

Systematic Reviews

There are no reports of SRs of LLLT for meniscal knee pain.

Randomized Controlled Trials

Malliaropoulos (2013) reported on a randomized, double-blind, placebo-controlled study of LLLT in 64 patients with unilateral medial knee pain for more than six weeks that was related to meniscal pathology (i.e., grade 3 tiny attenuation or intrasubstance tears on MRI). Pain improved significantly more with LLLT than placebo ($p<0.0001$). However, four patients (12.5 %) did not have improvement with LLLT. Pain returned in three patients at six months and in five patients after one year. Repeat MRIs were not performed.

Section Summary

The current evidence consists of one RCT that is limited by a small study population, does not report long-term health outcomes, and does not establish the clinical utility of LLLT for the treatment of meniscal knee pain.

ORAL MUCOSITIS

Systematic Reviews

A SR with meta-analysis evaluating the relative effects of LLLT and/or cryotherapy in cancer patients with oral mucositis (OM) was published by Lai (2021).[31] Twenty-six RCTs (N=1830) comparing groups receiving interventions of combined cryotherapy and LLLT, LLLT, cryotherapy and usual care (the control group) in patients with cancer were included. Treatment effects of combined cryotherapy and LLLT were better than those of usual care for none/mild and severe OM (ORs=106.23 [95% CI=12.15 to 929.17] and 0.01 [95% CI=0 to 0.57], respectively). Treatment effects with cryotherapy alone and LLLT alone were better than those with usual care for none/mild and severe OM (ORs = 3.13 [95% CI=1.56 to 6.27]; ORs=7.56 [95%CI = 3.84 to 14.88] and 0.25 [95% CI = 0.11 to 0.54]; ORs = 0.13 [95%CI0.07 to 0.24], respectively). For patients with none/mild OM, treatment effects with combined cryotherapy and LLLT were better than those with only LLT or cryotherapy (ORs=14.06 [95% CI=1.79 to 110.30] and 33.95 [95% CI=3.50 to 329.65], respectively). No difference in

treatment effects among cryotherapy and/or LLLT intervention in cancer patients with moderate OM was found. Heterogeneity in treatment protocols and outcome measures were noted limitations across studies.

Peng (2020) conducted a SR with meta-analysis comparing LLLT to placebo, usual care, or no therapy in patients receiving chemotherapy or radiotherapy for hematologic malignancies with or without hematopoietic stem cell transplant (HCT) or head and neck squamous cell cancer (HNSCC).[32] The SR included 30 studies including one with a stratified analysis. For the purposes of the meta-analysis, this was treated as an additional trial. Fourteen studies were conducted in Brazil and 10 were published between 2014 and 2018. Patients underwent HCT or chemotherapy in 19 studies: radiotherapy in five studies, and chemoradiotherapy in six studies. The application of LLLT was prophylactic in 26 studies and six studies reported on therapeutic LLLT use. Nineteen were considered high-quality (Jadad score of ≥3 out of 5) and 10 trials were low risk for bias. For use of prophylactic LLLT, a total of 22 studies (N=1190) evaluated the incidence of the primary outcome of severe oral mucositis during the treatment of hematologic disorders or head and neck cancer. Severe oral mucositis occurred significantly less in patients receiving LLLT compared to control (relative risk, 0.40; 95% CI, 0.25 to 0.57; p <0.01). This significant reduction in severe oral mucositis incidence with LLLT therapy was sustained in multiple subgroup analyses including assessment by underlying condition/ treatment regimen: HCT (relative risk, 0.46; 95% CI, 0.23 to 0.94; p =0.03), chemotherapy (relative risk, 0.2; 95% CI 0.05 to 0.92; p =0.04), and radiotherapy (relative risk, 0.36; 95% CI, 0.27 to 0.50; p <0.01). An analysis of 15 trials (N=900) found that prophylactic LLLT numerically, but not significantly, reduced the incidence of oral mucositis of any grade (relative risk, 0.90; 95% CI, 0.98 to 1.00; p =0.06). A subgroup analysis of patients receiving chemotherapy showed a significant reduction in any grade of mucositis with LLLT (relative risk, 0.73; 95% CI, 0.55 to 0.96; p =0.03); this difference was not significant in patients receiving radiotherapy and chemoradiotherapy (relative risk, 1.00; 95% CI, 0.92 to 1.09; and relative risk, 1.00; 95% CI, 0.98 to 1.01, respectively).

Anschau (2019) published a SR with meta-analysis of RCTs on oral mucositis (OM) in patients during and/or after cancer therapy and in which the therapeutic approach was LLLT.[33] Grade of OM was analyzed as a dichotomous variable, as improvement or no improvement in severe OM on the seventh day of therapy. Across the five RCTs (N= 315) a 62% risk reduction of severe mucositis on the seventh day of evaluation (RR = 0.38 [95% CI, 0.19-0.75]) was identified. A mean reduction of 4.21 days in the time of complete resolution of OM (CI - 5.65 to - 2.76) was found with LLLT.

In 2014, the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) issued guidelines that reiterated findings from their 2012 SR recommending LLLT for the prevention of oral mucositis in patients receiving hematopoietic stem cell transplantation (HSCT) conditioned with high-dose chemotherapy and for patients undergoing head and neck radiotherapy, without concomitant chemotherapy.[34] The 2012 SR included 24 trials on a variety of prophylactic treatments. The recommendation on which LLLT for prevention of oral mucositis in patients receiving HSCT was based on what the authors considered to be one well-designed, placebo-controlled, randomized trial (described in more detail next),[35] together with observational studies. The trial was double-blind and sham-controlled with 70 patients. Patients were randomized to 650 nm laser, 780 nm laser, or placebo.[35] Patients in the 650-nm laser group were more likely to have received a total body irradiation (TBI)–containing regimen compared with the other two groups; otherwise, the groups were comparable. LLLT began on the first day of conditioning and continued for

three days posttransplant. Of the 70 patients, 47 (67%) had complete or nearly complete mucositis measurements over time; the average number of visits per patient was similar among the three groups. The difference between groups in mean oral mucositis scores was greatest at day 11 (placebo, 24.3; 650 nm, 16.7; 780 nm, 20.6), but this difference between the 650-nm group and placebo group was not statistically significant (p=0.06). Patient-specific oral mucositis scores differed significantly between the two groups only when adjusted for TBI exposure. Of the 70 patients in the study, 17 (24%) were assessed for oral pain. With group sizes of five and six, the 650-nm group had significantly lower patient-specific average pain scores (15.6) than the placebo group (47.2). No adverse events from LLLT were noted. This study was flawed because it did not achieve statistical significance for the primary outcome measure and had a very small percentage of patients with pain assessments.

The MASCC/ISOO recommendation for LLLT for the prevention of oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer was based on “weaker evidence” from three studies that showed positive results but had major flaws. Evidence was considered encouraging but insufficient to recommend LLLT in other populations. The authors emphasized that due to the range of laser devices and variations in individual protocols, results of each study applied exclusively to the cancer population studied and the specific wavelength and settings used.

Additional SRs have been published since the 2012 MASCC/ISOO SR.[36, 37] Oberoi (2014) reported on a SR and meta-analysis of 18 RCTs on LLLT versus no treatment or placebo for oral mucositis.[37] Eight RCTs assessed patients undergoing HSCT, eight evaluated head and neck cancer patients receiving radiotherapy or chemoradiation, and the rest studied patients with other conditions receiving chemotherapy. The investigators used the Cochrane risk of bias tool to evaluate the RCTs. Most studies were considered at low risk of bias on most domains. For example, 68% were at low risk of bias for blinding of patients and personnel, and 89% were at low risk of bias on incomplete outcome data. The primary outcome measure for the review was the incidence of severe mucositis. Ten studies (total N=689 patients) were included in a pooled analysis of this outcome. The overall incidence of severe mucositis (grades 3-4) decreased with prophylactic LLLT, with a risk ratio (RR) of 0.37 (95% CI 0.20 to 0.67, p=0.001). Moreover, the absolute risk reduction in the incidence of severe mucositis (-0.35) significantly favored LLLT (95% CI -0.48 to -0.21, p<0.001). Among secondary outcomes, LLLT also significantly reduced the overall mean grade of mucositis (standardized mean difference [SMD], -1.49; 95% CI, -2.02 to -0.95), duration of severe mucositis (WMD -5.32, 95% CI -9.45 to -1.19), and incidence of severe pain (VAS; RR=0.26, 95% CI 0.18 to 0.37). In a subgroup analysis of the primary outcome (incidence of severe mucositis), the investigators did not find a statistically significant interaction between the type of condition treated and the efficacy of LLLT.

Randomized Controlled Trials

de Carvalho e Silva (2023) published an RCT evaluating the effectiveness of LLLT in the management of both xerostomia and oral mucositis in 53 patients with squamous cell carcinoma of the head and neck.[38] The participants were being treated with radiation therapy or chemoradiotherapy with curative intent. Twenty-six patients were randomized to LLLT and 27 were randomized to a sham treatment on the first day of treatment. There was no significant different in baseline dental health between the two groups (p>0.05). Outcome measures were arithmetic means of a xerostomia-related quality of life (QOL) questionnaire and the presence or absence of oral mucositis lesions. Differences in mean scores on the

QOL questionnaire were considered clinically relevant if they were ≥20%. In the sham treatment group, there was an increase in mean score for several items that indicated symptoms of xerostomia (p<0.0001). In the treatment group, mean scores decreased, indicating absent or very mild xerostomia (p=0.0074). Differences in mean scores were ≥20% for eight of the 15 questions on the QOL questionnaire. Higher grades of oral mucositis were found in the sham group compared to those treated with LLLT (p=0.0001). The study findings indicate that LLLT reduces both xerostomia and oral mucositis in patients being treated for head and neck cancer.

Legouté published the results of a phase III trial of LLLT to treat OM lesions grade ≥ 2 in patients with oral cavity or oro/hypopharyngeal cancers (stage III or IV) from seven French oncology centers.[39] Severity of OM (incidence and duration of grades ≥3) was the primary endpoint. Among the 97 randomized patients, 83 (85.6%) were assessed; 32 patients had no laser therapy because of unreachable OM lesions. An acute OM (grade ≥ 3) was observed in 41 patients (49.4%): 23 patients (54.8%) of the active laser group versus 18 (43.9%) in the control group (modified intend to treat, p = 0.32). Tolerance was noted as excellent for every session for 91% of patients and 4.5% in most sessions. The five-year follow-up is targeted for March of 2021.

Two large RCTs evaluating LLLT for prevention of oral mucositis were published by Gautam in 2012.[40, 41] One of these studies reported LLLT for the prevention of chemoradiotherapy-induced oral mucositis in 121 oral cancer patients.[41] The second publication reported LLLT for the prevention of chemoradiotherapy-induced oral mucositis in 221 head and neck cancer patients.[40] There is an apparent overlap in patients in these two reports, with the head and neck cancer study including the 121 patients with a primary tumor site in the oral cavity. Patients in these studies received LLLT before radiotherapy at 66 Gy delivered daily in 33 fractions, five days per week and concurrent with cisplatin. LLLT was delivered at a wavelength of 632.8 nm, power density of 24 mW/cm^2, and a dosage of 3 to 3.5 J. In the report on oral cancer, LLLT before radiotherapy led to significant reductions in the incidence of severe oral mucositis (29% vs 89%) and its associated pain (18% vs 71%, with a VAS score >7), opioid analgesic use (7% vs 21%), and total parenteral nutrition (30% vs 39%), all respectively, during the last weeks of chemoradiotherapy. LLLT also reduced the duration of severe oral mucositis (4.07 days vs 13.96 days), severe pain (5.31 days vs 9.89 days), and total parenteral nutrition (14.05 days vs 17.93 days), all respectively. In the 221 patients treated for head and neck cancer, LLLT was reported to lead to significant reductions in the incidence and duration of severe oral mucositis (8.19 days vs 12.86 days) and its associated pain (VAS score of approximately 4 vs 7), total parenteral nutrition (45.0% vs 65.5%), and opioid analgesic use (9% vs 26% for step III), respectively.

The next year, Gautam (2013) published an assessment of patient-reported outcomes from the same study of 221 head and neck cancer patients using the Oral Mucositis Weekly Questionnaire-Head and Neck (OMWQ-HN) and the Functional Assessment of Cancer Treatment- Head and Neck (FACT-HN) questionnaire.[42] Patients received LLLT as described earlier in this paragraph. Patients in the LLLT group reported significantly better outcomes than the placebo group with lower scores on both the OMWQ-HN (p<0.001) and FACT-HN (p<0.05).

A number of small, double-blind, sham-controlled RCTs on prevention of oral mucositis in patients undergoing cancer treatment were published in the last several years. Gautam (2015) reported on 46 patients with head and neck cancer scheduled for radiotherapy and found

significant reductions in the incidence and duration of severe oral mucositis (p=0.002) and severe pain (p=0.023) after LLLT versus sham.[43] Oton-Leite (2015) reported on 30 head and neck cancer patients undergoing chemoradiation and found that oral mucositis grades were significantly lower in the LLLT group than in the control group at the week 1, 3, and 5 evaluations.[44] For example, at the last clinical evaluation (week 5), the rates of grade 3 oral mucositis were 25% in the LLLT group and 54% in the control group. The third RCT, by Ferreira (2015), included 36 patients with hematologic cancer undergoing HSCT.[45] The overall incidence of oral mucositis did not differ significantly between groups (p=0.146). However, the rate of severe oral mucositis (grade 3 or 4) was significantly lower in the laser group (18%) than in the control group (61%; p=0.015).

Section Summary

The literature on LLLT for the prevention of oral mucositis includes several SRs. A 2014 SR of LLLTs for prevention of oral mucositis included 18 RCTs, generally considered at low risk of bias, and found statistically significantly better outcomes with LLLT than with control conditions on primary and secondary outcomes. These findings were recapitulated in a 2019 SR which focused on only RCTs. A 2020 SR not limited to patients undergoing HCT showed benefit with using prophylactic LLLT compared to control in reducing the incidence of severe oral mucositis in patients undergoing chemotherapy or radiotherapy. A large SR including 26 RCTs and 1830 patients found LLLT to be beneficial for the reduction of mild and severe OM in patients with cancer.

OROFACIAL PAIN

Systematic Reviews

A SR on studies using LLLT for the treatment of trigeminal neuralgia was published by Ibarra in 2021.[46] The review included five RCTs and one nonrandomized clinical trial. Sample sizes ranged from 12 to 53 across studies, for a total sample of 193. Study designs included one sham-controlled study, one study evaluating the same population at two timepoints, one comparing LLLT to electromagentic therapy, one evaluating LLLT as an adjuvant therapy to ganglion block, and two studies evaluating photobiomodulation as an adjuvant therapy to pharmacotherapy. Risk of bias ranged from high (two studies) to low (three studies). Low sample size precluded pooled analysis. While the authors found that, qualitatively, LLLT appears to be as effective as conventional therapies for trigeminal neuralgia, they conclude that additional data with consistent outcome parameters and longer follow-up are needed.

DePedro (2020) published a SR of LLLT for the management of neuropathic orofacial pain which included 13 studies (eight RCTs, two prospective studies, and three case series).[47] Ten of the studies were on burning mouth syndrome, three were on trigeminal neuralgia, and one on occippital neuralgia. Although all studies showed a reduction in pain intensity, not all were statistically significant. No meta-analysis was reported. The authors concluded that studies assessing medium and long-term outcome measures of chronic pain are needed, as is standardization of the technique.

Tengrungsun (2012) assessed the effectiveness of LLLT as a treatment for orofacial pain in 33 studies[48] represented by 1,522 chronic pain patients meeting inclusion criteria in a SR. Trials were included if they were randomized, had a comparison group, had a study population with an orofacial pain condition including dentin hypersensitivity and musculoskeletal pain, and

included a measurement of pain relief. In addition, a high-quality scoring system was used the literature was analyzed by two independent researchers. Of the 23 RCTs reviewed, all but two were rated as low quality. The review concluded there was limited evidence to conclude that LLLT was more effective than placebo, sham laser, and other active treatments.

Randomized Control Trials

Manca (2014) investigated the effects of ultrasound and LLLT on myofascial trigger points (MTP) of the upper trapezius muscle (uTM).[49] In the double-blind, randomized, placebo-controlled study, 60 participants with at least one active MTP in uTM (28 women and 32 men; mean age 24.5 ± 1.44 years) were recruited and randomly assigned to one out of five groups: active ultrasound (n = 12), placebo US (n = 12), active LLLT (n = 11), placebo LLLT (n = 11) and no therapy (control, n = 14). After the 2-week intervention, all groups showed pressure pain threshold, numerical rating scale and cervical lateral flexion significant improvements ($p < 0.05$), which were confirmed at the follow-up. The authors concluded that ultrasound and LLLT provided significant improvements in pain and muscle extensibility.

A double-blind, randomized trial by Magri (2017) compared LLLT with placebo in a group of women with temporomandibular disorders.[50] LLLT was performed twice a week for a total of eight sessions. Both LLLT (n=31) and placebo (n=30) groups showed decreases in pain from baseline, though only the LLLT group maintained a reduction in pain after 30 days. There were no changes in pain sensitivity noted with either treatment.

In a small RCT not included in the above SR, the effects of LLLT on masticatory performance, pressure pain threshold (PPT), and pain intensity in 21 patients with myofascial pain were evaluated.[51] Patients were either assigned to the laser group (n=12) or the placebo group (n=9). A reduction in the geometric mean diameter of crushed particles and an increase in PPT were seen only in the laser group when comparing the baseline and end-of-treatment values. Both groups showed a decrease in pain intensity at the end of treatment. Authors concluded that LLLT promoted an improvement in MP and PPT of the masticatory muscles. This is a study of limited sample size and the randomization of the patient population is not clear.

Section Summary

Findings from published RCTs on the use of LLLT in orofacial pain are insufficient to determine the added benefit of the technology on net health outcomes due to the methodological limitations in the study designs.

ORTHODONTIC PAIN

Systematic Reviews

He (2013) investigated the efficacy of LLLT in the management of orthodontic pain.[52] Four RCTs, two quasi-RCTs, and two controlled clinical trials (CCTs) were selected from 152 relevant studies, including 641 patients. The meta-analysis demonstrated that 24% risk of incidence of pain was reduced by LLLT (RR = 0.76, 95% CI range 0.63-0.92, P = 0.006). In addition, compared to the control group, LLLT brought forward "the most painful day" (MD = -0.42, 95% CI range -0.74- -0.10, P = 0.009). Furthermore, the LLLT group also implied a trend of earlier end of pain compared with the control group (MD = -1.37, 95% CI range -3.37-0.64, P = 0.18) and the pseudo-laser group (MD = -1.04, 95% CI range -4.22-2.15, P = 0.52). Authors concluded due to the methodological shortcomings and risk of bias of included trials, the evidence for LLLT in delaying pain onset and reducing pain intensity was insufficient.

Randomized Controlled Trials

Owayda published the results of a RCT on analgesic effects of LLLT and paracetamol-caffeine in controlling orthodontic pain induced by elastomeric separators in a total of 54 patients.[53] Group 1 (n = 18) received a single dose of laser treatment with a placebo medication, group 2 (n = 18) received paracetamol-caffeine tablets with a placebo light-emitting diode (LED) light, and patients in group 3 (n = 18) were exposed to the two placebo procedures. An 11-point numeric rating scale was used to assess spontaneous and chewing pain perception immediately and at one hour, 24 hour, 48 hours, and one week after separator placement. The authors report similar pain levels in the laser and drug groups and decreased pain in the LLLT group compared with the placebo group. No impact of paracetamol-caffeine or LLLT were found for overall health related quality of life measures.

Celebi (2019) found no significant reduction in pain with LLLT compared to control or mechanical vibration following placement of an orthodontic archwire in 60 subjects [54] However, reduction in pain levels were found in LLLT treated patients compared to control in 84 subjects following placement of an orthodontic archwire in a study published by Lo Giudice (2019).[55] Martins (2019) published the results of a randomized, double-blinded, placebo-controlled study in 62 patients, which found reduced pain immediately following separation of an orthodontic device, but no difference at 24 hours in patients treated with LLLT compared to control.[56] AlSayed Hasan (2017) evaluated two levels of LLLT (4 Joule or 16 Joule) in 26 patients treated with a fixed orthodontic appliance.[57] The study used a blinded, split-mouth design, in which one molar from each patient received the laser treatment, while one molar had sham treatment. The outcome measures of pain by VAS scale during mastication at various timepoints after LLLT were not significantly different between treatment groups.

Section Summary

The evidence from published studies on the use of LLLT to reduce orthodontic pain has not demonstrated consistent findings of improved outcomes. These inconsistent findings may be due to methodological limitations of the published studies.

OSTEOARTHRITIC (OA) KNEE PAIN

Systematic Reviews

Malik (2023) published a systematic review and meta-analysis assessing the effect of LLLT plus exercise on pain, range of motion (ROM), muscle strength, and function.[58] Fourteen RCTs involving 820 patients were included. There was a significant difference in pain both immediately after therapy (SMD: -058, p=0.001) and during follow-up (SMD: -1.35, p=0.05) but no significant differences in ROM, strength, or knee function either right after therapy or during follow-up.

Huang (2015) published a SR of RCTs comparing at least eight treatment sessions of LLLT and sham laser treatment in knee osteoarthritis patients.[59] To be eligible for inclusion in the review, trials had to report pain and/or functional outcomes and a PEDro quality score. A total of nine trials (total n=518 patients) met eligibility criteria. In these studies, interventions included between eight and 20 laser or sham sessions over two to six weeks. All nine trials were considered high quality, as assessed using the PEDro scale (score of 7; maximum score, 11 points). Primary outcomes of interest were posttreatment pain measured by VAS scores and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores (Pain

and Function). Meta-analyses did not find that LLLT led to significantly better pain scores than the sham control, either immediately after treatment or at the three-month follow-up. For example, a meta-analysis of five studies that reported 12-week pain scores did not find a statistically significant between-group difference (SMD = -0.06; 95% CI, -0.30 to 0.18). Moreover, there were no statistically significant differences between active and sham laser interventions on WOMAC Stiffness scores or WOMAC Function scores. The secondary outcome (range of motion after therapy) also did not significantly favor LLLT over a sham intervention.

Bjordal (2007) published a SR of placebo-controlled RCTs to determine the short-term efficacy of physical interventions for osteoarthritic knee pain.[60] They included a total of 36 RCTs. The largest proportion of trials evaluated transcutaneous electrical nerve stimulation (n=11), followed by eight trials on LLLT and seven on pulsed electromagnetic fields. Also included were trials on electroacupuncture, manual acupuncture, static magnets, and ultrasound. The authors did not report findings of pooled analyses on LLLT for knee osteoarthritis. In a qualitative analysis, they stated that all the physical interventions but two (manual acupuncture, ultrasound) showed better results with active treatment over placebo.

Randomized Controlled Trials

Elboim-Gabyzon (2023) published a single-blinded RCT comparing LLLT to pulsed electromagnetic field therapy (PEFT) in 40 people with low-grade knee osteoarthritis.[61] Twenty patients were treated with LLLT and 20 were treated with PEFT. Primary outcomes were pain intensity and functional level. All patients completed therapy and no adverse events were documented. Both groups had significant improvement in pain intensity ($p<0.0001$), but the PEFT group had a greater effect size in three of four activities (resting, standing, and climbing stairs). Similarly, both groups had significant improvement in function after therapy ($p\leq0.0003$), but the PEFT group had a larger effect size. Limitations of the study include the results may not be generalizable to people with higher grades of knee osteoarthritis, and the researchers did not take participants medication usage into account.

De Matos Brunelli Braghin (2018) published the results of a RCT of LLLT on pain, stiffness, function, and spatiotemporal gait in patients with bilateral knee osteoarthritis.[62] Patients with knee OA (Grades 1-3) were and randomized into four groups: Control Group (CG), untreated; Laser Group (LG), treated with LLLT; Exercise Group (EG), treated with exercise; and Laser + Exercise Group (LEG), treated with laser and exercises. Treatment was twice a week for two months. Significant improvement in pain ($p = 0.006$) and function ($p = 0.01$) was found only in the EG. At eight weeks, all groups receiving intervention showed a significant increase in gait speed: LG versus CG ($p = 0.03$); EG versus CG ($p = 0.04$) and LEG versus CG ($p = 0.005$). Only the LEG group showed a significant increase in the cadence and duration of single right limb support ($p=0.009$ and 0.04, respectively), and only the EG and LEG groups showed significant decreases in the duration of right limb support ($p = 0.035$ and $p = 0.003$, respectively) compared to the CG. No long-term outcomes were reported.

Gopal Nambi (2016) evaluated LLLT in 34 patients with knee osteoarthritis in a double-blind, randomized trial.[63] The placebo treatment consisted of laser therapy with the minimum emission of energy. The 17 subjects each in the LLLT group and placebo group had treatment sessions three times a week for four weeks, with additional exercise therapy and Kinesio taping. Pain was assessed by VAS. After eight weeks, VAS scores were significantly lower in the LLLT group than in the placebo group.

Section Summary

Though RCTs are available on the use of LLLT for the treatment of osteoarthritic knee pain, the interpretation of the results is limited due to small patient sizes and limited long-term follow-up of patients. Study results have been inconsistent. Systematic reviews have not shown that LLLT consistently improves pain and function for people with osteoarthritic knee pain.

PLANTAR FASCIITIS

Systematic Reviews

Ferlito (2023) published a systematic review and meta-analysis of 19 RCTs involving 1089 participants to assess the effects of LLLT related to pain and disability due to plantar fasciitis when compared to control conditions, other interventions, and adjunct treatments.[64] The analysis found that LLLT may reduce short-term pain compared to placebo/control intervention with moderate certainty evidence (mean difference (MD) = -22.02, 95% CI -35.21 to -8.83, I^2=46%, p<0.001) based on three trials, but a fourth study found LLLT did not improve short-term pain compared to placebo with low certainty evidence (MD-3.08, 95% CI –15.90 to 22.06). LLLT with exercise compared to exercise alone was associated with improved pain intensity based on moderate certainty evidence (MD= -21.84, 95% CI -26.14 to -17.54, p<0,00001). When compared to extracorporeal shockwave therapy (ESWT) an analysis of six studies found LLLT with exercise was better than ESWT with exercise with low certainty evidence (MD= -19.59, 95% CI -29.03 to -10.15, I^2 = 67%, p=0.0005). LLLT with exercise compared to ultrasound therapeutic (UST) plus exercise in four studies found LLLT was not superior to UST for short-term pain based on low certainty evidence (MD= -5.05, 95% CI -8.19 to -1.91, p=0.02). One study found LLLT to be superior to UST for medium term pain with low certainty evidence (MD=-10.79, 95% CI -14.51 to -7.07). LLLT with or without exercise did not improve disability when compared to placebo/control, exercise alone, or ESWT. There is some evidence LLLT with exercise is superior to UST with exercise for disability but the effect size is small so its clinical relevance is questionable (SMD = -.039, 95% CI -0.77 to 0.01, p=0.04). The authors point out that the LLLT dosage was not addressed. Further research is needed to understand if there is a dose-response relationship that is important in the delivery of LLLT to achieve therapeutic goals.

Guimaraes (2023) published a systematic review and meta-analysis of multiple therapeutic interventions for plantar fasciitis that have been evaluated with RCTs.[65] Nineteen treatments from 236 studies were evaluated. Outcomes were short, medium, and long-term pain. For short-term pain, LLLT was compared to a control group in five studies involving 231 participants. The meta-analysis found improvement in pain with moderate quality evidence (p<0.01). Two studies involving 172 subjects compared high-intensity laser therapy to LLLT and found no significant difference in short-term pain (p=0.28). No studies evaluated LLLT for medium or long-term pain.

Naterstad (2022) published a systematic review and meta-analysis of 18 RCTs evaluating LLLT in patients with lower extremity tendinopathy (seven trials of patellar or Achilles tendinopathy) or plantar fasciitis (11 trials).[66] In an analysis of LLLT versus any control, both pain and disability were improved with LLLT. VAS scores were reduced immediately after therapy (n=260; SMD, 0.39; 95% CI, 0.09 to 0.7; I2=30%) and at 4 to 9 weeks follow-up (n=222; SMD, 0.32; 95% CI, 0.05 to 0.59; I2=4%) compared with control. LLLT did not significantly improve disability compared with other interventions immediately after therapy

(n=76; SMD, 0.25; 95% CI, -0.21 to 0.7; I2=0%) or at 4 to 8 weeks follow-up (n=76; SMD, 0.24; 95% CI, -0.21 to 0.7; I2=0%).

Guimaraes (2022) published a systematic review (SR) with meta-analysis of 14 studies (N=817) comparing LLLT (alone or combined with other interventions) and control (placebo and other interventions) in patients with plantar fasciitis.[67] Compared to the placebo group, LLLT improved pain in the short term of 0 to 6 weeks (four studies, N=234; moderate-quality evidence; MD, -2.28; 95% CI, -2.58 to -1.97; p<0.00001; I^2=0%). No significant difference in short-term disability was found for individuals in the LLLT group compared to the placebo group. Compared to the conventional rehabilitation alone group, LLLT combined with conventional rehabilitation improved pain in the short term of 0 to 6 weeks (two studies, N=90; moderate-quality evidence; MD, -2.01; 95% CI, -2.89 to -1.13; p<0.00001; I^2=0%). However, compared to extracorporeal shock wave therapy (ESWT), LLLT did not significantly reduce pain intensity in the short term (four studies, N=175; low-quality evidence; MD, 0.45; 95% CI, -2.0 to 2.9; p=.72; I^2=94%). The meta-analysis was limited by insufficient data for longer-term outcomes, the lack of multicenter studies, and lack of a large sample. Additionally, the quality of evidence for the outcome disability were low.

Wang (2019) published a SR with meta-analysis of six RCTs (N=315) comparing LLLT (alone or combined with other interventions) and controls (placebo or other interventions) in the treatment of plantar heel pain or plantar fasciitis.[68] Compared with controls, VAS for pain was significantly reduced after treatment (SMD=-0.95; 95% CI -1.20 to -0.70; p<0.001), as well as remaining significantly better at 3 months (SMD= -1.13; 95% CI -1.53 to -0.72; p<0.001). The meta-analysis was limited by the small number of studies included, its small sample size, and insufficient data for longer-term outcomes.

Randomized Controlled Trials

Cinar (2018) conducted a prospective, single-blinded RCT investigating combination therapy consisting of LLLT plus exercise and orthotic care compared with orthotic care alone in persons with plantar fasciitis.[69] Forty-nine individuals were randomized to LLLT (n=27) or a control therapy (n=22). Each person performed a home exercise routine and received orthotic care; persons in the LLLT group received treatment three times a week for a total of ten sessions. The function subscale of the American Orthopedic Foot and Ankle Society Score, a VAS, and the 12-minute walk test were used to measure progress. Scores were recorded at baseline, three weeks, and three months after treatment. At week three, both groups saw a significant improvement in American Orthopedic Foot and Ankle Society total score (LLLT, p<0.001; control, p=0.002). However, at the three-month follow-up, only the LLLT group progressed as assessed on the American Orthopedic Foot and Ankle Society total score (p=0.04). At all check-ins, the group scores for the 12-minute walk test were comparable. Both groups showed significant pain reductions at the three-month follow-up (LLLT, p<0.001; control, p=0.01); however, the LLLT group had a more significant reduction in pain at month three (p=0.03). Thus, reviewers concluded that combination therapy plus LLLT was more effective in reducing pain and improving function for patients with plantar fasciitis than orthotic care alone. Limitations included a lack of a control group, which would have accounted for the natural progression of recovery in patients with plantar fasciitis; another limitation is that the LLLT dose may or may not have been precise enough for the conditions of this study. The same group also published a randomized trial comparing LLLT (n=24) to extracorporeal shock wave therapy (ESWT) (n=25) or usual care (n=17).[70] Significant improvements in pain were seen over three months for all groups, with the LLLT group demonstrating lower pain than the

ESWT group (p=0.003) and control group (p=0.043). It was not clear whether different patients were used for these trials.

A double-blinded RCT by Macias (2015) assessed 69 patients with unilateral chronic plantar fasciitis and chronic heel pain of three months or longer that was unresponsive to conservative treatments (e.g., rest, stretching, physical therapy).[71] Patients were randomized to twice weekly treatment for three weeks of LLLT or sham treatment. The primary efficacy outcome, reduction of heel pain pre- to posttreatment, differed significantly between groups (p<0.001). Mean VAS scores decreased from 69.1 to 39.5 in the LLLT group and from 67.6 to 62.3 in the sham group. The difference in Foot Function Index scores did not differ significantly between groups.

An RCT on LLLT was reported by Kiritsi (2010) on LLLT in 30 subjects with plantar fasciitis.[72] The trial was double-blinded and sham-controlled trial and included 30 patients. Twenty-five (83%) patients completed the study, with treatment three times a week over six weeks. At baseline, plantar fascia thickness, measured by ultrasound was significantly greater in symptomatic compared with asymptomatic feet (5.3 mm vs 3.0 mm). Plantar fascia thickness decreased in both the LLLT and the sham groups during the study. Although plantar fascia thickness after 6 weeks of treatment did not differ significantly between the two groups (3.6 mm in LLLT, 4.4 mm in sham), there was a significant difference between groups in the change in thickness (1.7 mm LLLT vs 0.9 mm sham). VAS scores after night rest or daily activities improved significantly more in the LLLT group (59% improvement) than in the sham group (26% improvement). At baseline, pain after daily activities was rated as 67 out of 100 by both groups. At the end of treatment, VAS scores after daily activities were rated as 28 out of 100 for LLLT and 50 out of 100 for sham.

Section Summary

Sham-controlled RCTs have evaluated LLLT for plantar fasciitis, but findings were inconsistent. One RCT compared LLLT plus therapy with orthotic care alone, and while a significant advantage was observed in the LLLT treatment group, this treatment was a part of combination therapy. None of the studies presented long-term follow-up data. Three systematic reviews found that studies of LLLT for the treatment of plantar fascitis are limited by a lack of high quality evidence, small sample sizes, absence of long-term outcomes.

RHEUMATOID ARTHRITIS (RA)

Systematic Reviews

Lourinho (2023) conducted a systematic review and meta-analysis on the effects of LLLT in adults with rheumatoid arthritis.[73] Their literature search included 18 RCTs (n=793). There were varying intervention durations of four weeks to six months among the studies. Also, treatment regimens and comparisons varied among the studies. Some studies investigated laser acupuncture. The meta-analyses for the outcomes of interest, including pain, morning stiffness, handgrip strength, functional capacity, inflammation, and disease activity, were reported in subgroups of two to four studies, with no statistically significant differences in effects. The authors noted that 17 of the 18 studies had an overall high risk of bias and the results show a low quality of evidence for LLLT in rheumatoid arthritis.

A 2005 Cochrane Review included five placebo-controlled randomized trials and found that relative to a separate control group, LLLT reduced pain and morning stiffness, and increased

tip-to-palm flexibility.[74] Other outcomes did not differ between groups, including functional assessment, range of motion, and local swelling. For RA, relative to a control group using the opposite hand (one study), there was no difference observed between the control and treatment hand for morning stiffness duration and no significant improvement in pain relief. The authors noted that "despite some positive findings, this meta-analysis lacked data on how LLLT effectiveness is affected by four important factors: wavelength, treatment duration of LLLT, dosage and site application over nerves instead of joints."

Randomized Controlled Trials

A randomized double-blind placebo-controlled trial comparing outcomes of pain reduction and improvement in hand function in 82 patients with RA treated with low-level laser or placebo laser was reported by Meireles (2010).[75] However, co-treatment (such as pain medication) was not controlled during the trial and durability of treatment effects was not measured, limiting interpretation of these findings.

Section Summary

Studies on the use of LLLT for the treatment of rheumatoid arthritis have methodological limitations that preclude the interpretation of the results; therefore, valid conclusions cannot be made to determine if the use of LLLT leads to improved health outcomes.

SHOULDER PAIN

Systematic Reviews

A 2015 SR and meta-analysis evaluated 17 RCTs (13 high quality; four moderate quality) LLLT studies that included outcome measures of pain relief by VAS and relative risk for global improvement.[76] Results showed that patients treated with LLLT experienced significant and clinically relevant pain relief compared with placebo, for LLLT as monotherapy and as adjunct to exercise therapy. In addition, when LLLT was used in combination with physiotherapy, patients achieved significant pain reduction on VAS compared with placebo. Relative risks for global improvement were also statistically significant at 1.96 (95% CI 1.25 to 3.08) and 1.51 (95% CI 1.12 to 2.03), for laser as monotherapy or adjunctive in a physiotherapy regime, respectively. Study authors concluded that LLLT can offer clinically relevant pain relief and hasten improvement, both alone and in combination with physiotherapy.

A 2014 Cochrane review evaluated LLLT and other electrotherapy modalities for frozen shoulder.[77] The review found limited evidence to draw conclusions on the effectiveness of electrotherapy modalities for frozen shoulder. Only one RCT of 40 patients compared LLLT with placebo. This trial administered LLLT for six days. On the 6th day, LLLT was considered to have some improvement in a global assessment of treatment success when compared to placebo. However, this study was considered to be of low quality and the small size and short follow-up limited interpretation of results. Another RCT on LLLT discussed in the Cochrane review, by Stergioulas (2008), was considered to be of moderate quality.[78] In this study, 63 patients with frozen shoulder were included in an RCT comparing an 8-week program of LLLT (n=31) or placebo (n=32). Both groups also participated in exercise therapy. Compared with the sham group, the active laser group had a significant decrease in overall, night, and activity pain scores after four weeks and eight weeks of treatment, and at the end of eight more weeks of follow-up. At the same time intervals, a significant decrease in SPADI scores, and Croft shoulder disability questionnaire scores was observed, while a significant decrease in

Disability of Arm, Shoulder, and Hand Questionnaire scores was observed at eight weeks of treatment and at 16 weeks postrandomization; and a significant decrease in health assessment questionnaire scores was observed at four weeks and eight weeks of treatment. However, 11 patients included in the original randomization were excluded from analysis after leaving the study to seek other treatments. It is not known how this loss might have biased the final outcomes of the study.

Favejee (2011) published results from a SR of RCTs on the use of non-surgical treatment (including LLLT) for frozen shoulder (adhesive capsulitis).[79] Five Cochrane reviews and 18 RCTs were evaluated. The researchers reported finding a strong association between LLLT and reduced pain and disability. However, commentary on these findings points to the lack of distinction between primary (or idiopathic) capsulitis versus secondary adhesive capsulitis (due to trauma, diabetes, or thyroid dysfunction).[80] Because secondary capsulitis is less responsive to treatment, lack of sub-group analysis of treatment outcomes by patient type may limit the generalizability of these results to a specific patient population.

Randomized Controlled Trials

Badil Güloğlu (2021) randomized 64 patients with a recent diagnosis of subacromial impingement syndrome without treatment in the preceding four weeks to 15 sessions of LLLT (n=34) every weekday for three weeks or to weekly sessions of extracorporeal shock wave treatment (ESWT; n=30) for three weeks.[81] In both groups, all range of motion measurements, visual analogue scale pain scores, and SPADI scores showed significant improvements both at the end of treatment and at the third month after treatment ($p<0.05$). There was no significant difference in abduction between the groups except the change at the end of treatment. The ESWT group showed greater improvements in terms of SPADI disability and total scores at the end of treatment compared to LLLT. The improvements in VAS pain scores and SPADI scores at the third month after treatment was significantly more evident in the ESWT group ($p<0.05$).

Alfredo (2021) randomized 122 patients to LLLT plus exercise (group 1, n=44; 42 included in analysis), exercise alone (group 2, n=42), or LLLT alone (group 3, n=42) for the treatment of subacromial impingement syndrome:[82] Therapy was given three times a week for eight weeks. The primary outcome was the change in shoulder pain and disability index (SPADI) and numeric pain rating scale and medication intake were secondary outcomes. SPADI scores at baseline, two month, and three month follow-up ($p=0.001$) were 60.8 (37.7 to 70.8), 3.8 (0.0 to 10.8) and 2.3 (0.8 to 10.8) for group 1; 61.5 (41.5 to 71.5), 9.2 (3.8 to 29.2) and 14.2 (1.5 to 38.0) for the group I2; and 73.3 (59.2-80.8), 34.2 (16.9 to 54.6) and 33.1 (22.3 to 49.2) for the group 3, respectively, all $p<0.05$. Pain scores at baseline ($p=0.829$), two- month ($p=0.057$) and three- month follow-up ($p=0.004$) were 6.8 (4.7 to 7.7), 0.2 (0.0 to 0.5) and 0.3 (0.0 to 1.0) for group 1; 6.6 (5.7 to 8.0), 0.5 (0.2 to 2.0) and 0.2 (0.0 to 3.3) for group 2; and 6.5 (5.1 to 7.4), 2.4 (0.1 to 6.7) and 4.0 (2.0 to 5.0) for group 3, respectively. While patients in the LLLT plus exercise group had a significantly greater improvement in SPADI compared to other groups, no between-group comparison was performed for patients receiving LLLT alone and exercise alone. This study was also limited by lack of blinding.

Eslamian and others evaluated the effects of LLLT in combination with conventional physiotherapy endeavors in 50 patients with rotator cuff tendinitis.[83] A total of 25 patients were randomly assigned to the control group and received only routine physiotherapy. The additional 25 patients were assigned into the experimental group and received conventional

therapy plus LLLT. Authors concluded that LLLT combined with conventional physiotherapy had superiority over routine physiotherapy in decreasing pain and improving the patient's function, but no additional advantages were detected in increasing shoulder joint range of motion in comparison to other physical agents. This study had a limited study population and did not include a sham group for comparison.

Results from additional RCTs remain limited by lack of sham control [83-86] and/or lack of treatment durability assessment.[87-89]

Section Summary

In sumary, conflicting results from available RCTs limit the conclusions that can be drawn about the effectiveness of LLLT in shoulder disorders.

TEMPOROMANDIBULAR JOINT PAIN

Systematic Reviews

Zhang (2023) published a systematic review and meta-analysis of laser therapy on temporomandibular disorders, including 28 RCTs.[90] Overall, laser therapy had a statistically significant effect on VAS (21 studies; n=934; SMD: -1.88; 95% CI, -2.46 to -1.30; p<.00001; I^2, 93%), maximum active vertical opening (17 studies; n=732; MD, 4.90; 95% CI, 3.29 to 6.50; p<.00001; I^2, 72%), maximum passive vertical opening (5 studies; n=300; MD, 5.82; 95% CI, 4.62 to 7.01; p<.00001; I^2, 40%), and right lateral movement (6 studies; n=261; MD, 0.73; 95% CI, 0.23 to 1.22; p=.004; I^2, 0%). The authors note that while the results demonstrated effective pain relief, but limited effect on improvement of mandibular movement. There was variation among the included studies, including various laser parameter settings. RCTs with larger sample sizes are needed for higher quality evidence.

Arribas-Pascual (2023) published systematic review and meta-analysis on the effects of various physiotherapy interventions on pain and mouth opening in temporomandibular disorders.[91] They conducted a sub-analysis on four studies of LLLT. The found a statistically significant effect of LLLT on pain intensity (SMD, 0.8; 95% CI, 1.44 to 0.17; p<.001; I^2, 27%) and maximum mouth opening (SMD, 0.95; 95% CI, 1.5 to 0.39; p<.001; I^2, 21%). The overall confidence of studies included in the systematic review were low or critically low. The systematic review did not adequately report sample sizes among the studies used in the LLLT sub-analyses. Overall, the results are of a low quality of evidence.

Tournavitis (2023) published a systematic review and meta-analysis that assessed conservative treatments for temporomandibular joint (TMJ) related pain.[92] Twenty-eight studies were included and of those five included LLLT. Two studies used PMB, which the authors state is an umbrella term that includes LLLT. LLLT and PBM offered short-term improvement in TMJ pain when compared to a control group (LLLT vs. control; p = 0.001; LLLT vs. PBM vs control; p=0.033), but were less effective than occlusal splint (p = 0.35).

Hanna (2021) published a large systematic review of 44 RCTs of LLLT for temporomandibular joint (TMJ) pain.[93] All included trials were at low risk for reporting missing outcome data. Seventy percent of the included trials were at low risk, 28% were at high risk, and 2% had some concerns in terms of reporting outcome measurement. Of the RCTs included, 98% were at low risk of bias for selective reporting of the results. Overall, 38% of studies had a low risk of bias, 46% were at high risk, and 16% had some concerns. Comparators across RCTs included sham placebo, drug therapy and physiotherapy. The primary outcome of interest was was

change in pain intensity reduction from baseline, measured by a visual analogue scale (VAS). Thirty-three studies (N=1163) were eligible for inclusion in the meta-analysis. In a meta-analysis, pooled change in VAS score from baseline to final follow-up evaluation demonstrated a significantly greater reduction with LLLT compared to comparator groups (pooled SMD, -0.55; 95% CI, -0.82 to -0.27; p<0.0001), however, heterogeneity was high (I^2=78%).

Jing (2021) published the results of a SR with meta-analysis of 16 RCTs to evaluate the effects of different energy density LLLT in patients with TMJ pain.[94] D1 laser therapy (energy density ranging from 0 to 10 J/cm2) was associated with more pain reduction than placebo (MD = 2.49, 95% CI ranging from 1.28 to 3.71) immediately following treatment based on "moderate" quality evidence. One month following treatment, d1 laser therapy also performed better than placebo (MD = 1.69, 95% CI = -0.78, 4.16) based on "low" quality evidence.

Chang (2014) published a meta-analysis of seven RCTs on LLLT for TMJ pain.[95] Included RCTs compared LLLT to no treatment or placebo. Only six studies were sufficient to be included in the meta-analysis for a total of 223 patients. The number of treatment sessions ranged from 4 to 20. The pooled effect size of pain relief using the VAS was a mean decrease of 0.6 [95% confidence interval (CI) −0.47 to −0.73].

A SR by Maia (2012) investigated the effect of LLLT on TMJ disorders (TMD).[96] Of the 14 studies reviewed, authors concluded the lack of standardization across the studies limited the interpretation of the review's results. Authors suggested further research is necessary to obtain a consensus regarding the best application protocol for pain relief in patients with TMD.

Melis (2012) reviewed 14 studies evaluating the efficacy of LLLT for the treatment of TMD.[97] The outcomes of the trials were controversial and not related to any features of the laser beam, to the number of laser applications, or their duration. Authors concluded that based on the results of the review no definitive conclusions could be drawn on the efficacy of LLLT for the treatment of TMD.

A SR by Petrucci (2011) included six sham-controlled randomized clinical trials of LLLT for TMD.[98] Using change in pain by VAS as the primary treatment outcome, the researchers concluded that LLLT was not more effective than placebo alone.

Randomized Controlled Trials

Chamani (2024) randomized 42 patients with temporomandibular disorders into three groups: LLLT (n=14), placebo (n=15), or standard treatment (n=13).[99] The LLLT group received treatment twice per week for 10 sessions. All groups showed a statistically significant improvement in VAS (p=.0001), lateral jaw movements (p=.0001) forward jaw movement (p=.007), but not in maximum mouth opening. There was no significant difference between groups. The authors conclude that LLLT may be effective in treating temporomandibular disorders, but there was no difference to standard therapy. This study is limited by its small sample size and single-center design, so further evidence is needed.

Tanhan (2023) compared physical therapy (manual pressure release) with exercise to LLLT with exercise and to exercise alone in 75 participants with myofascial jaw pain and cervical myofascial pain.[100] Compared to baseline all groups had improvement in pain (p<0.01). The combination of LLLT with exercise and manual release pressure with exercise relieved pain better than exercise alone. The authors conclude that multimodal approaches to TMJ pain should include exercise.

Desai (2022) randomized 60 patients with TMJ disorders to LLLT or placebo given for 20 sessions over 8 weeks.[101]74, By week 8 both the placebo group and LLT group had improvements from baseline with a final mean VAS of 5.2 in the placebo group and 3.2 in the LLLT group. There was no statistical comparison reported between groups. Mouth opening and lateral movement were also improved in both groups compared to baseline; however, improvements were numerically greater in the LLLT group. The small sample size, single-center design, and lack of comparison between active and placebo treatment limit generalizability of these finding.

Del Vecchio (2021) randomized 90 patients between the ages of 18 and 73 years old with TMJ disorders to home LLLT (808 nm, 5 J/min, 250 mW, 15 KHz for eight minutes twice daily), sham control, or standard conventional drugs (nimesulide 100 mg daily with five days of cyclobenzaprine 10 mg daily) for one week.[102] Pain was measured using a 100-mm VAS, and the examiner was blinded. At the end of treatment, the reduction in VAS was greater in the LLLT group (MD, 13.030; p=0.036) and the drug group (MD, 14.409; p=0.17) compared to the sham group. However, no significant difference in pain reduction was observed between the LLLT group and the drug group (MD, 1.379; p=1). This study evaluated a specific at-home LLLT protocol limiting the generalizability of the findings to other LLLT regimens.

Aisaiti (2021) randomized 78 patients with TMJ pain to receive LLLT (810 nm, 6 J/cm2, applied at five points for 30 seconds) or placebo once daily for seven consecutive days.[103] Pain was measured on a 0 to 10 numerical rating scale and pressure pain thresholds. Only 50 patients, 25 per group, remained in the study to contribute data to analysis. Greater reduction in numerical rating scale pain scores were seen with LLLT than with placebo (p=0.014), but no significant interaction between time and intervention was found (p=0.35). For pressure pain thresholds, there was no significant difference found between interventions or interaction between time and intervention.

Madani (2020) published a randomized, double-blind clinical trial in 45 patients with TMD.[104] Patients were randomized to group 1 (LLLT applied to the painful masticatory muscles two times a week for 5 weeks), group 2 (laser acupuncture therapy [LAT] emitted bilaterally on acupuncture points with the same settings as the LLLT group) or group 3 (placebo underwent treatment with sham laser). Patients were evaluated before treatment, after five and ten laser applications, and at month. No significant difference in mouth opening between the groups was identified ($p > 0.05$), but the amount of lateral excursive and protrusive movements was significantly greater in LLLT and LAT groups than the placebo group at some intervals ($p< 0.05$). No mid- or long-term follow-up data were reported.

A double-blind, placebo-controlled randomized trial by Shobha (2017) investigated the effectiveness of LLLT in patients with TMJ pain.[105] Forty TMJ patients were evenly randomized to an active or a placebo group. Treatment included two to three weekly sessions of LLLT for a total of eight sessions. Patients were evaluated at baseline, after treatment, and at a 30-day follow-up. Both groups experienced pain reduction at all evaluation points. The most significant pain reduction was reported at the 30-day follow-up (p=0.001). There were no significant differences between groups at baseline (p=0.214), final session (p=0.000), or the 30-day follow-up (p=0.230). For a secondary outcome (the ability to open one’s mouth), while both groups showed improvement, the difference between groups was not significant (p=0.330). Therefore, LLLT was determined to have no greater impact on healing or pain reduction over placebo.

Another clinical trial, by Ahrari (2013), assessed LLLT in 20 patients with myogenic TMD.[106] Patients were randomly divided into laser and placebo groups. There was a significant increase in mouth opening and a significant reduction of pain symptoms in the laser group that was not observed in the placebo group. Between-group comparisons revealed no significant differences in pain intensity and mouth opening measurements at any of the evaluation time points. Using a very limited sample size, authors concluded that LLLT can produce a significant improvement in pain level and mouth opening in patients affected with myogenic TMD.

Additional RCTs lacking study of durability of treatment effects have also been published.[107-114]

Nonrandomized studies

Nonrandomized studies have been published evaluating the effectiveness of LLLT in TMD, but have not identified significant impacts on health outcomes.

Section Summary

There are several SRs of LLLT for TMJ syndrome. Findings from these reviews, as well as from RCTs of this treatment, are mixed, and most trials do not show a benefit of LLLT. RCTs have not compared the impact of LLLT with physical therapy on health outcomes.

WOUND HEALING

Systematic Reviews

Li (2018) published a SR and meta-analysis of 7 RCTs (N=194) evaluating LLLT as a treatment for a diabetic foot ulcer.[115] Ulcer area was significantly reduced with LLLT compared with control (WMD 34.18; 95% CI 19.38–48.99; p<0.001), and the complete healing rate significantly improved with LLLT (OR 6.72; 95% CI 1.99–22.64; p=0.002). The analysis was limited by the number of studies included and small sample size, and by each study having different parameters, demographic information, ulcer characteristics, follow-up time, and treatment period.

Machado (2017) published a SR evaluating the treatment of pressure ulcers with LLLT.[116] Reviewers identified four studies meeting eligibility requirements (total n=210 patients). Outcomes were the ulcer area, healing rate, and overall healing rate. Two of the four studies used LLLT with a single wavelength;[117, 118] and the other two used LLLT with probe cluster, which employs the simultaneous assimilation of different types of diodes and wavelengths.[119, 120] In the study that employed the 658 nm wavelength, reviewers found that particular frequency reduced pressure ulcers by 71%. The other wavelengths did not produce any significant findings related to the study outcome; moreover, the studies using the probe cluster technique were also not successful in producing significant findings. While studies should be conducted to investigate further the success found in single wavelength at 658 nm, at this time there is insufficient evidence to suggest LLLT can significantly benefit patients with pressure ulcers.

Suter (2017) published a SR on the use of LLLT in patients with aphthous stomatitis, also known as canker sores.[121] There were 11 studies included in the review, 10 of which were RCTs, and outcomes included pain relief, duration of wound healing, and reduction in frequency of episodes. Controls in the studies received either placebo, no therapy, or topical

corticosteroids. LLLT was associated with reductions in immediate pain in five out of six studies, reductions in late pain in seven out of 10 studies, and with faster wound healing in five out of nine studies. The authors noted, however, that only two of the studies were double-blinded and studies were of a generally low quality, with a mean Jadad score of 1.0 out of 5.

Santinoni (2017) evaluated LLLT and maxillofacial wound healing in a SR focused on six studies that evaluated bone repair.[122] Four of the studies showed improved bone formation with LLLT, two showed improvements at only one follow up point, and one showed no benefit. Because the LLLT treatments were not standardized, no specific conclusions could be drawn.

Additional evidence on LLLT for wound healing includes a SR from the Agency for Healthcare Research and Quality (AHRQ) in 2004 and a 2014 Cochrane review.

The evidence report on vacuum-assisted and low-level laser wound therapies for treatment of chronic non-healing wounds prepared for the AHRQ was based on 11 studies of LLLT.[123] The review concluded:

> "The best available trial [of low level laser wound therapy] did not show a higher probability of complete healing at 6 weeks with the addition of low-level laser compared to sham laser treatment added to standard care. Study weaknesses were unlikely to have concealed existing effects. Future studies may determine whether different dosing parameters or other laser types may lead to different results."

In 2014 a Cochrane review of RCTs on light therapy, including phototherapy, ultraviolet and laser, for pressure ulcers was published.[124] The few trials available for analysis were of small size and very low quality. The reviewers found the available evidence overall was insufficient to draw conclusion on the effects light therapy on pressure ulcers.

Randomized Controlled Trials

Since the publication of the Cochrane review described above, there have been a number of RCTs evaluating LLLT for the healing of various wounds, including diabetic ulcers,[125] sternotomy incisions,[126] hip arthroplasty incisions,[127] skin graft donor wounds,[128] soft tissue injuries due to trauma,[129] and periodontal wounds.[130-134] For the most part, these have been small studies of varied quality, and they have yielded mixed results.

Section Summary

Evidence is limited on the use of LLLT for the treatment of wound healing and therefore valid conclusions cannot be made to determine if the use of LLLT leads to improved health outcomes.

OTHER INDICATIONS

LLLT has been studied in RCTs for use in indications such as treatment of venous leg ulcers,[117] perineal pain after episiotomy,[135] chronic periodontitis,[136] sternotomy healing,[137] and improvement of visual acuity in amblyopia.[138] A SR of active-control clinical trials (some lacking randomization to treatment) has also been published on the use of LLLT for treatment of hypertrophic scars.[139] A SR of LLLT in the management of tinnitus evaluated ten RCTs and concluded the effectiveness of the technology was not established and adequately powered RCTs with longer-term outcomes were needed.[140] A SR evaluating studies of LLLT for acceleration of orthodontic tooth movement concluded that further studies are needed to

overcome limitations resulting from heterogeneity among study designs.[141] Before this evidence can be used to make determinations about treatment benefit in this indications, all individual studies require replication with one or more subsequent RCTs to validate any findings of treatment benefit.[117, 135, 136, 138] Where present evidence lacks placebo control,[117, 136, 139] any such replication should include comparison with sham.

Section Summary

Available evidence is therefore considered insufficient to make conclusions about the effectiveness of LLLT in venous leg ulcers, perineal pain after episiotomy, chronic periodontitis, and improvement of visual acuity in amblyopia.

LASER ACUPUNCTURE (LA)

HEADACHE

Ebneshahidi (2005) performed a single-blind, randomized, placebo-controlled trial of 50 patients with chronic tension headache and reported that laser acupuncture using a LLLT device may provide benefit over placebo.[142] The study was small and the acupuncturists administering the true or sham treatments as well as the assessors were aware of the allocation and thus could have positively influenced the laser acupuncture group. In addition, the baseline measures were different from the subsequent measurements performed in follow-up. The results from this small study need to be validated in a larger, randomized, double-blind clinical trial.

A trial of laser acupuncture on 43 children with both migraine and tension headaches provided highly individualized treatment and additional therapies which do not permit conclusions regarding the independent effects of laser treatment.[143]

LOW BACK PAIN

Yang (2023) published a RCT of laser acupuncture for low back pain in nurses in China.[144] Seventy-six nurses were randomized to have low-level laser acupuncture combined with auricular acupressure or sham acupuncture without laser energy output. Outcome measures were pain using the Brief Pain Inventory and quality of life measured with the Roland-Morris Disability Questionnaire. Pain was measured at 2.4, and 8 weeks after intervention, and significant differences were seen in favor of laser acupuncture at each time-point. Quality of life was also better in the treatment group at weeks 4 and 8. Participants were similar in their usage of pain medication and muscle relaxants but the study results do not account for medication usage.

Cheng (2022) performed an RCT comparing laser acupuncture to usual care in post-partum women with low back pain.[145] The study included 106 women and the treatment group had 10 sessions of laser acupuncture. Laser acupuncture was associated with significantly lower pain ($p<0.001$), fewer limitations of daily activities ($p<0.001$) and physical activities ($p<0.001$) and less perceived stress ($p=0.001$). Salivary cortisol levels were also lower in the treatment group ($p=0.02$). It is not known if the participants also used medication for low back pain.

Glazov (2014) assessed the effect of infrared LA for reducing pain and disability in treatment of chronic low back pain (LBP).[146] The double-blind sham laser controlled trial included 144 adults with chronic non-specific LBP. Participants were followed-up at one and six weeks, and six and 12 months post-treatment. The analysis showed no difference between sham and the

laser groups at six weeks for pain or disability. There was a significant reduction in mean pain and disability in all groups at six weeks (p<0.005); Numerical Pain Rating Scale (NPRS): sham (-1.5, 95% CI -2.1 to -0.8), low dose (-1.3, 95% CI -2.0 to -0.8), high dose (-1.1, 95% CI -1.7 to -0.5). ODI: sham (-4.0, 95% CI -7.1 to -1.0), low dose (-4.1, 95% CI -6.7 to -1.5), high dose (-2.6, 95% CI -5.7 to 0.5). All secondary outcomes also showed clinical improvement over time but with no differences between groups. The authors concluded that laser acupuncture using energy density range (0-4 J/cm^2) for the treatment of chronic non-specific LBP resulted in clinical improvement unrelated to laser stimulation.

A randomized, placebo-controlled, double-blind trial by Shin (2015) evaluated laser acupuncture for low back pain.[147] Study participants were randomly assigned to either the laser acupuncture group (n = 28) or the sham laser acupuncture group (n = 28). The study only lasted for one week and included three sessions. There were no significant differences in any of the measured outcomes.

OTHER MUSCULOSKELETAL PAIN

Da Silva Mira (2024) published a systematic review and meta-analysis of the use of LLLT to acupuncture points to treat TMJ.[148] Seven studies were included that involved 275 participants. Three studies were placebo-controlled RCTs. The included studies had low to moderate heterogeneity. Compared to a control group, LLLT at acupoints reduced spontaneous pain (p<0.0001). The increase in mouth opening was statistically significantly improved after LLLT application (p=0.002). However, the studies were inconsistent in the density and dose of laser irradiation, as well as irradiation time. The authors note the importance of determining the irradiation parameters for safe and effective delivery of LLLT at acupuncture points.

Han (2024) published a systematic review and meta-analysis of laser acupuncture (LA) use for knee osteoarthritis.[149] Twenty-five RCTs involving 2075 participants were included. Comparators to LA included for the meta-analysis were sham treatment, LLLT without acupuncture, LA plus acupuncture compared to LA alone, acupuncture without LLLT. The authors concluded that LA is “more or less effective” for osteoarthritis, and its overall efficacy is similar to LLLT. However, some studies found LA superior to acupuncture alone. The authors noted barriers to outcome comparisons included variability in disease staging and laser parameters, as well as selection of acupoints; and called for standardization of participant selection and LA interventions in future research.

Huang (2022) published a single-blind, placebo-controlled RCT that randomized 82 patients who had total knee arthroplasty (TKA) to receive post-operative laser acupuncture or placebo acupuncture.[150] The laser acupuncture group had less pain at hours 10-72 post surgery (p<0.05) and less morphine consumption at hours 48 and 72 (p<0.05).

A sham-controlled study by Kibar (2017) randomized 73 patients with subacromial impingement syndrome.[151] At baseline and after 15 sessions of laser or sham treatment, pain (VAS), range of motion, and functional status were assessed. All outcomes showed significantly more improvement in laser acupuncture group compared with the sham group.

Fleckenstein (2016) reported results of a five-arm RCT comparing needle acupuncture, laser acupuncture, sham needle acupuncture, sham laser acupuncture, and no intervention for delayed-onset muscle soreness.[152] There were 60 participants that had delayed-onset muscle

soreness induced in the study. None of the interventions were found to improve the outcomes assessed: pain intensity, pain threshold, or maximum isometric voluntary force.

Two studies reported no significant difference between patients treated with active vs. sham laser acupuncture for the treatment of whiplash injury[153] and knee osteoarthritis[154]. A third RCT[155] assessed the effectiveness of acupuncture plus stretching to reduce pain and improve range of motion in patients afflicted by cervical myofascial pain syndrome (n=19). Health outcomes were measured immediately after treatment and up to 30 minutes following treatment. Patients had significantly increased range of motion after the application of acupuncture and stretching compared with sham placebo ($p<0.05$). However, the study was limited by lack of generalizability to wider patient populations.

Results of laser acupuncture are conflicting for knee osteoarthritis. An RCT evaluated laser acupuncture for the treatment of knee osteoarthritis among older adults.[156] Results showed that neither laser nor needle acupuncture resulted in treatment benefits compared with sham therapy in this patient population, and study authors do not recommend its use. Another small RCT[157] showed that short-term application of LLLT to specific acupuncture points in association with exercise and advice is effective at significantly reducing pain and improving quality of life (QOL) in patients with knee osteoarthritis. Both studies evaluated small patient populations and lacked statistical power. Results were generally not generalizable to wider patient populations.

WEIGHT LOSS

In a study by Tseng (2016), 52 obese subjects were randomly assigned to either the laser acupuncture group or the sham group.[158] Treatment lasted for eight weeks and then after a two-week washout period, the opposite treatment. The authors concluded that laser acupuncture improved anthropometric measurements and appetite sensations in obese subjects. This was a small study with methodological limitations. A similar, single-blind study by Hung (2016) randomized 66 postpartum patients to laser acupuncture or sham for weight loss.[159] Treatment was performed five times per week for 12 sessions. There were no significant differences between groups for any of the outcomes measured, including body mass index and body fat percentage.

A study by El-Mekawy (2015) evaluated laser acupuncture combined with a diet and exercise intervention for metabolic syndrome.[160] Twenty-eight obese, post-menopausal women were randomly assigned and followed for 12 weeks. Both groups showed a significant decrease in the anthropometric and metabolic parameters. The laser acupuncture group showed a significantly greater decrease in the waist and hip circumferences, cholesterol, and insulin levels compared to the control group.

OTHER INDICATIONS

Abd El Azeem (2023) conducted an RCT comparing laser acupuncture along with behavioral therapy and dietary modification to a laxative combined with behavioral therapy and dietary modification in 40 children with chronic constipation.[161] The therapy was over four weeks with four-month follow-up. Both groups had higher median frequency of bowel movements from baseline, but the laser acupuncture group was higher than the control group both after treatment ($p=0.01$) and at three months ($p=0.03$). Laser acupuncture was also associated with improved stool consistency after treatment compared to the laxative group ($p=0.03$). The authors noted that prior research has shown conflicting results and more study is needed to

know whether laser acupuncture is superior to other treatments for chronic constipation in children.

Laser acupuncture with usual vitamin supplementation was studied in post-menopausal women by Hassan (2023) to determine if laser acupuncture is an effective therapy for pain and osteoporosis.[162] Sixty-eight women were randomized to receive laser acupuncture with usual vitamin therapy (calcium and vitamin D3) or vitamin therapy alone. Both groups showed increased bone density after treatment. The laser acupuncture group had a significantly higher increase in bone density and improved pain scores than the vitamin group alone ($p<0.0001$). The study is limited by short follow-up and small sample size.

Kannon (2022) published a systematic review and meta-analysis on the use of acupuncture in children for the treatment of nocturnal enuresis.[163] Thirteen studies involving 890 participants were included and six studies used laser acupuncture. Only one study was deemed to have low risk of bias. Meta-analysis did not find significant differences in studies that compared laser acupuncture to sham acupuncture or in studies comparing laser acupuncture to pharmacologic intervention.

Juan (2019) published the results of a RCT on efficacy of laser acupuncture in patients with idiopathic mild-to-moderate carpal tunnel syndrome (CTS).[164] Eighty-four consecutive patients were randomly divided into the treatment arm, treated once a day, five times a week for four weeks ($n = 43$) or the sham arm using the same device and protocol with the laser acupuncture device switched off ($n = 41$). Patients completed the Global Symptom Score (GSS) at baseline and two and four weeks later. Nerve conduction studies (NCSs) were performed at baseline and repeated at the end of the study. There was a significantly greater reduction in GSS in the treatment group than in the placebo group at week two (-9.30 ± 4.94 vs. -2.29 ± 4.27, respectively, $p < 0.01$) and at week four (-10.67 ± 5.98 vs. -2.90 ± 5.61, respectively, $p < 0.01$). However, no significant difference in NCS between the two groups was found. No long-term outcomes were reported.

Laser acupuncture was evaluated as a treatment for pain from kidney biopsy in mainly pediatric patients in a double-blind trial by Oates (2017).[165] A total of 69 treatments were given to patients aged 7 to 26 years: 33 low-level laser applications to 10 acupuncture points and 36 low-level laser applications to sham points. There were significant differences in favor to the acupuncture group for changes pain scores (0.044), heart rate ($p=0.043$), and respiratory rate ($p=0.045$), but the clinical significance of these differences is uncertain.

Alsharnoubi (2017) reported the results of a trial comparing laser acupuncture to treatment with desmopressin for nocturnal enuresis in children.[166] The 45 children in the study were randomized to receive either laser acupuncture, desmopressin acetate, or a combination of both treatments. Laser treatments were given twice a week for three months, and desmopressin (60µg) was given daily for three months. All patients were provided with behavioral therapy in addition to other treatments. There was a significantly higher rate of complete recovery in the acupuncture group (73.3%) compared with the desmopressin alone group (20.0%), or the combination therapy group (13.3%). The authors explained the surprisingly low cure rate in the combination group by stating that only seven of the 15 children in this group actually received the complete treatment course, but there was no mention of the compliance rate in the other groups.

Dabbous (2016) evaluated low-level laser on acupuncture points compared to conventional physiotherapy in hemiplegic spastic cerebral palsy children.[167] Forty spastic hemiplegic

cerebral palsy children aged one to four years were randomly divided into control (n=20) and study groups (n=20). The low-level laser group had significantly better muscle tone (wrist flexors and plantar flexors) but there was no different for range of motion. The authors concluded that laser acupuncture has a beneficial effect on reducing spasticity in spastic cerebral palsy, however there was no blinding in the study, which indicates significant potential for bias.

A study by Lee (2016) compared the effects of laser acupuncture, manual acupuncture, and electromagnetic field stimulation on heart rate variability in 56 patients.[168] Patients were randomized to four groups: the three treatment groups and a control group that received no stimulation. Heart rate variability was calculated from electrocardiogram (ECG) and assigned to high frequency (HF: 0.15 to 0.4 Hz), low frequency (LF: 0.04 to 0.15 Hz) domains. The LF and LF/HF ratio were found to be higher in the laser acupuncture group and lower in the manual acupuncture and electromagnetic stimulation groups, compared to controls, while this pattern was reversed for variation in the HF domain. The authors attribute these findings to differential stimulation of the parasympathetic and sympathetic nervous systems, but did not offer a potential mechanism for these differences.

Section Summary

The current evidence base does not permit conclusions concerning the impact of laser acupuncture on health outcomes for any of these conditions. The evidence is limited by small sample size and short-term follow-up and is significantly heterogenous.

PRACTICE GUIDELINE SUMMARY

NORTH AMERICAN SPINE SOCIETY

In 2020, the North American Spine Society published a guideline on the diagnosis and treatment of low back pain. The guideline was based on a systematic review of the literature to address key clinical questions regarding the diagnosis and treatment of adults with nonspecific low back pain and included the following regarding laser therapy:

Guideline Recommendation (Grade of Recommendation)

- It is suggested that the combination of laser therapy (low-level or high-level) with exercise provides better short-term relief of pain than either exercise or laser therapy alone. (B=Fair evidence [Level II or III studies with consistent findings] for or against recommending intervention)
- There is conflicting evidence that the combination of laser therapy with exercise provides better short-term improvement in function compared to exercise or laser therapy alone. (I=Insufficient or conflicting evidence not allowing a recommendation for or against intervention.)
- It is suggested that there is no short-term benefit of laser therapy (low-level or high-level) when compared with exercise alone. (B=Fair evidence [Level II or III studies with consistent findings] for or against recommending intervention)

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS (AAOS)

The AAOS published an updated guideline on the management of carpal tunnel syndrome in 2024 that includes laser therapy as a non-operative treatment that does not improve long-term outcomes for carpal tunnel syndrome.[169] The quality of evidence was rated “high.”

The AAOS 2016 clinical practice guideline on the treatment of carpal tunnel syndrome rated laser therapy as having “limited evidence.”[170] The guidelines state: “limited evidence supports that laser therapy might be effective compared to placebo.”

AMERICAN COLLEGE OF PHYSICIANS (ACP)

In 2020, the ACP and American Academy of Family Physicians published joint guidelines on the nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults.[171] The guideline recommends interventions that improved at least two outcomes related to pain and function. The guideline notes that laser therapy improved only one outcome (symptom relief) and with low-certainty evidence.

The 2017 ACP clinical practice guideline on noninvasive treatments for acute, subacute, and chronic low back pain list LLLT among a number of potentially recommended treatments for patients with chronic low back pain based on low-quality evidence.[172]

AMERICAN PHYSICAL THERAPY ASSOCIATION (APTA)

In 2023, the APTA published clinical practice guidelines for plantar fasciitis that state, “Clinicians should use low-level laser therapy as a part of a rehabilitation program in those with acute or chronic plantar fasciitis to decrease pain in the short term;” Grade B (moderate evidence).[173]

In 2018, the American Physical Therapy Association published an updated guideline on the diagnosis and treatment of Achilles tendinitis.[174] The use of LLLT was given a level D recommendation, meaning that no recommendation could be made due to contradictory evidence.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE (ACOEM)

- In recommendations regarding treatment of carpal tunnel syndrome (CTS) published in 2011, the ACOEM recommended against the use of LLLT for CTS.[175] This recommendation was based upon Level C evidence (at least intermediate evidence that harms and costs exceed benefits based on limited evidence”).

- In a 2009 update to existing guidelines on disorders other than CTS of the hand, wrist, and forearm, the ACOEM recommended against the use of LLLT for treatment of hand or finger osteoarthrosis based upon a Level B recommendation (“moderately not recommended,” based upon “intermediate evidence that the intervention is ineffective, or that harms or costs outweigh benefits”).[176]

MUCOSITIS PREVENTION GUIDELINE DEVELOPMENT GROUP

In 2021, the Clinical Practice Guideline for the Prevention of Oral and Oropharyngeal Mucositis in Pediatric Cancer and Hematopoietic Stem Cell Transplant Patients was updated from the 2017 Mucositis Prevention Guideline Development Group.[177] Regarding PBM, the guideline states:

- Use intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients undergoing autologous or allogeneic HSCT and for pediatric patients who will receive radiotherapy for head and neck carcinoma (Strong recommendation, high-quality evidence).
- Consider using intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients who will receive radiotherapy for head and neck cancers other than carcinoma (Conditional recommendation, moderate quality evidence).

MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER AND INTERNATIONAL SOCIETY OF ORAL ONCOLOGY

In 2020, the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) updated the guidelines on the management of mucositis secondary to cancer therapy.[178] The guidelines state:

- The panel recommends the use of intraoral PBM therapy using low-level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without TBI, using one of the selected protocols listed in Table 2 (Level of evidence: I).
- The panel recommends the use of intraoral PBM therapy using low-level laser therapy for prevention of OM in adults receiving RT to the H&N (without CT) (Table 2); safety considerations unique to patients with oral cancer should be considered (Level of evidence: II).
- The panel recommends the use of intraoral PBM therapy using low-level laser therapy for the prevention of OM in adults receiving RT-CT for H&N cancer (Table 2); safety considerations unique to patients with oral cancer should be considered (Level of evidence: I).
- For all PBM guidelines, it is recommended that the specific photobiomodulaton therapy parameteres of the selected protocol will be followed for optimal therapy.

Table 2: Recommended Intraoral Photobiomodulation Therapy Protocols for the Prevention of Oral Mucositis

Cancer Treatment Modality	Wavelength, nm	Power Density (Irradiance), mW/cm^2	Time per Spot, s	Energy Density (Fluence), J/cm^2	Spot Size, cm^2	No. of Sites	Duration
HSCT	632.8	31.25	40	1.0	0.8	18	From the d after cessation of conditioning for 5 d
	650	1000	2	2.0	0.04	54-70	From the first d of conditioning to d +2 post-HSCT (for 7-13 d)
RT	632.8	24	125	3.0	1.00	12	Entire RT course

RT-CT	660	417	10	4.2	0.24	72	Entire RT course
	660	625	10	6.2	0.04	69	Entire RT course

Abbreviations: CT, chemotherapy; HSCT, hematopoietic stem-cell transplantation; RT, radiotherapy.

SUMMARY

There is enough research to show that low-level laser therapy (LLLT) can improve health outcomes for people with an increased risk of oral mucositis due to some cancer treatments and/or hematopoietic cell transplantation. Therefore, LLLT may be considered medically necessary for prevention of oral mucositis in patients undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy and/or radiotherapy, and/or hematopoietic cell transplantation.

There is not enough research to show that low-level laser therapy (LLLT), including laser acupuncture, can improve health outcomes for patients that have conditions other than oral mucositis, including but not limited to carpal tunnel syndrome, various musculoskeletal conditions, and wound healing. Therefore, low-level laser therapy (LLLT) remains investigational for all indications except prevention of oral mucositis.

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CODES

Codes	Number	Description
CPT	0552T	Low-level laser therapy, dynamic photonic and dynamic thermokinetic energies, provided by a physician or other qualified health care professional
	97037	Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction
	97039	Unlisted modality (specify type and time if constant attendance)
HCPCS	S8948	Application of a modality (requiring constant provider attendance) to one or more areas; low level laser, each 15 minutes

Date of Origin: *January 2003*

Regence

Medical Policy Manual Medicine, Policy No. 140

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

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

Radioembolization, transarterial embolization (TAE), and transarterial chemoembolization (TACE) involve delivery of small radioactive, chemotherapeutic, or inert beads for treatment of various conditions.

MEDICAL POLICY CRITERIA

I. Radioembolization may be considered **medically necessary** for any of the following:
   A. Locations other than the liver; or
   B. Primary or metastatic liver tumors, when any of the following are met:
      1. Unresectable primary liver tumors (hepatocellular carcinoma [HCC]); or
      2. As a bridge to transplantation in primary HCC; or
      3. Unresectable hepatic metastases from neuroendocrine or colorectal tumors, or melanoma when any of the following are met:
         a. Neuroendocrine tumors (carcinoid and noncarcinoid) when both of the following criteria (i. and ii.) are met:

i. The disease is liver-dominant and diffuse (defined as tumor tissue spread throughout the affected organ) and symptomatic; and

ii. Systemic therapy has failed to control symptoms, or the patient is not a candidate for systemic therapy.

b. Colorectal tumors, including but not limited to adenocarcinoma when both of the following criteria (i. and ii.) are met:

i. The disease is liver-dominant, progressive, and diffuse (diffuse is defined as tumor tissue spread throughout the affected organ); and

ii. The patient is refractory to or not a candidate for chemotherapy.

c. Melanoma (ocular/uveal or cutaneous) when the disease is liver-dominant, progressive, and diffuse.

4. Unresectable primary intrahepatic cholangiocarcinoma.

II. Transarterial embolization (TAE) with non-radioactive agents may be considered **medically necessary** for any indication.

III. Transarterial chemoembolization (TACE) may be considered **medically necessary** for any indication.

IV. Radioembolization for the treatment of primary and metastatic tumors of the liver is considered **investigational** for all other scenarios not meeting the policy criteria above.

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

POLICY GUIDELINES

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 adeno carcinoids, 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:

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 requests pertaining to primary or metastatic liver tumors:

- Description of the planned therapy including the approach and the embolization agent to be used
- Specific description of the disease including the following:
  - Tumor type (primary vs. metastatic)
  - Extent and location of disease including whether the tumor is liver-dominant, progressive, and diffuse, and the presence or absence of extra-hepatic disease
  - For neuroendocrine metastases, description of the presence or absence of tumor-related symptoms
- Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
- Prior treatments, if any, and tumor response
- Rationale for the determination that the patient is not a candidate for initial or continued systemic therapy
- For treatment of hepatocellular carcinoma, specify if whether treatment is proposed as a bridge to transplantation

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
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. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204

BACKGROUND

TRANSARTERIAL EMBOLIZATION

According to the National Cancer Institute, transarterial embolization is defined as:[2]

> A procedure in which the blood supply to a tumor or an abnormal area of tissue is blocked. During transarterial embolization, a small incision (cut) is made in the inner thigh and a catheter (thin, flexible tube) is inserted and guided into an artery near the tumor or abnormal tissue. Once the catheter is in place, small particles made of tiny gelatin sponges or beads are injected. This blocks the artery and stops the flow of blood to the tumor or abnormal area of tissue. Transarterial embolization is used to treat some types of liver cancer, kidney cancer, and neuroendocrine tumors. It may also be used to treat uterine fibroids, aneurysms, and other conditions. Also called arterial embolization and TAE.

Types of transarterial embolization include bland embolization, chemoembolization, and

radioembolization (RE). This policy is predominantly focused on information and evidence regarding RE, which is also a form of radiation therapy.

Transarterial embolization (TAE) with non-radioactive (bland embolization) agents and transarterial chemoembolization (TACE) are also used to treat some types of cancer and other conditions, including uterine artery embolization for the treatment of fibroids. These techniques may be considered medically necessary.

RADIOEMBOLIZATION

RE, formerly referred to as selective internal radiation therapy (SIRT), is the intra-arterial delivery of small beads (microspheres) impregnated with yttrium-90 via the bloodstream. This technique is used to treat cancer – most commonly cancer in the liver, which is the focus of this policy. In treating cancer in the liver, the microspheres, which become permanently embedded, are delivered to tumor preferentially to normal liver, as the hepatic circulation is uniquely organized, whereby tumors greater than 0.5 cm rely on the hepatic artery for blood supply while normal liver is primarily perfused via the portal vein. Yttrium-90 is a pure beta-emitter with a relatively limited effective range and short half-life that helps focus the radiation and minimize its spread. RE is generally reserved for patients with adequate functional status (Eastern Cooperative Oncology Group [ECOG] 0-2), adequate liver function and reserve, Child Pugh score A or B, and liver-dominant metastases. Candidates for RE are initially examined by hepatic angiogram to identify and map the hepatic arterial system, and at that time, a mixture of albumin particles is delivered via the hepatic artery to simulate microspheres. After, single-photon emission CT gamma imaging is used to detect possible shunting of the albumin particles into gastrointestinal or pulmonary vasculature.

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other organs. Potentially curative local treatments include surgical resection with tumor-free margins, liver transplantation, ablative techniques, and external-beam radiation therapies. Unfortunately, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size and number of lesions, concurrent nonmalignant liver disease, or insufficient hepatic reserve.

The use of external beam radiotherapy, 3-D or more advanced radiotherapy approaches such as intensity-modulated radiotherapy [IMRT]) may be of limited use in patients with diffuse, multiple lesions due to the low tolerance of normal liver to radiation compared to the higher doses of radiation needed to kill the tumor.

Various nonsurgical and non-external irradiation based ablative techniques have been investigated that seek to cure or palliate unresectable hepatic tumors by improving locoregional control. These techniques rely on extreme temperature changes, particle and wave physics (microwave or laser ablation), or arterial embolization therapy including chemoembolization, bland embolization, or RE.

UNRESECTABLE PRIMARY LIVER CANCER [HEPATOCELLULAR CARCINOMA (HCC)]

The majority of patients with HCC present with unresectable disease and treatment options are limited secondary to the chemoresistance of HCC and the intolerance of normal liver parenchyma to tumoricidal radiation doses.

Other Treatment Options

- RE. In general, RE is used for unresectable HCC that is greater than 3 cm.

- TACE. Results of two randomized controlled trials have shown a survival benefit using TACE versus supportive care in patients with unresectable HCC.[3, 4]
- TAE. In one study, patients were randomly assigned to TACE, TAE, or supportive care. One-year survival rates for TACE, TAE, and supportive care were 82%, 75%, and 63%, respectively and two-year survival rates were 63%, 50%, and 27%, respectively.
- Targeted therapies. A 2007 multicenter, randomized, double-blind placebo controlled Phase III trial that enrolled 602 patients with advanced HCC randomly assigned patients to receive sorafenib versus placebo.[5] Overall survival was significantly longer in the sorafenib group compared with placebo (10.7 versus 7.9 months, respectively hazard ratio for sorafenib 0.69, $p<0.001$).

UNRESECTABLE METASTATIC COLORECTAL CARCINOMA

The role of local (liver-directed) therapy (including RE, chemoembolization, and conformal radiation therapy) for complete tumor removal or destruction is widely accepted in clinical practice. Incomplete “debulking” of unresectable metastatic disease in the liver remains controversial.[6]

Fifty to sixty percent of patients with colorectal cancer develop metastases, either synchronously or metachronously. Emphasis on treating patients with potentially curable disease is on complete destruction or removal of all tumor tissue. The majority of patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease.

Other Treatment Options

- In patients with metastatic disease limited to the liver, preoperative chemotherapy is sometimes used in an attempt to downsize the metastases in order to convert the metastatic lesions to a resectable status (conversion chemotherapy).
- In patients with unresectable disease that cannot be converted to resectable disease, the primary treatment goal is palliative, with survival benefit shown with both second and third-line systemic chemotherapy.
- Advances in chemotherapy have doubled the median survival in this population from less than one year to more than two years.
- Palliative chemotherapy by combined systemic and hepatic artery infusion therapy (HAI) may increase disease-free intervals for patients with unresectable hepatic metastases from colorectal cancer.
- Ablation techniques (see Cross References)
- Radiation therapy (see Cross References).

UNRESECTABLE METASTATIC NEUROENDOCRINE TUMORS

Neuroendocrine tumors are an uncommon, heterogeneous group of mostly slow-growing, hormone-secreting malignancies, with an average patient age of 60 years. Primary neuroendocrine tumors vary in location, but most are either carcinoids (which most commonly arise in the midgut) or pancreatic islet cells. Carcinoid tumors, particularly if they metastasize to the liver, can result in excessive vasoactive amine secretion including serotonin and are commonly associated with the carcinoid syndrome (diarrhea, flush, bronchoconstriction, and right valvular heart failure).

Although they are considered to be indolent tumors, at the time of diagnosis, up to 75% of

patients have liver metastases. The five-year survival rates with metastases to the liver are less than 20%. Less than 10% of patients are eligible for resection as most patients have diffuse, multiple lesions.

Conventional therapy is largely considered to be palliative supportive care to control, eradicate, or debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching.

Other Treatment Options

- Medical treatment includes somatostatin analogs, like octreotide or lanreotide, or systemic chemotherapy. Although patients often achieve symptom relief with octreotide, the disease eventually becomes refractory, with a median duration of symptom relief of approximately 13 months, with no known effect on survival. Systemic chemotherapy for these tumors has shown modest response rates of limited duration, is better for pancreatic neuroendocrine tumors compared to carcinoids, and is frequently associated with significant toxicity.[7]
- Radiofrequency or cryosurgical tumor ablation (see Cross References)
- TACE. Chemoembolization has shown response rates of nearly 80%, but the effect is of short duration and a survival benefit has not been demonstrated.[7]
- TAE with non-radioactive agents
- Radiation therapy (see Cross References)

UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA

Cholangiocarcinomas are tumors that arise from the epithelium of the bile duct and are separated into intrahepatic and extrahepatic types. Intrahepatic cholangiocarcinomas appear in the hepatic parenchyma and are also known as peripheral cholangiocarcinomas.[8] Resection is the only treatment with the potential for cure and five-year survival rates have been in the range of 20% to 43%.

Other Treatment Options

Patients with unresectable disease may select among fluoropyrimidine-based or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, or best supportive care.

MISCELLANEOUS METASTATIC TUMORS

Small case reports have been published on the use of RE in many other types of cancer with metastases, including breast, head, and neck (including parotid gland), pancreaticobiliary, anal, thymic, thyroid, endometrial, lung, kidney, gastric, small bowel, esophageal, ovarian, cervical, prostatic, bladder, and for melanoma, sarcoma and lymphoma.[9]

REGULATORY STATUS

Currently, two commercial forms of yttrium-90 microspheres are available: a glass sphere, TheraSphere® (MDS Nordion, Inc. used under license by BTG International) and a resin sphere, SIR-Spheres® (Sirtex Medical Limited). Noncommercial forms are mostly used outside the U.S. While the commercial products use the same radioisotope (yttrium-90) and have the same target dose (100 Gy), they differ in microsphere size profile, base material (i.e., resin vs. glass), and size of commercially available doses. These physical characteristics of the active and inactive ingredients affect the flow of microspheres during injection, their retention at the tumor site, spread outside the therapeutic target region, and dosimetry calculations.

Note also that the U.S. Food and Drug Administration (FDA) granted premarket approval of SIR-Spheres® for use in combination with 5-floxuridine (5-FUDR) chemotherapy by HAI to treat unresectable hepatic metastases from colorectal cancer. In contrast, TheraSphere® was approved by humanitarian device exemption (HDE) for use as monotherapy to treat unresectable HCC. In January 2007, this HDE was expanded to include patients with hepatocellular carcinoma who have partial or branch portal vein thrombosis. On March 17, 2021, TheraSphere® received approval through the premarket approval process for use as SIRT for local tumor control of solitary tumors (one to eight cm in diameter), in patients with unresectable hepatocellular carcinoma, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. Results obtained with one product do not necessarily apply to other commercial (or noncommercial) products.

EVIDENCE SUMMARY

This evidence review does not include summaries for TAE with non-radioactive agents or TACE, which may be considered medically necessary.

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 RE on these outcomes, well-designed randomized controlled trials (RCTs) are needed that compare this therapy with standard medical and/or surgical treatment of tumors in the liver.

RADIOEMBOLIZATION FOR UNRESECTABLE PRIMARY LIVER CANCER [HEPATOCELLULAR CARCINOMA (HCC)]

The following literature review on RE for unresectable HCC focused on systematic literature reviews and comparative studies (randomized and nonrandomized).

Systematic Reviews

Various meta-analyses have been performed to compare the effects of TACE, drug-eluting bead (DEB) plus TACE (DEB-TACE), and RE in patients with unresectable HCC, each of which performed slightly different analyses (e.g., pairwise vs. indirect comparisons and assessment of different outcomes or comparator groups). Results of these meta-analyses are summarized below.

Pollock (2021) conducted a systematic review and network meta-analysis of first-line treatments for unresectable HCC in TACE-ineligible patients.[10] Two RCTs comparing sorafenib to resin microspheres were analyzed, finding no significant differences in overall survival (hazard ratio [HR] 0.92, 95% CI 0.79 to 1.08).

Abdel-Rahman (2020) conducted a meta-analysis of RCTs comparing RE alone or combined with other systemic or locoregional treatments to placebo, no treatment, or other similar interventions in patients with unresectable HCC.[11] Six RCTs (total n=1,340) were identified, all of which were assessed by authors as being at high risk of bias. The authors reported the certainty of evidence as low to very low. Meta-analysis was able to be performed using data from more than one RCT for few comparisons. Based on meta-analysis of two RCTS, disease

control rate was not significantly different between RE and sorafenib (relative risk [RR] 0.94, 95% confidence interval [CI] 0.84 to 1.05), though RE was associated with less hand-foot skin reactions (RR 0.02, 95% CI 0.00 to 0.06), skin rash (RR 0.11, 95% CI 0.04 to 0.34), diarrhea (RR 0.11, 95% CI 0.04 to 0.34), and hypertension (RR 0.10, 95% CI 0.01 to 0.88). Based on meta-analysis of three RCTs, the risk of serious adverse events did not differ between RE and TACE (RR 1.47, 95% CI 0.66 to 3.25). Meta-analysis could not be performed for other comparisons; thus, results of other included trials are described individually in the section below on RCTs.[12, 13]

Venerito (2020) performed a meta-analysis to assess the noninferiority of SIRT as monotherapy or followed by sorafenib versus sorafenib monotherapy on OS.[14] A noninferiority margin of 1.08 for the HR was prespecified. Three RCTs were included (total n=1,243), and meta-analysis demonstrated SIRT with or without sorafenib was noninferior to sorafenib monotherapy in OS (median 10.2 and 9.2 months, HR 0.91, 95% CI 0.78 to 1.05). Treatment-related severe adverse events were reported in 28.9% vs. 43.3% of patients treated with SIRT and sorafenib monotherapy, respectively (p<0.01).

Yang (2020) conducted a meta-analysis of RCTs to compare effects of DEB-TACE, TACE, and RE on the primary outcome of overall survival.[15] Compared with TACE, RE was associated with similar one-year OS (RR 0.91, 95% CI 0.79 to 1.05), but a better OS than TACE at two years (RR 0.87, 95% CI 0.80 to 0.95) and three years (RR 0.90, 95% CI 0.85 to 0.96). Overall survival was not significantly different between RE and DEB-TACE at one year (RR 0.83, 95% CI 0.68 to 1.02), but DEB-TACE was associated with better OS at two years than RE (RR 0.40, 95% CI 0.19 to 0.84). However, pooled HRs indicated that RE was superior to TACE in overall survival (HR 0.84, 95% CI 0.70 to 1.00) and that DEB-TACE was superior to RE in overall survival (HR 0.59, 95% CI 0.38 to 0.91).

Tao (2017) reported on a network meta-analysis comparing nine minimally invasive surgeries for treatment of unresectable HCC.[16] The interventions included were TACE, TACE plus sorafenib, sorafenib, TACE plus high-intensity focused ultrasound, TACE plus percutaneous ethanol injection, DEB-TACE, yttrium-90 RE (90Y RE), TACE plus external-beam radiation therapy (EBRT), and ethanol ablation. The network included 17 studies with 2,669 patients and four studies with 230 patients including 90Y RE. In a pairwise meta-analysis, patients treated with 90Y RE were more likely to achieve complete remission than those who received TACE (odds ratio [OR] 4.5, 95% CI 1.3 to 15.1). However, in the network meta-analysis, there was no significant difference between the corresponding eight treatments and TACE with respect to complete remission, partial response, stable disease, and objective response rate. The treatments were ranked for several outcomes using surface under the cumulative ranking curves (SUCRA). TACE plus EBRT had the highest SUCRA ranking in complete remission (77%), partial response (89%), progressive disease (95%), and objective response rate (81%).

Ludwig (2017) conducted an indirect meta-analysis of studies that indirectly compared DEB-TACE with 90Y RE for HCC.[17] Fourteen studies (total n=2,065 patients) comparing DEB-TACE or 90Y RE with conventional TACE for primary HCC treatment were included. The pooled estimate of median survival was 23 months for DEB-TACE and 15 months for RE. The estimated one-year survival was significantly higher for DEB-TACE (79%) than for RE (55%, OR 0.57, 95% CI 0.36 to 0.92, p=0.02). Survival did not differ statistically significantly at two or three years but did favor DEB-TACE. At two years, survival was 61% for DEB-TACE and 34% or RE (OR 0.65, 95% CI 0.29 to 1.44, p=0.29) and at three years survival was 56% and 21% (OR 0.71, 95% CI 0.21 to 2.55, p=0.62), respectively.

Two systematic reviews published in 2016 compared RE with TACE for the treatment of unresectable HCC. Lobo (2016) selected five retrospective observational studies (total n=533 patients).[18] Survival at one year did not differ statistically between RE (42%) and TACE (46%, RR 0.93, 95% CI 0.81 to 1.08, p=0.33). At two years, the survival rate was higher for RE (27% vs. 18%, RR 1.36, 95% CI 1.05 to 1.76, p=0.02), but there was no statistically significant difference in survival rates at three, four, or five years. Postprocedural complications were also similar in the two groups. Facciorusso (2016) included 10 studies (total n=1,557 patients), two of which were RCTs.[17] The OR for survival was not statistically significant at one year (OR 1.0, 95% CI 0.8 to 1.3, p=0.93) but favored RE in years two (OR 1.4, 95% CI 1.1 to 1.90, p=0.01) and three (OR 1.5, 1.0 to 2.1, p=0.04).

Vente (2009) conducted a meta-analysis evaluating tumor response and survival in patients who received glass or resin microsphere 90Y RE for the treatment HCC or metastases from CRC.[19] (See below under unresectable metastatic CRC section for the data from the meta-analysis as pertains to that disease.) Included studies were from 1986 onward and presented tumor response measured by CT scans and data on median survival times. To allow comparability of results regarding tumor response, the category of “any response” was introduced, and included complete response, partial response, and stable disease. Overall tumor response could only be assessed as any response because response categories were not uniformly defined in the analyzed studies.

In 14 articles, clinical data were presented on tumor response and survival for 425 patients with HCC who had received 90Y RE. Treatment with resin microspheres was associated with a significantly higher proportion of any response than glass microsphere treatment (0.89 vs. 0.78, respectively, p=0.02). Median survival was reported in seven studies in which survival time was defined as survival from microsphere treatment or from diagnosis or recurrence of HCC. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4 to 24.0 months. The authors of the meta-analysis concluded that 90Y RE is associated with high response rates, both in salvage and first-line settings, but that the true impact on survival will only become known after publication of several ongoing and/or to-be-initiated Phase III studies, as well as the results of trials in which 90Y RE and modern chemotherapy agents are combined with novel biologic agents.

In May 2013 a comparative effectiveness review of local therapies (i.e., ablation, embolization, and radiotherapy) for patients with unresectable HCC was conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ).[20] The review sought to report on overall survival and quality of life outcomes and adverse events. Transplant candidates were excluded from this review. Three prospective case series and one retrospective case series with a total of 187 participants met inclusion criteria for review. There were no RCTs and no comparative trials that met inclusion criteria. Therefore, the strength of evidence was rated as insufficient to evaluate the outcomes of interest. One study reported a one-year survival rate of 75%; three studies reported a median survival range of 11 to 15 months. Quality of life, local recurrence, and disease progression were not reported in any of the included studies. Adverse events were rare, and no liver failure or hepatic abscess was reported. The authors recommended studies that compare various embolization techniques including RE.

Randomized Controlled Trials

Dhondt (2022) reported on results from the Transarterial Radioembolization versus Chemoembolization for the Treatment of Hepatocellular Carcinoma (TRACE), an open-label, single-center, superiority RCT.[21] The primary endpoint was time to overall tumor progression, with study sample size calculations assuming a 20% improvement with RE. A planned interim analysis for efficacy was performed when 45 disease progression events were observed, at which point the null hypothesis would be rejected when the HR was greater than 2.60 or less than 0.39 or when the p value was less than 0.0024. Patients with unresectable Barcelona Clinic Liver Cancer stage A and B HCC were randomized to treatment with glass microsphere-based RE (n=38) or DEB-TACE (n=34). The median time to progression was 17.1 months and 9.5 months for RE and DEB-TACE groups, respectively (HR 0.36, p=0.002). With HR <0.39 for the primary end point in favor of RE at interim analysis, the null hypothesis was rejected, and the study was terminated on ethical grounds. Median PFS was 11.8 months in the RE arm and 9.1 months in the DEB-TACE arm (HR 0.40, 95% CI 0.24 to 0.67, p<0.001). Downstaging led to transplant in 10 patients treated with RE and four patients treated with DEB-TACE. Median OS in RE and DEB-TACE groups was 30.2 months and 15.6 months, respectively (HR 0.48, 95% CI 0.28 to 0.82, p=0.006).

Kolligs (2014) reported results of a small pilot RCT comparing RE with TACE for the treatment of unresectable HCC (SIR-TACE study).[12] The study included 28 subjects with unresectable HCC, preserved liver function, and an ECOG Performance Status of 2 or less, with no vascular invasion or extrahepatic spread, who had five or fewer liver lesions or a single lesion of 10 cm or less. Patients were randomized to RE (n=13) or TACE (n=15). Over posttreatment follow up, partial response rates were 13.3% for TACE and 30.8% for RE, with rates of disease control of 73.3% for TACE and 76.9% for RE. Median PFS was 3.6 months for TACE and 3.7 months for RE.

Pitton (2014) reported results from a small RCT comparing RE with TACE with drug eluting beads TACE (DEB-TACE) for the treatment of unresectable HCC.[13] The study included 24 patients, 12 randomized to each group. No deaths occurred within 30 days of the procedure for either group. There were no statistically significant differences between the groups in terms of in PFS (180 days for RE vs. 216 for TACE, p=0.619) and OS (592 days for RE vs. 788 for TACE, p=0.927).

Nonrandomized Comparison Studies

A propensity score matching analysis reported by Martelletti (2021) compared patient outcomes between transarterial RE (TARE) and sorafenib.[22] HCC patients (total n=65) were treated with TARE (n=41) or sorafenib (n=24). Downstaging to curative-intent surgery occurred in 10 of 41 TARE patients and one of 24 sorafenib patients. In the non-downstaged patients, median survival was 20.3 in the TARE patients and 9.1 months in the sorafenib patients (p=0.0001), and one-, two-, and three-year OS rates were 64.5%, 42.6% and 37.3%, respectively, in the TARE patients and 39.1%, 13.0% and 0%, respectively, in the sorafenib patients. Propensity score and Bayesian model averaging analyses indicated that there was an improvement in overall survival in the TARE group compared with sorafenib treatment.

Bekki (2021) reported a comparative study of portal vein embolization versus radiation lobectomy before resection of hepatocellular carcinoma in chronic liver disease patients.[23] A total of 73 patients were treated with portal vein embolization and 22 with RE. Additional procedures were required for tumor control in 47% of portal vein emblization patients and 27% of RE patients. The degree of hypertrophy was 63% for RE and 36% for portal vein

embolization (p<0.01). Resectability rate was 85% for portal vein embolization and 64% for RE (p=0.03). For 18% of patients not pursuing surgery follow RE, the reason was complete tumor control.

Facciorusso (2020) performed a retrospective analysis that compared patients with HCC treated with RE plus sorafenib (n=45) with propensity score-matched patients treated with sorafenib alone (n=90).[24] No significant differences were identified in median OS, median PFS, and objective response rate.

Padia (2017) reported on a single-center, retrospective study comparing segmental RE with segmental chemoembolization in 101 patients with localized, unresectable HCC not amenable to ablation.[11] Patients receiving chemoembolization had poorer ECOG Performance Status ratings and Child-Pugh class while those receiving RE had larger and more infiltrative tumors. Overall complete remission was 84% with RE and 58% with chemoembolization (p=0.001). Median PFS was 564 days and 271 days (p=0.002) and median OS was 1,198 days and 1,043 days (p=0.35), respectively, for the RE group and the chemotherapy group.

Soydal (2016) reported a retrospective study comparing outcomes of patients receiving RE and TACE for HCC.[25] Each group included 40 patients. RE patients had a mean survival of 39 months versus 31 months for TACE (p=0.014). There was no significant difference in chronic complications and recurrence of disease.

Oladeru (2016) reported a retrospective study based on SEER registry data comparing survival outcomes of patients receiving RE and EBRT of HCC.[26] A total of 189 patients with unresectable HCC (77 receiving RE, 112 receiving EBRT) who were treated between 2004 and 2011 were evaluated. Median OS for RE was 12 months compared to 14 months for EBRT. Median disease-specific survival was identical for both groups at 14 months. After adjustment for differences between patients, multivariable survival analysis showed no association of treatment and OS or disease-specific survival.

El Fouly (2015) reported results of a nonrandomized study comparing 90Y RE with TACE among 86 patients with intermediate stage, nonresectable HCC.[27] Sixty-three patients at one institution were treated with TACE, while 53 patients at a second institution were treated with RE. Median OS in for TACE and RE was not significantly different between groups (18 months for TACE vs. 16.4 months for RE); similarly median time to progression (TTP) was not significantly different between groups (6.8 months for TACE vs. 13.3 months for RE). TACE patients had higher numbers of treatment sessions, hospital times, and rates of adverse events.

Gramenzi (2015) conducted a retrospective cohort study to compare 90Y RE with sorafenib for intermediate- or advanced-stage HCC.[28] Patients with HCC refractory to other therapies and no metastases or systemic chemotherapy were included, 74 of whom were treated with sorafenib and 63 treated with RE. Median OS between groups was similar (14.4 months for sorafenib-treated patients vs. 13.2 months for RE-treated patients). After propensity-score matching of 32 subjects in each group, there were no significant differences in median OS or one-, two-, and three-year survival rates between groups.

RADIOEMBOLIZATION AS A BRIDGE TO LIVER TRANSPLANTATION FOR PRIMARY HCC

Systematic Reviews

Kulik (2018) published a systematic review of 18 comparative studies and 31 noncomparative studies that included patients with unresectable HCC who needed a liver transplant and received transplant alone or some type of bridging therapy as well.[16] Of the 18 comparative studies, two studies (n=257 patients) reported on the incidence of dropout from transplantation wait-lists, and patients receiving bridging therapy. This group had reduced risk of dropout due to disease progression compared with those receiving transplantation alone (RR 0.32). Between-group differences were not statistically significant for mortality (five comparative studies, n=531 patients) or recurrence rate (10 comparative studies, n=889 patients). Subgroup analysis was conducted for types of bridging therapy: for all-cause mortality after transplantation, the RR was 1.124 with TAE compared with transplantation alone (one cohort). For disease recurrence, the RR for this bridging therapy type was 2.374 compared with transplantation alone. No RCTs were identified, and most of the selected studies had a high risk of bias on patient selection, adequate follow-up, and funding source when reported.

Randomized Controlled Trials

Salem (2016) reported on results of a phase 2 RCT comparing conventional TACE and TheraSphere® Y90 RE for treatment of unresectable, unablatable HCC.[14] Twenty-four patients were assigned to Y90 RE and 21 patients to conventional TACE; the ultimate goal of treatment for these patients was liver transplantation. The primary outcome was TTP using intention-to-treat analysis. Median follow-up was 17 months. In the conventional TACE group, there were seven transplants at a median of nine months (range 3 to 17 months). In the Y90 RE group, there were 13 transplants at a median of nine months (range 4 to 15 months). Median TTP exceeded 26 months in the Y90 RE group and 6.8 months in the conventional TACE group (HR 0.12, 95% CI 0.03 to 0.56, p=0.007). Median survival was 19 months in Y90 RE and 18 months in conventional TACE (p=0.99). Adverse events were similar between groups, with the exception of more diarrhea (21% vs. 0%) and hypoalbuminemia (58% vs. 4%) in the conventional TACE group. A limitation of the OS analysis was the censoring of the survival outcome at liver transplantation given that transplantation is related to the treatment effect.

Kulik (2104) reported results of a pilot RCT of 90Y RE with or without sorafenib for patients with HCC awaiting liver transplantation.[29] The study randomized 23 subjects; after accounting for losses due to self-withdrawal from the study, failure to confirm HCC, and death, the modified intention-to-treat population included 10 subjects randomized to RE alone and 10 randomized to RE with sorafenib. Overall, 17 of 20 patients underwent liver transplantation, with no difference in median time-to-transplant between groups. However, the addition of sorafenib was associated with increased peritransplant biliary complications, and acute rejection.

Nonrandomized Studies

Salem (2021) reported the results of the multicenter, single-arm, retrospective LEGACY trial investigating 90Y RE with TheraSphere® for the treatment of solitary, unresectable HCC.[30] The aim of the study was to evaluate the objective response rate and the duration of response based on modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria as evaluated by blinded, independent, central review. Eligibility criteria included: solitary HCC ≤8 cm, Child-Pugh A cirrhosis, and ECOG performance status 0 to 1. Of 162 enrolled patients, 60.5% were ECOG 0 and RE served as neoadjuvant therapy for transplantation or resection in 21% and 6.8% of patients, respectively. Median follow-up duration was 29.9 months. Objective

response rate (best response) was 88.3% (95% CI 82.4 to 92.4) with 62.2% (95% CI 54.1 to 69.8) exhibiting a response duration of ≥6 months. Three-year OS was 86.6% for all patients and 92.8% for neoadjuvant patients resected or transplanted. This study supported FDA premarket approval of TheraSphere® for use in HCC.[31]

Pellegrinelli (2021) reported on an eight-year single-center experience utilizing RE for the treatment of patients with unresectable HCC (n=44), metastatic colorectal cancer (n=20), and intrahepatic cholangiocarcinoma (n=6).[32] Treatment with prior chemotherapy was reported in 48.6% of all patients, and RE-related grade 3 or higher adverse events impacted 17.1% of patients. Patients were treated with RE as bridge to transplant (4.3%), for downstaging prior to surgical resection (15.7%), as ablative therapy (1.4%), and for palliative treatment (78.6%). Median follow-up was 32.1 months, during which disease progression occurred in 63 (90%) of all patients. Among patients with HCC at study end, complete and partial responses were achieved in one and two patients, respectively. Median OS was 16.1 months (range, 1.0 to 72.5 months) with no significant differences in survival among disease groups.

Gabr (2020) performed a retrospective review that reported on long-term outcomes of liver transplantation for patients with HCC who were bridged or downstaged with RE.[33] From 2004 to 2018, 207 patients underwent transplant after RE. Median OS from transplant was 12.5 years, with median time to liver transplantation of 7.5 months (interquartile range 4.4 to 10.3). Overall, 169 patients were bridged and 38 were downstaged to liver transplant. OS rates at 3, 5, and 10 years were 84%, 77%, and 60%, respectively.

Zori (2020) performed a retrospective cohort analysis that compared patients with HCC undergoing bridging locoregional therapy with RE (n=28) or TACE (n=37) prior to liver transplant.[34] Three-year survival was not significantly different with RE vs. TACE (92.9% vs. 75.7%, p=0.052). However, microvascular invasion occurred in 3.6% versus 27% of patients treated with RE versus TACE (p=0.013).

In a retrospective review, Tohme (2013) reported on 20 consecutive HCC patients on liver transplant waiting lists who received RE as bridge therapy.[35] When RE began, Milan criteria (extent of disease) for liver transplantation were met by 14 patients and sustained until transplantation. Of the six patients who did not meet Milan criteria initially, RE was able to downstage two patients to meet Milan criteria. Complete or partial radiologic response to RE on modified RECIST occurred in nine patients. Additionally, on pathologic examination, five patients who met Milan criteria had complete tumor necrosis with no evidence of viable tumor.

Ramanathan (2014) reported on multimodality therapy, including RE, for 715 HCC patients of which 231 were intended for transplant.[36] In the intention-to-treat with transplantation arm, 60.2% were able to receive a transplant. Survival rates posttransplant were 97.1% and 72.5% at one and five years, respectively. Tumor recurrence rates were 2.4%, 6.2%, and 11.6% at one, three, and five years, respectively. Since this study included multimodality therapy, it is not possible to isolate the effect of RE.

Lewandowski (2009) compared RE with chemoembolization in the efficacy of downstaging 86 patients with HCC from stage T3 to T2 (potentially making patients liver transplant candidates).[37] Patients were treated with either 90Y RE microspheres (n=43) or TACE (n=43). Median tumor size was similar between the two treatment groups (5.7 and 5.6 cm, for TACE vs. RE, respectively.) Partial response rates were 61% versus 37% for RE vs. TACE, respectively, with downstaging from T3 to T2 in 58% of patients treated with RE versus 31% with TACE ($p<0.05$).

RADIOEMBOLIZATION FOR UNRESECTABLE METASTATIC COLORECTAL CARCINOMA (CRC)

Systematic Reviews

A 2009 Cochrane review[38] and a 2009 systematic review with meta-analysis[19] concluded that data from large Phase III trials were needed in order to fully understand the impact of RE on survival in patient with CRC metastases in the liver.

Two additional systematic reviews were published in 2013:

Rosenbaum (2013) considered RE, either as monotherapy or concomitant with chemotherapy, to be an emerging treatment for CRC liver metastases, with a limited amount of data from heterogeneic studies.[39] This review evaluated 13 articles on RE as monotherapy and 13 studies on RE combined with chemotherapy for chemoresistant, unresectable CRC liver metastasis. Heterogeneity between studies prohibited pooling of data. This heterogeneity included varying patient inclusion criteria such as the amount of intrahepatic and extrahepatic tumor burden, patient performance status, previous systemic treatments, and protocols for assessing tumor response. Complete response, partial response, and stable disease rates ranged from 29% to 90% with RE alone and from 59% to 100% for RE with chemotherapy. At 12 months, survival ranged from 37% to 59% with RE alone and from 43% to 74% for RE combined with chemotherapy. As with prior reviews, the authors concluded that additional data is needed from high-quality randomized trials.

In contrast to the prior systematic reviews, Saxena (2014) considered the evidence sufficient to recommend increased utilization of RE as salvage treatment for CRC liver metastases.[40] The review evaluated a total of 979 patients in 20 studies including two RCTs[41, 42]. The majority of patients had previously undergone at least three lines of chemotherapy (range of two to five). After RE, the average reported complete and partial responses from 16 studies was 0% (range 0% to 6%) and 31% (range 0% to 73%), respectively. The median time to intrahepatic progress was nine months (range 6 to 16 months) and the median survival time was 12 months (range 8.3 to 36 months). The mean rate of acute toxicity was 40.5% (range 11% to 100%); most cases were mild and did not require intervention. Despite concluding that RE was safe and effective, the authors noted the need for continued evaluation of clinical outcomes.

Randomized Controlled Trial

Mulcahy (2021) reported on outcomes from the Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) trial, an open-label phase 3 trial studying the impact of RE with TheraSphere in combination with second-line systemic chemotherapy for colorectal liver metastases in 428 patients from 95 centers in North America, Europe, and Asia.[43] Patients who had progressed on first-line chemotherapy were randomized 1:1 to receive second-line oxaliplatin- or irinotecan-based chemotherapy with (n=215) or without RE (n=213). The study was designed to detect a HR of 0.71 for PFS and 0.65 for hepatic PFS favoring RE plus chemotherapy. The median PFS was 8.0 months (95% CI 7.2 to 9.2) and 7.2 months (95% CI 5.7 to 7.6), respectively, with a corresponding hazard ratio of 0.69 (95% CI 0.54 to 0.88, p=0.0013) favoring RE. The median hepatic PFS was 9.1 months (95% CI 7.8 to 9.7) and 7.2 months (95% CI 5.7 to 7.6) for patients treated with and without RE, respectively (HR 0.59, 95% CI 0.46 to 0.77, p<0.0001). Delayed progression was also observed for tumors with KRAS mutation, left-sided primary tumor, hepatic tumor burden of 10-25%, ≤3 lesions, the addition of a biologic agent, and resected primary. Median overall

survival was 14.0 months (95% CI 11.8 to 15.5) and 14.4 months (95% CI 12.8 to 16.1, p=0.7229) for the RE and chemotherapy groups, respectively (HR 1.07, 95% CI 0.86 to 1.32). However, it was noted that the study was not designed or powered for overall survival and the outcome may be confounded by subsequent locoregional therapies including RE in the control arm. The frequency of grade 3 adverse events was higher with the addition of RE to chemotherapy (68.4% versus 49.3%). Overall, the investigators noted that the addition of RE to chemotherapy resulted in a statistically significant delay of disease progression. However, further research will be pursued to better identify patients who might benefit most from treatment, as well as dosimetric considerations to optimize the risk-benefit profile.

A phase 3 RCT by van Hazel (2016) of 530 patients compared modified fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy and FOLFOX chemotherapy plus SIRT in patients with chemotherapy-naive, liver-dominant, metastatic disease.[44] Bevacizumab was allowed as additional treatment at the discretion of the treating physician. About 40% of patients had extrahepatic metastases at randomization. About 28% of patients had more than 25% liver involvement of metastases. The primary end point was overall (any site) PFS. Secondary end points included liver-specific outcomes such as PFS in the liver, tumor response rate, and liver resection rate. The primary end point of PFS at any site showed no difference between groups (10.2 months for control vs. 10.6 months for RE, HR 0.93, p=0.43). Secondary liver-specific end points of median PFS in the liver and objective response rate in the liver were improved in the RE group (liver PFS 12.6 months for controls vs. 20.5 months for RE, liver response rate 68.8% for controls vs. 78.7% for RE). This finding was consistent irrespective of tumor burden, bevacizumab therapy, or performance status. Wasan (2017) analyzed OS from this study in combination with two other studies of chemotherapy with and without RE.[45] Overall, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned FOLFOX plus SIRT. Overall survival was not significantly different between groups (HR 1.04, 95% CI 0.90 to 1.19).

Nonrandomized Studies

Since the systematic reviews were published, a number of additional nonrandomized studies have reported outcomes of RE for patients with CRC liver metastases who failed or were not candidates for chemotherapy.[46-49] The majority of these were noncomparative studies which precluded conclusions on the survival benefit of RE compared to other treatments. There was a wide range of clinical response to RE; although the rate of complete response was low, partial response averaged 35% and stable disease was reported in 32 to 71% of patients. The few studies that compared RE to best supportive care reported a statistically significant survival benefit with RE. The rates of Grade 3 to 4 toxicities ranged from 0% to 39% and included absolute lymphocyte, alkaline phosphatase, bilirubin, and albumin. Factors associated with poorer prognosis included large tumor volume, poor radiological response to treatment, and the number of prior chemotherapy treatments.

A comparative study published by Mokkarala (2019) performed a propensity score-matched retrospective analysis of patients with colorectal metastases treated with DEB-TACE (n=47) or RE (n=155).[50] Extra-hepatic metastasis was more frequent with DEB-TACE (68.1% vs. 47.7%, p=0.014), as was occurrence of ≥10 liver lesions (42.2% vs. 68.8%, p=0.001). Toxicity was not significantly different between DEB-TACE and RE (27% vs. 9.1%, respectively, p=0.057). Treatment with DEB-TACE was not a prognostic factor for survival (HR 0.94, 95% CI 0.54 to 1.65).

A study by Haber (2021) evaluated the addition of RE to systemic therapy in the salvage setting for hepatic metastases from CRC.[51] Twenty-one patients who underwent RE plus systemic therapy were matched with a cohort of 173 patients who received systemic chemotherapy alone in the salvage setting, defined as progression on at least two different regimens of systemic chemotherapy. The difference in median survival from the date of primary diagnosis between groups was not statistically significant (38, 95% CI 26 to 50 for RE with systemic therapy vs. 25, 95% CI 15 to 35 months for systemic therapy alone, p=0.17). When measured from the date of hepatic metastases, median survival was 31 (95% CI 23.8 to 38.2) for those treated with RE with systemic therapy compared to 20 months (95% CI 10.2 to 29.8) for those treated with systemic therapy alone (p=0.03).

RADIOEMBOLIZATION FOR MELANOMA METASTASES IN THE LIVER

Many studies of metastatic melanoma focus on patients with uveal melanoma in whom the liver is the most common site of metastatic disease.

Systematic Reviews

Alexander (2022) published a systematic review of RE for hepatic metastases of uveal melanoma.[52] Eleven studies representing 268 individuals were identified for review. Nine of the studies were retrospective. The disease control rate was 67.5% and the median overall survival was 12.3 months. Median hepatic PFS was 5.4 months.

Rowcroft (2020) planned to perform a meta-analysis of studies of patients with liver-only metastases of uveal melanoma treated with systemic therapy, isolated hepatic perfusion, hepatic artery infusion, TACE, SIRT, and immunoembolization.[53] However, due to heterogeneity in available data, meta-analysis was not performed. The authors descriptively reported that six non-comparative retrospective cohort studies (n=150, range 8 to 71) evaluated the use of SIRT, which reported median OS ranged from 9 to 24 months.

Randomized Controlled Trials

No randomized controlled trials were identified for RE of melanoma metastases in the liver.

Nonrandomized Comparative Studies

Gonsalves (2019) performed a prospective study of patients with liver metastases of uveal melanoma treated with RE.[54] Among patients who were treatment-naive, complete response, partial response, or stable disease was achieved in 20 of 23 patients (87.0%, 95% CI 66.4% to 97.2%), median PFS from liver metastasis was 8.1 months (95% CI 6.4 to 11.8), and median OS was 18.5 months (95% CI 11.3 to 23.5). Among patients who progressed after immunoembolization, complete response, partial response, or stable disease was achieved in 14 of 24 patients (58.3%, 95% CI 36.3% to 77.9%), median PFS from liver metastasis was 5.2 months (95% CI 3.7 to 9.8), and median OS was 19.2 months (95% CI 11.5 to 24.0).

Xing (2014) conducted a retrospective observational study to compare outcomes for patients with unresectable melanoma (both uveal and cutaneous) liver metastases refractory to standard chemotherapy treated with either 90Y RE (n=28) or best supportive care (n=30).[55] The groups were similar at baseline in terms of Child-Pugh class, ECOG performance status scores, age, sex, and race. However, patients treated with RE had significantly larger tumor size at baseline than those treated with best supportive care (mean of 7.28 cm vs. 4.19 cm, p=0.02). Median OS from diagnosis of melanoma liver metastases was longer in RE-treated

subjects (19.9 months vs. 4.8 months, p<0.000), as was the median OS from diagnosis of the primary melanoma (119.9 months vs. 26.1 months, p<0.001). Pre- and post-treatment imaging studies were available for 24/28 (85.7%) of those treated with RE. Of those, no patients had a complete response, five patients (17.9%) had partial response, nine patients (32.1%) had stable disease, and 10 patients (35.7%) had progressive disease. Two patients receiving RE had major (grade 5) clinical toxicities (ascites and hepatic encephalopathy and eventual mortality). Significant factors for longer OS were ≤10 metastatic liver lesions, absence of extrahepatic metastases, and Child-Pugh class A. Although this study was retrospective and included small sample sizes, it included relatively long-term follow-up and provided comparison between RE and best supportive care.

Nonrandomized Non-comparative Studies

Eldredge-Hindy (2014) retrospectively evaluated outcomes for the use of 90Y RE in 71 patients with biopsy-confirmed uveal melanoma liver metastases.[56] The median time from the diagnosis of liver metastases to RE was 9.8 months (95% CI 7.4 to 12.2 months), and 82% of patients had received prior liver-directed therapies. Sixty-one patients (86%) had CT or magnetic resonance imaging (MRI) evaluation of treatment response at three months post-RE. Of those, five patients (8%) had a partial response, 32 patients (52%) had stable disease, and 24 patients (39%) had disease progression. Median OS RE was 12.3 months (range, 1.9 to 49.3 months).

Small studies (n=8 to 32) have reported on use of RE in patients with hepatic metastases from melanoma.[57-63] Five of the studies included only patients with ocular melanoma, and two included patients with ocular, cutaneous, or other-site melanoma. Three studies excluded those patients with poor performance status. Median age was in the 50s for four studies and 61 in one study. One article did not describe any previous treatment and one described it incompletely. Four studies reported tumor response data, by RECIST criteria.

- Treatment response. Among 32 patients in the study by Gonsalves (2011), one patient had a complete response (3%), one had a partial response, 18 patients had stable disease (56%) and 12 patients had progressive disease (38%). In the study of 13 patients published by Klingenstein (2013), none had a complete response, eight had a partial response (62%), two had stable disease (15%) and three had progressive disease (23%). Nine of 11 patients in the article by Kennedy (2009) provided response data: one had a complete response, six had a partial response, one had stable disease and one had progressive disease. Of the eight patients in the Schelhorn (2015) study, four (50%) had stable disease and four (50%) had progressive disease. Memon (2014) reported progressive disease and stable disease in 13 (81%) patients and progressive disease in three (19%) patients. Ponti (2020) reported disease control at six months post-RE in 52% of patients.

- Survival. Median survival in Gonsalves (2011), Klingenstein (2013), Schelhorn (2015), Ponti (2020), and Kennedy (2009) were 10.0 months, 19 months, 20 months, 18 months, and not yet reached, respectively.

- Toxicity. Gonsalves (2011) reported four patients (12.5%) with grade 3 to 4 liver toxicity and Ponti (2020) reported grade 3 to 4 biologic and clinical toxicities in 24% of patients. Klingenstein (2013) observed one patient with marked hepatomegaly. Kennedy (2009) described one grade 3 gastric ulcer. Memon (2014) reported Grade 3 toxicity in two (12%) (absolute lymphocyte toxicity) and one (7%) (aspartate aminotransferase toxicity) patients;

and grade 4 bilirubin toxicity in one patient. One study[60] (n=12) did not include any toxicity data.

RADIOEMBOLIZATION FOR UNRESECTABLE METASTATIC NEUROENDOCRINE TUMORS

Systematic Reviews

Ngo (2021) conducted a meta-analysis of six retrospective cohort studies with a total of 643 patients treated with TACE (n=422) or RE (n=221) for neuroendocrine liver metastases.[64] Patients treated with TACE exhibited significantly improved OS (OR 1.92, 95% CI 1.14 to 3.22, p=0.014) compared to those treated with RE. No significant differences in hepatic progression-free survival (p=0.96) or overall tumor response (p=0.99) were observed. Although the overall proportion of patients with unresectable disease is unclear, the history of resection or ablation in the two groups was not significantly different (OR 1.20, 95% CI 0.71 to 2.02, p=0.49). Patients receiving RE were more likely to have received prior systemic chemotherapy (OR 0.48, 95% CI 0.27 to 0.83, p=0.009) and octreotide therapy (OR 0.50, 95% CI 0.30 to 0.84, p=0.009).

Frilling (2019) reported results from a case series of 24 patients that were then included in a meta-analysis of patients treated with SIRT for neuroendocrine liver metastases.[65] Overall, 26 additional studies were included in the meta-analyses, which reported a fixed effects weighted averages for objective response rate of 51% (95% CI 47% to 54%) and disease control rate (complete response, partial response, or stable disease) of 88% (95% CI 85% to 90%).

A 2012 systematic review evaluated the safety and efficacy of chemoembolization, bland embolization, and RE in patients with unresectable metastatic neuroendocrine tumors in the liver.[66] A total of 37 studies with 1575 total patients were reviewed for response to treatment, survival outcome, and toxicity. The authors reported that each of these therapies were found to be safe and effective, and recommended additional prospective trials to compare relative efficacy and toxicity.

In 2014, a meta-analysis of 12 studies that met inclusion criteria reported complete and partial responses of 50% for RE of metastatic neuroendocrine tumors in the liver.[67] Weighted average disease control was 86%. It was noted that the presence of pancreatic metastatic neuroendocrine tumors was marginally associated with poorer response (p=0.03). The authors concluded that the meta-analysis confirmed the effectiveness of RE for hepatic metastatic tumors.

Randomized Controlled Trials

No RCTs were found for RE of metastatic neuroendocrine tumors in the liver.

Nonrandomized Comparative Studies

Egger (2020) performed a retrospective cohort analysis comparing patients with neuroendocrine liver metastases treated with RE (n=51) or TACE (n=197).[68] Between RE and TACE, there were no differences in overall morbidity (13.7% vs. 22.6%, respectively, p=0.17), grade 3/4 complication (5.9% vs. 9.2%, p=0.58), 90-day mortality (9.8% vs. 5.2%, p=0.21), median OS (35.9 months vs. 50.1 months, p=0.3), or progression-free survival (15.9 vs. 19.9 months, p=0.37). However, disease control rate was greater for TACE compared with RE (96% vs. 83%, p<0.01).

Engelman retrospectively compared locoregional therapies including transarterial, liver-directed therapies including RE, hepatic artery embolization, and hepatic artery chemoembolization in 42 patients treated for metastatic neuroendocrine tumors.[69] Treatment decisions were at the discretion of the referring physician and interventional radiologist, but the decision to proceed with therapy was typically based on progression of symptoms nonresponsive to octreotide therapy or rapid progression of liver tumor burden on imaging. Seventeen patients had hepatic artery chemoembolization, 13 had hepatic artery embolization, and 12 had RE. Among the 27 patients with symptoms from their liver metastases, there were no statistically significant differences in symptom improvement at three months after first liver-directed therapy across treatment modalities (6/13 for hepatic artery chemoembolization, 4/8 for hepatic artery embolization, 5/6 for RE, p=0.265). There were no differences between treatment modalities in radiographic response at six months postprocedure (p=0.134), TTP (p=0.968), or OS (p=0.30).

Nonrandomized Non-Comparative Studies

Peker (2015) reported on 30 patients with unresectable metastatic hepatic neuroendocrine tumors who received resin-based RE.[70] Post-treatment response was assessed by imaging using the RECIST guidelines. Mean follow-up was 23 months. Median OS was 39 months (range 12.6-65.4 months) with 1- and 2-year survival rates of 71% and 45%, respectively. Partial response was 43%, complete response 3%, stable disease 37%, and PD 17%. The following were not significant prognostic factors: extrahepatic disease, radiographic response, age, and primary neuroendocrine tumor site.

Cao (2010) reported the outcomes of 58 patients with unresectable neuroendocrine liver metastases from two different hospitals treated with 90Y RE microspheres (SIR-Spheres) from 2003 to 2008. Data were examined retrospectively from a database.[71] Response was assessed with radiographic evidence before and after RE and measured by RECIST guidelines. Patients typically had a CT scan within three months of treatment and every three to six months until disease progression or death. Systemic chemotherapy was routinely given at one institution but not the other. Mean patient age at the time of RE was 61 (range 29 to 84 years), and 67% of patients were men. Primary tumor site was variable and included small bowel, pancreas, colon, thyroid, lung, and unknown. Thirty-one patients underwent surgical resection of their primary tumor, which was classified as low-grade in 15, intermediate-grade in seven, and high-grade in seven. Forty-three percent of patients had extrahepatic metastatic disease at study entry. Prior therapies before RE included liver resection in 19 patients, TAE or TACE in six, ablation or percutaneous ethanol injection in 10, previous chemotherapy in 20, concurrent chemotherapy in 34, and post-RE chemotherapy in five patients. Median follow-up was 21 months (range 1 to 61 months). Fifty-one patients were evaluable, and six achieved a complete response, 14 a partial response, 14 had stable disease, and 17 had disease progression. OS rates at one, two, and three years were 86, 58, and 47%, respectively. Median survival was 36 months (range 1 to 61 months). Prognostic factors for survival included extent of tumor involvement of the liver, radiographic response to treatment, presence of extrahepatic disease at the time of RE, histological grade of tumor, and whether patients were responders (versus nonresponders) to RE. Factors that were not significant prognostic features included age, sex, ECOG status, and previous therapy.

King (2008) reported outcomes in patients treated in a single-institution prospective study.[7] Thirty-four patients with unresectable neuroendocrine liver metastases were given radioactive microspheres [SIR-Spheres] and concomitant seven-day systemic infusion of 5-FU, between

2003 and 2005. Mean patient age was 61 years (range 32 to 79 years), and 65% were men. Mean follow-up was 35.2 +/- 3.2 months. The mean interval from diagnosis of hepatic metastases and treatment with SIR therapy was 36.6 +/- 6.7 months. Primary tumor sites were variable and included bronchus (n=1), thyroid (n=2), gastrointestinal (n=15), pancreas (n=8), and unknown (n=8). Subjective changes from baseline hormone symptoms were reported every three months. At baseline assessment, 24 patients (71%) had symptoms of carcinoid syndrome, including diarrhea, flushing, or rash. At three months, 18 of 33 patients (55%) reported improvement of symptoms, as did 16 of 32 (50%) at six months. Radiologic tumor response was observed in 50% of patients and included six complete responses (18%), and 11 partial responses (32%). Mean OS was 29.4 +/- 3.4 months.

RADIOEMBOLIZATION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Systematic Reviews

Schartz (2022) reported on the efficacy and survival profile of RE for unresectable intrahepatic cholangiocarcinoma (ICC).[72] Twenty-one studies representing 921 patients with follow-up duration from 3 to 36 months were evaluated, finding an overall disease control rate of 82.3% (95% CI 76.7% to 87.8%, I^2=81%), median PFS of 7.8 months (95% CI 4.2 to 11.3, I^2=94%), and median OS of 12.7 months (95% CI 10.6 to 14.8, I^2=62%). Patients were downstaged for surgical resection in 11% of cases (95% CI 6.1% to 15.9%, I^2=78%). The analysis is limited by inclusion of primarily retrospective study designs and considerable clinical and methodologic heterogeneity.

Edeline (2021) conducted a systematic review and pooled analysis of locoregional therapies in patients with unresectable ICC.[73] Ninety-three studies were pooled for analysis, representing 15 cohorts (n=645) for ablation, 18 cohorts (n=541) for EBRT, 27 cohorts (n=1,232) for RE, 22 cohorts for TACE, and 16 cohorts (n=331) for HAI. Pooled weighted mean PFS was 15.6, 7.8, 15.0, and 10.1 months for EBRT, RE, TACE, and HAI, respectively. Pooled weighted mean overall survival was 30.2, 18.9, 14.1, 15.9, and 21.3 months for ablation, EBRT, RE, TACE, and HAI, respectively. The authors noted that the quality of the studies was insufficient to derive strong recommendations, with the exception of consistently good outcomes for ablation. Instead, the pooled results are presented to establish benchmarks for the design of future clinical trials.

Yu (2021) reported on outcomes in a systematic review and meta-analysis of RE compared to EBRT in the treatment of unresectable ICC.[74] Between 2000 and 2020, 29 and 20 studies representing 732 and 443 patients were identified for RE and EBRT groups, respectively. From initial treatment, median overall survival for RE and EBRT was 12.0 months (95% CI 10.8 to 14.6) and 13.6 months (95% CI, 11.1 to 16.0), respectively. As first-line therapy, median overall survival for RE was 36.1 months (95% CI 20.6 to 39.5) compared to 11.0 months (95% CI 9.3 to 13.6) for EBRT. Downstaging to surgery among treatment-naive patients was reported in 30.5% and 18.3% of RE and EBRT groups, respectively. Patients treated with RE experienced higher rates of post-embolization abdominal pain, ulcer, nausea, anorexia, thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia. In contrast, EBRT was associated with higher rates of anemia and neutropenia. The authors noted that comparison between groups is limited due to significant population and treatment heterogeneity.

Mosconi (2021) published a systematic review and meta-analysis of TACE and TARE for unresectable ICC.[75] Of the 31 total articles included, 13 were on TACE (906 patients) and 18 were on TARE (789 patients). There was moderate heterogeneity between groups for clinical

and tumor characteristics. The median survival after treatment was 13.5 months (95% CI 11.4 to 16.1) and 14.2 months (95% CI 11.6 to 17.6) for RE and TACE groups, respectively. The survival difference between groups was negligible at two and three years . Clinical adverse events occurred at a higher frequency in patients treated with TACE (58.5%) compared to RE (43.0%).

Boehm (2015) conducted a meta-analysis to compare hepatic artery-based therapies including hepatic arterial infusion, TACE, DEB-TACE, and 90Y RE for unresectable ICC.[76] Twenty studies met inclusion criteria, five of which evaluated 90Y RE. Median OS across studies was 22.8 months for arterial infusion, 13.9 months for RE, 12.4 months for TACE, and 12.3 months for DEB-TACE. Complete or partial responses occurred in 56.9% of patients treated with arterial infusion, compared with 27.4% of those treated with RE and 17.3% of those treated with TACE. While arterial infusion showed the highest median OS, it also had the highest rate of grade 3 and 4 toxicity.

Randomized Controlled Trials

No randomized controlled trials were found for RE of ICC.

Nonrandomized Studies

Edeline (2019) published results from the phase 2 MISPHEC trial (Yttrium-90 Microspheres in Cholangiocarcinoma), which included 41 patients with unresectable ICC treated in the first-line setting with cisplatin, gemcitabine, and RE in French centers with experience with glass microspheres.[77] Fifteen (37%) patients underwent more than one RE treatment. The response rate at three months according to RECIST version 1.1 criteria was 39% (90% CI 26% to 53%) according to local review, with a disease control rate of 98%. After a median follow-up of 36 months, median PFS was 14 months (95% CI 8 to 17 months) and median OS was 22 months (95% CI 14 to 52 months). Of 41 patients, 29 (71%) experienced grade 3 and 4 toxic events, including neutropenia (51%), thrombocytopenia (24%), asthenia (225), anemia (20%), and abdominal pain (12%). Fourteen patients experienced hepatic failure, including five nonreversible cases in patients with cirrhosis who had received whole-liver RE. Nine patients (22%) were downstaged to surgical intervention, with eight cases achieving an R0 surgical resection. A follow-up phase 3 trial randomizing patients with unresectable ICC to chemotherapy alone or RE followed by chemotherapy in the first-line setting is currently underway.

Numerous small case series (range 19 to 115 patients) evaluating RE for unresectable ICC have been published.[78-89] Predominantly retrospective case reviews have assessed heterogeneous populations, making it difficult to ascertain which patients may benefit most from RE. Populations within and between studies have differed in terms of performance status, tumor distribution (e.g., unilobar versus bilobar[81, 86]), morphology (e.g., infiltrative), metastatic disease (eg, lymph node or extrahepatic metastases), prior treatments (e.g., chemotherapy,[80, 83] surgery, and other liver-directed therapies), treatment setting (e.g., neoadjuvant,[88] palliative[81]), and comorbidities. Several studies have reported on resection outcomes following downstaging treatment with RE alone[79, 82, 86, 88] or in combination with chemotherapy.[78, 81] One study compared outcomes with glass versus resin microspheres, finding no significant difference in overall survival between groups.[79] Across series, the median survival in patients treated with RE ranged from 6 to 22 months. Several studies identified favorable subgroups with respect to overall survival, reporting prolonged outcomes in

treatment-naive patients,[75] and for tumor burden ≤25%,[83, 87] peripheral tumor type,[85, 86] and an ECOG performance score of 0.[83, 85, 86]

RADIOEMBOLIZATION FOR METASTATIC BREAST TUMORS

Systematic Reviews

Liu (2022) published a systematic review and meta-analysis assessing the evidence for Y90 SIRT in liver metastatic breast cancer.[90] A total of 24 studies (n=412) were included, most of which were retrospective or non-comparative. Patient demographic information was not summarized in this publication. The median survival time after SIRT was 9.8 months (95% CI 9 to 11.6 months). The cumulative OS rates at six months and one, two, and three years were 65.6% (95% CI 60.8% to 70.0%), 39.0% (95% CI 34.3% to 43.7%), 13.3% (95% CI 10.3% to 16.8%), and 4.4% (95% CI 2.7% to 6.6%), respectively. Patients who had a hepatic metastatic burden exceeding 25% experienced a median survival time of 6.8 months, while those with a burden less than 25% had a median survival time of 10.5 months (p<0.0001).

Aarts (2021) published a systematic review and meta-analysis of intra-arterial therapies for breast cancer metastatic to the liver.[91] Twenty-six studies (1,266 patients), 11 on TARE, 10 on TACE and four on chemo-infusion met inclusion criteria. One study was a retrospective comparative study of TARE and TACE. According to the meta-analysis, pooled response rates were 49% for TARE (95% CI 32 to 67%), 34% for TACE (95% CI 22 to 50%) and 19% for chemo-infusion (95% CI 14 to 25%) and pooled median survival was 9.2 months (range 6.1 to 35.4 months) for TARE, 17.8 months (range 4.6 to 47.0) for TACE and 7.9 months (range 7.0 to 14.2) for chemo-infusion. Missing survival rates at specific time points (one- and two-year OS) and large heterogeneity prevented comparisons of OS.

A systematic review by Smitz (2013) included six studies with a total of 198 patients with breast cancer metastases in the liver.[92] Five studies reported tumor response. Overall disease control (complete response, partial response, and stable disease) at two to four months post-treatment ranged from 78% to 96%. Median survival was reported in four studies and ranged from 10.8 to 20.9 months. Adverse effects included gastric ulceration in 10 patients (5%) and treatment-related mortality in three patients (2%). The authors concluded that these studies showed safety and effectiveness of treatment and strongly encouraged comparative studies, in particular, combining RE with systemic therapy.

Nonrandomized Studies

Ridouani (2021) published the results of a retrospective study reviewing all breast cancer patients undergoing RE of liver metastases from 2011 to 2019 at a single center.[93] RE was performed with glass (66%) or resin (34%) microspheres based on operator preference. Imaging response assessments were available for 60/64 patients, of which 46 (77%, 95% CI 64% to 86%) achieved an objective response, demonstrating a 30% or greater reduction in metabolic activity. Patients with an objective response had a high median dose deliver to the tumor (167 Gy) compared to patients not achieving an objective response (54 Gy, p<.001). Eight patients developed grade 3 or higher treatment-related hepatotoxicity.

Davisson (2020) retrospectively reviewed 24 patients with chemotherapy-refractory hepatic metastases from breast cancer who underwent RE from 2013 to 2018.[94] Extrahepatic metastases were reported in 18 and 20 continued to receive concurrent chemotherapy and/or immunotherapy. Median OS was 35.4 months from first RE. RE within six months of hepatic

metastasis diagnosis and estrogen receptor-positive status were identified as positive predictors of overall survival.

Table 1. Retrospective Case Series of Radioembolization for Liver Metastases in Breast Cancer

Study (Year)	Populations	Outcomes
Pieper (2016)[95]	44 women with unresectable liver-dominant breast metastases who had failed 2+ lines of chemotherapy who underwent 90Y RE at a single center from 2006-2015	ORR: 29% Disease control rate: 71% Median TTP: 101 d Median survival: 184 d Grade 2 toxicity: 1 (cholecystitis) Grade 3 toxicity: 1 (duodenal ulceration)
Gordon (2014)[96]	75 women with stable extrahepatic disease who had hepatic tumor progression after systemic chemotherapy treated with 90Y RE at a single center	30-day mortality: 4% Median OS: 6.6 mo (95% CI 5.0 to 9.2 mo) Median hepatic TTP: 3.2 mo (95% CI 1.2 to 8.5 mo) Median distant TTP: 4.1 mo (95% CI 2.7 to 7.0 mo)
Saxena (2014)[97]	40 women with unresectable, chemo-resistant breast cancer–related liver metastases treated from 2006-2012 at a single institution who had received at least one line of systemic chemotherapy	Grade 1 or 2 clinical toxicity: 40% Of 38 women with ≥1 mo follow-up: CR: 5% PR: 26% SD: 39% PD: 29% Median survival: 13.6 mo
Cianni (2013)[98]	52 women with chemotherapy-refractory breast cancer and inoperable liver metastases; chemotherapy administered previously to all patients, surgery in 17.3%, TACE in 3.8%, and RFA in 3.8%	CR: 0% PR: 56% SD: 35% PD: 10% Median OS: 11.5 mo
Haug (2012)[83]	58 women with chemotherapy-refractory breast cancer and unresectable hepatic metastases	Mean follow-up: 27.5 wk CR: 0% PR: 25.6% SD: 62.8% PD: 11.6% Median OS: 47 wk
Jakobs (2008)[33]	30 (29 women, 1 man) patients who underwent RE with resin microspheres in a single-session, whole-liver treatment for breast cancer metastases and had failed prior polychemotherapy regimens	For 23 patients with follow-up data, after median follow-up of 4 mo: PR: 61% SD: 35% PD: 4% One death due to treatment-related hepatic toxicity after median follow-up of 14.2 mo Median OS: 11.7 mo
Bangash (2007)[34]	27 women with progressive liver metastases from breast cancer while on polychemotherapy	After 90-d follow-up CR: 39% PR: 39% SD: 52% PD: 9% Median survival ECOG Performance Status 0: 6.8 mo

		ECOG Performance Status 1-3: 2.6 mo
Coldwell (2007)[45]	44 patients with hepatic metastases at three hospitals who failed 1st-, 2nd-, or 3rd-line treatment for primary breast tumor and were not candidates for RFA, TACE, resection, IMRT, or SRT	After 12-wk follow-up PR: 47% No radiation-related liver failures were observed Median survival: >14 mo

90Y: yttrium-90; CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group; IMRT: intensity-modulated radiotherapy; ORR: response rate; OS: overall survival; PD: progressive disease; PR: partial response; RE: radioembolization; RFA: radiofrequency ablation; SD: stable disease; SRT: stereotactic radiotherapy; TACE: transarterial chemoembolization; TTP: time to progression.

OTHER METASTATIC TUMORS IN THE LIVER

Data on the use of RE in other tumors metastatic to the liver are limited and included numerous methodologic limitations such as patient heterogeneity, lack of a control group, and patient numbers too small to draw meaningful conclusions. For example, a retrospective data analysis was reported by Michl (2014) on RE for liver metastases from pancreatic cancer. Nineteen patients were included, 16 of whom had received previous palliative chemotherapy.[99] Median local PFS in the liver was 3.4 months (range 0.9 to 45.0). Median OS was nine months (range 0.9 to 53.0), and one-year survival was 24%. Adverse effects were grade ≤3 (e.g., nausea, vomiting, fatigue, fever, abdominal pain) in the short term and long-term effects included liver abscess, gastroduodenal ulceration, cholestasis and cholangitis, ascites, and spleen infarction. The lack of a control group precludes conclusions about any survival benefits and complication rates of RE.

RADIOEMBOLIZATION AS A BRIDGE TO HEPATIC RESECTION

Vouche (2013) reported on 83 patients treated with RE as a technique to control or limit tumor progression in unresectable, unilobar hepatic disease and to hypertrophy a small future liver remnant.[100] Patients included in the study had right unilobar disease with HCC (n=67), cholangiocarcinoma (n=8), or metastatic CRC (n=8). One month after RE, significant right lobe atrophy (p=0.003), left lobe hypertrophy (p<0.001), and future liver remnant hypertrophy (p<0.001) were observed and remained during follow-up. Successful right lobectomy was later performed in five patients, and six patients received liver transplants. However, further studies are needed to assess RE as a bridge to hepatic resection.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

All the following statements are category 2A recommendations unless specified.

Primary Hepatocellular Carcinoma

National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma (v.2.2023) indicate that the use of arterially directed therapies, including TAE, TACE, and DEB-TACE, and RE with yttrium-90 microspheres may be appropriate provided that the arterial blood supply can be isolated without excessive nontarget treatment.[8] They recommend considering locoregional therapies for patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies. They also state that “all tumors irrespective of location may be amenable to arterially directed therapies [including bland TAE, TACE and DEB-TACE, and 90Y RE with microspheres] provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.”

NCCN discussion indicates that there is limited evidence available on the utility of RE as a bridge to liver transplant for patients on a liver transplant waiting list. However, most NCCN member centers use RE as a bridge to transplant.

Primary Intrahepatic Cholangiocarcinoma

Biliary tract cancer recommendations (v.2.2023) for unresectable intrahepatic cholangiocarcinoma (ICC) include chemotherapy, clinical trial, radiotherapy, arterially directed therapies, and supportive care.[101] Locoregional therapy is discussed as “a treatment option that may be considered for patients with unresectable disease or metastatic cancer without extrahepatic disease.

Metastatic Colorectal Cancer

NCCN guidelines for colon cancer (v.2.2023) and rectal cancer (v.4.2023) recommend the use of intra-arterial embolization including RE for highly selected patients with chemotherapy-resistant/-refractory disease without obvious systemic disease, with predominant hepatic metastases.[6, 102] Additionally, for hepatic metastases that are not optimally resectable, portal vein embolization and 90Y RE are among the options that can be considered. The guidelines also note that further investigation is necessary to identify the role of radioembolization at earlier stages of disease, particularly in patients with right-sided primary origin.[6]

Metastatic Neuroendocrine Tumors

For unresectable liver metastases (carcinoid or neuroendocrine tumors of the pancreas, e.g., islet cell), NCCN guideline (v.1.2023) recommendations include hepatic regional therapy which includes RE for lobar or segmental disease distribution and in patients with prior Whipple surgery or biliary tract instrumentation.[1]

Metastatic Breast Cancer

NCCN guidelines for breast cancer (v.4.2023) do not discuss the use of RE in the treatment of metastatic breast cancer.[103]

Metastatic Melanoma

Current NCCN guidelines for cutaneous melanoma (v.2.2023) do not discuss the use of RE in the treatment of metastatic disease.[104] Guidelines for uveal melanoma (v.1.2023) state that "further study is required to determine the appropriate patients for and risk and benefits" of selective internal radiation therapy for patients with liver metastases using 90Y.[105]

AMERICAN COLLEGE OF RADIOLOGY APPROPRIATENESS CRITERIA®

The American College of Radiology (ACR) published Appropriateness Criteria for radiologic management of hepatic malignancy.[106]

Primary Hepatocellular Carcinoma

ACR Appropriateness Criteria consider TARE with Y90 beads to be a treatment option for multifocal HCC. The guideline recommendations included statements that RE may be appropriate for solitary HCC tumor <3cm and is usually appropriate for larger HCC tumors.

Metastatic Colorectal Cancer

The ACR reports that published evidence suggests that TACE and RE may be an option for patients with metastatic colorectal tumors or for solitary colorectal liver metastasis.

Metastatic Neuroendocrine Tumors

The ACR states that transarterial therapies are “an important treatment strategy for multifocal liver dominant metastatic neuroendocrine tumors. TAE, TACE, DEB-TACE, and TARE have all shown efficacy for overall survival, tumor growth reduction, and symptom control, without clear superiority of one transarterial therapy over the others.”

AMERICAN COLLEGE OF RADIOLOGY/AMERICAN SOCIETY FOR RADIATION ONCOLOGY/SOCIETY OF INTERVENTIONAL RADIOLOGY ET AL

A joint practice parameter from the American College of Radiology (ACR), American Brachytherapy Society (ABS), American College of Nuclear Medicine (ACNM), American Society for Radiation Oncology (ASTRO), Society of Interventional Radiology (SIR), and Society of Nuclear Medicine and Molecular Imaging (SNMMI) on selective internal radiation therapy list indications for RE which include, but are not limited to:[107]

- Unresectable and/or inoperable primary or secondary liver malignancies that are liver dominant but not necessarily exclusive to the liver; and
- Performance status that will allow them to benefit from the therapy (e.g., ECOG performance status of 0 or 1 or KPS of 70 or more); and
- Life expectancy of at least three months

RADIOEMBOLIZATION BRACHYTHERAPY ONCOLOGY CONSORTIUM

Members met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology. Using level 2A evidence (panel consensus with low-level evidence), 14 recommendations were made. They concluded that there was sufficient evidence to support the safety and efficacy of yttrium-90 microsphere therapy and that its use requires multidisciplinary management, adequate patient selection, and meticulous angiographic technique. They also stated that the initiation of clinical trials was necessary to further define the role of yttrium-90 microsphere therapy in relation to other currently available therapies.[108]

SUMMARY

TRANSARTERIAL EMBOLIZATION WITH NON-RADIOACTIVE AGENTS

There is enough research to show that transarterial embolization (TAE) with non-radioactive agents improves health outcomes for people with cancer and various conditions. Therefore, transarterial embolization (TAE) with non-radioactive agents may be considered medically necessary for any indication.

TRANSARTERIAL CHEMOEMBOLIZATION

There is enough research to show that transarterial chemoembolization (TACE) improves health outcomes for people with cancer and various conditions. Therefore, transarterial chemoembolization (TACE) may be considered medically necessary for any indication.

RADIOEMBOLIZATION

Primary Hepatocellular Carcinoma (HCC)

Studies have demonstrated that radioembolization is comparable to transarterial chemoembolization (TACE), which is considered to be the therapy of choice for patients with unresectable primary hepatocellular carcinoma (HCC) in terms of tumor response and overall survival. However, disadvantages of TACE include the necessity of multiple treatment sessions and hospitalization, its contraindication in patients with portal vein thrombosis, and its poorer tolerance by patients. Therefore, radioembolization may be considered medically necessary for the treatment of unresectable primary HCC or as a bridge to transplantation in primary HCC.

Metastatic Colorectal Cancer in the Liver

A major cause of morbidity and mortality in patients with colorectal disease metastatic to the liver is liver failure, as this disease tends to progress to diffuse, liver-dominant involvement. Therefore, the use of radioembolization to decrease tumor bulk and/or halt the time to tumor progression and liver failure may lead to prolonged progression free and overall survival in patients with no other treatment options (i.e., those with chemotherapy refractory liver-dominant disease). Other uses include palliation of symptoms from tumor bulk. Radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer may be considered medically necessary in carefully selected patients when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer when the patient does not meet criteria. Therefore, radioembolization for the treatment of unresectable hepatic metastases from colorectal cancer is considered investigational when criteria are not met.

Metastatic Neuroendocrine Tumors in the Liver

Studies of radioembolization for treatment of metastatic neuroendocrine tumors in the liver have included heterogeneous patient populations, making interpretation of survival data difficult. However, relief of symptoms from carcinoid syndrome has been reported in a proportion of patients. Surgical debulking of liver metastases has shown palliation of hormonal symptoms; similarly, debulking by radioembolization may lead to symptom relief in some patients. Therefore, radioembolization for the treatment of unresectable hepatic metastases from neuroendocrine tumors may be medically necessary in carefully selected patients when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of hepatic metastases from neuroendocrine tumors when the patient does not meet criteria. Therefore, radioembolization for the treatment of hepatic metastases from neuroendocrine tumors is considered investigational when criteria are not met.

Metastatic Melanoma in the Liver

In patients with uveal melanoma, the liver is the most common site of metastatic disease. Studies of radioembolization for treatment of metastatic melanoma (uveal or cutaneous) in

the liver consists of one comparative study and several relatively small observational studies. In general, these studies predict good tumor response to radioembolization and report significant increases in overall survival compared to those treated with best supportive care. Therefore, radioembolization may be considered medically necessary for the treatment of diffuse, symptomatic hepatic metastases from melanoma when criteria are met.

There is insufficient evidence on the use of radioembolization for the treatment of hepatic metastases from melanoma when the patient does not meet criteria. Therefore, radioembolization for the treatment of hepatic metastases from melanoma is considered investigational when criteria are not met.

Primary Intrahepatic Cholangiocarcinoma (ICC)

The current evidence on the use of radioembolization (RE) in patients with primary intrahepatic cholangiocarcinoma (ICC) is limited to data from small studies that do not compare the health outcomes of RE with other treatments. These study designs make interpretation of the data on tumor response and survival difficult to interpret. However, ICC is a rare tumor, so large comparative studies may never become available. The available studies have consistently reported beneficial effects in patients who are not candidates for surgical tumor resection. Because there are currently limited treatment options for these patients, radioembolization may be medically necessary for the treatment of unresectable primary ICC. Since surgical resection is currently the preferred treatment for these tumors, radioembolization is considered investigational for resectable primary ICC.

Miscellaneous Metastatic Tumors in the Liver

The current evidence on the use of radioembolization in intrahepatic cholangiocarcinoma and metastatic tumors in the liver other than those from colorectal carcinoma, melanoma or neuroendocrine tumors is too limited to draw meaningful conclusions due to methodologic limitations such as small numbers of heterogeneous patients. Therefore, radioembolization for these other tumors, including metastatic tumors from breast and pancreatic cancer, is considered investigational.

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CODES

NOTE: CPT code 37243 can be used for both *radioactive* and *non-radioactive* embolization procedures performed for numerous conditions/locations. Embolization codes requiring prior authorization are listed on the "Pre-authorization List" web page. There may be codes related to embolization, such as CPT 37242 which may be used for prostate artery embolization, that do not require prior approval. Embolization codes not listed on the pre-authorization website do not require prior approval.

Codes	Number	Description
CPT	37242	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)
	37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	77778	Interstitial radiation source application; complex
	79445	Radiopharmaceutical therapy, by intra-arterial particulate administration
HCPCS	C2616	Brachytherapy source, non-stranded, yttrium-90, per source
	C9797	Vascular embolization or occlusion procedure with use of a pressure-generating catheter (e.g., one-way valve, intermittently occluding), inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
	S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

Date of Origin: *December 2010*

Regence

Medical Policy Manual Medicine, Policy No. 142

Orthopedic Applications of Stem Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow

Effective: February 1, 2025

Next Review: October 2025
Last Review: December 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

Mesenchymal stem cells (MSCs) are multipotent cells (also called “stromal multipotent cells”) that possess the ability to differentiate into various tissues including organs, trabecular bone, tendon, articular cartilage, ligaments, muscle, and fat. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

MEDICAL POLICY CRITERIA

Note: Use of platelet rich plasma is addressed in Medicine Policy No. 77 (see Cross References section). This policy does not apply to the use of unmanipulated bone marrow aspirate for spinal indications which may be considered medically necessary.

I. Mesenchymal stem cell therapy, including but not limited to manipulated or unmanipulated bone marrow, fat, and amnion cells, is considered **investigational** for all orthopedic applications, including but not limited to use in repair or regeneration of musculoskeletal tissue.

II. Allograft bone products containing viable stem cells are considered **investigational** for all orthopedic applications, including but not limited to demineralized bone matrix (DBM) with stem cells.

III. Synthetic bone graft substitutes that must be combined with autologous bone marrow are considered **investigational** for all orthopedic applications.

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

CROSS REFERENCES

1. Autologous Blood-Derived Growth Factors as a Treatment for Wound Healing and Other Conditions, Medicine, Policy No. 77
2. Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia, Medicine, Policy No. 100
3. Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141
4. Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions, Surgery, Policy No. 87

BACKGROUND

MSCs are associated with the blood vessels within bone marrow, synovium, fat, and muscle where they can be mobilized for endogenous repair, as occurs with healing of bone fractures. Stimulation of endogenous MSCs is the basis of procedures such as bone marrow stimulation (e.g., microfracture) and harvesting/grafting of autologous bone for fusion. Bone-marrow aspirate is considered to be the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. However, harvesting MSCs from bone marrow requires an additional procedure that may result in donor-site morbidity. In addition, the number of MSCs in bone marrow is low, and the number and differentiation capacity of bone marrow-derived MSCs decreases with age, limiting their efficiency when isolated from older patients.

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with MSCs and/or bioactive molecules such as growth factors. In vivo, the fate of stem cells is regulated by signals in the local 3-dimensional microenvironment from the extracellular matrix and neighboring cells. It is believed that the success of tissue engineering with MSCs will also require an appropriate 3-dimensional scaffold or matrix, culture conditions for tissue-specific induction, and implantation techniques that provide appropriate biomechanical forces and mechanical stimulation. Given that each tissue type requires different culture conditions, induction factors (e.g., signaling proteins, cytokines, growth factors), and implantation techniques, each preparation must be individually examined. The ability to induce cell division and differentiation, without adverse effects such as the formation of neoplasms, remains a significant concern.

The U.S. Food and Drug Administration (FDA) stated:

“Cell-based therapies show great promise for repairing, replacing, restoring, or regenerating damaged cells, tissues and organs. Researchers are working to develop cell-based treatments that are both effective and safe. Many cell-based therapies use stem cells (SC) that are removed from the body and put into cultures in the laboratory, where they multiply before being

infused into the patient. SCs are immature cells that replicate themselves and have the ability to give rise to a variety of different types of cells. For cell therapies based on embryonic stem cells, stem cells are first stimulated to mature before they are given to a patient. However, embryonic stem cells can cause tumors, so products based on them should not have undifferentiated embryonic stem cells contaminating the product given to patients. Also, more mature cells may be better suited for replacing specific types of damaged or lost cells, or for repairing damaged tissue.

A major challenge posed by SC therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue. In response to this challenge, FDA scientists are developing laboratory techniques that will enable the agency to carefully evaluate and characterize these products in order to reliably predict whether they will be safe and effective."

REGULATORY STATUS

Concentrated autologous MSCs do not require approval by the U.S. Food and Drug Administration (FDA).

Demineralized bone matrix (DBM), which is processed allograft bone, is considered minimally processed tissue and does not require FDA approval. At least four commercially available DBM products are reported to contain viable stem cells:

- Allostem® (AlloSource) is partially demineralized allograft bone seeded with adipose-derived MSCs
- Allopatch®,
- Osteocell Plus® (NuVasive): an allograft cellular bone matrix containing native MSCs.
- Trinity Evolution Matrix™ (Orthofix): an allograft that is processed and cryopreserved to maintain viable adult MSCs and osteoprogenitor cells.

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent upon the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product's intended use with an investigational new drug and Biologics License Application (BLA).

Other products contain DBM and may be mixed with bone marrow aspirate. Some of the products that are currently available are:

- DBX® Putty (Musculoskeletal Transplant Foundation [MTF]) may be mixed with blood or bone marrow.
- Fusion Flex™ (Wright Medical): a dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate.
- Ignite® (Wright Medical): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

- PliaFX® Prime (LifeNet Health) consists of demineralized bone fibers that may be combined with autograft or allograft materials.

Other commercially available products are intended to be mixed with bone marrow aspirate and have received 510(k) clearance, such as:

- CopiOs sponge or paste (Zimmer): synthetic bone graft material consisting of mineralized, lyophilized collagen.
- Collage™ Putty (Orthofix): Composed of type-1 bovine collagen and beta Tri-calcium phosphate.
- Vitoss® (Stryker, developed by Orthovita): composed of beta tricalcium phosphate.
- nanOss® Bioactive (XTant Medical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.

No products using engineered MSCs have been approved by the FDA for orthopedic applications.

In 2008, the FDA determined that the mesenchymal stem cells sold by Regenerative Sciences for use in the Regenexx™ procedure would be considered drugs or biological products and thus require submission of a New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. In 2014, a federal appellate court upheld FDA's power to regulate adult stem cells as drugs and biologics and ruled that the Regenexx cell product fell within FDA's authority to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps) (Section 351).[1] To date, no NDA or BLA has been approved by the FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx™ network facilities in the U.S. provide same-day stem cell and blood platelet procedures, which do not require FDA approval.

EVIDENCE SUMMARY

At this time, the literature consists mainly of articles describing the potential of stem cell therapy for orthopedic applications in humans, along with basic science experiments on sources of mesenchymal stem cells (MSCs), regulation of cell growth and differentiation, and development of scaffolds.[2] Although the evidence base has been steadily increasing, authors indicate that the technology is in an early stage of development. In order to assess the safety and efficacy of orthopedic applications of MSCs and allograft bone products, such as demineralized bone matrix, high-quality randomized trials (RCTs) are required that compare health outcomes with versus without the use of these products.

CARTILAGE DEFECTS

Systematic Reviews

Sadeghirad (2024) published a systematic review and meta-analysis of randomized studies to assess the effectiveness of MSC for chronic knee pain due to osteoarthritis (OA). [3] The study involved 16 trials and 807 participants. Thirteen studies used autologous MSC cells and three used allografts. MSC sources were bone-marrow derived in six studies and adipose-derived in eight studies. One study used cells from stromal vascular fraction, and one used placenta-derived cells. At 3-6 months follow-up the analysis found low certainty evidence that MSC injection may reduce pain compared to placebo or conservative management, however high heterogeneity was noted (weighted mean difference [WMD] -2.04 cm on a 10 cm VAS, 95% CI: -2.87 to -1.21; I^2 = 87.2%). At six months, moderate certainty evidence found little to no pain relief (WMD -0.74 cm on a 10cm VAS, 95% CI -1.16 to 1.0.33; I^2 = 0). Similarly at one-year follow-up from six studies (252 participants) there was low certainty evidence of reduced

pain (WMD -1.77 cm on a 10 cm VAS, 95% CI: -3.23 to -0.32, I^2 =87%) and moderate certainty evidence reported less pain relief (WMD -.0.73 cm on a 10 cm VAS, 95% CI: -1.69 to 0.24, I^2=49.6%). There was also no evidence of improvement in physical function and some evidence that MSC therapy may increase risk of any adverse event (risk ration [RR] 2.67, 95% CI 1.19 to 5.99).

Jin (2022) published a systematic review and meta-analysis of 6 RCTs (N=452) that evaluated intra-articular MSC injection in patients undergoing high tibial osteotomy (HTO).[4] Results demonstrated that there were no significant differences in the International Knee Documentation Committee (IKDC) score and KOOS Pain and Symptoms subscales in patients who underwent HTO with or without the MSC injection. However, patients who received MSC injection had significantly greater improvements in Lysholm scores (mean difference, 2.55; 95% CI, 0.70 to 4.40; p=.007), and greater proportions of International Cartilage Regeneration and Joint Preservation Society (ICRS) grade 1 (p=.03) and grade 2 (p=.02) cartilage repair in the medial femoral condyle and grade 2 cartilage repair in the tibial plateau (p=.04).

Rinonpoli (2021) summarized the state of art in the application of stem cells for the treatment of meniscal damage both at pre-clinical and clinical level.[5] Of the 18 studies, 13 were preclinical studies, and 5 were clinical trials. The most commonly used cells were mesenchymal stem cells (MSC), derived from bone marrow (BMMSC), synovial tissue (SMSC), or adipose tissue (ADSC). Follow-ups ranged from 2 to 16 weeks for the pre-clinical studies and from 3 to 24 months for the clinical studies. All studies documented good results in terms of laboratory markers/scores, clinical and radiologic evaluation. The authors concluded that based on the currently available data, it is not possible to establish the best cell source or delivery method for the treatment of meniscal injuries.

Wiggers (2021) conducted a systematic review of RCTs evaluating autologous MSC therapy on patient-reported outcome measures and disease severity.[6] Fourteen RCTs were identified in searches conducted through December 2020. Meta-analysis was precluded because most of the original trial data were not available for pooling and due to heterogeneity across studies. A total of 408 patients with knee osteoarthritis received MSC therapy derived from bone marrow, adipose tissue or activated peripheral blood. After 1 year, 19 of 26 (73%) clinical outcome measures improved with MSCs compared with control. In the MSC group, patients improved by 1.8 to 4.4 points on the Visual Analogue Scale (0 to 10) and 18 to 32 points of the Knee Osteoarthritis Outcome Score (0 to 100). Four studies showed better disease severity on imaging after MSC compared with control at 1 year. Although the reviewers found a positive effect of autologous MSC therapy compared with control treatments, the certainty of the evidence was rated low to very low due to high risk of bias in the included studies (e.g., 10 of 14 RCTs were at high risk of bias on all outcomes) and high heterogeneity in the source, method of preparation, and dosage of injected stem cells in included RCTs.

A systematic review and meta-analysis by Maheshwer (2020) identified 25 studies with 439 participants that used MSCs for treatment of OA.[7] Although 13 studies were considered level I RCTs by the authors (range of 7 to 40 participants), low quality RCTs would normally be downgraded to level II. Meta-analysis suggested improvement in self-reported function, but only in patients who underwent concomitant surgery, and there was no significant improvement in pain. Few studies reported on cartilage quality. Most of the studies were rated as poor or fair quality. Conclusions are limited due to substantial variability in MSC source, preparation, and concentration in the current literature.

A systematic review by Borakati (2018) included 13 studies comparing patients with osteoarthritis who were treated either with MSCs or with a control treatment that was identical other than the inclusion of MSCs (i.e., studies using chondrogenic cellular therapy as a control were not included).[8] Pain assessment results were noted for each of the controlled studies, resulting in a pooled standardized mean difference (SMD) of -1.27 (95% confidence interval [CI] -1.95 to -0.58) in favor of the group treated with MSCs. Reviewers reported a Z-statistic effect size of 3.62, again in favor of the groups treated with MSCs ($p<0.001$); although they noted the high heterogeneity across controlled studies ($I^2=92\%$). Additionally, 34 uncontrolled studies (n=737 patients) were summarized and evaluated qualitatively: reviewers noted consistent cartilage regrowth and reduction of pain following treatment with MSCs in these studies; however, as pain medication was often given concurrently, interpretation of the latter outcome is limited.

Emadedin (2018) reported a triple-blind placebo-controlled phase 1/2 trial of expanded MSCs in 47 patients with OA of the knee.[9] Compared to the placebo group, the MSC group showed statistically significant improvements in WOMAC pain and function subscales but not VAS. The WOMAC stiffness subscale improved to a similar extent in the two groups. Minimum Clinically Important Improvement and Patient Acceptable Symptom State were not significantly different between the two groups. Study limitations included the short duration of follow-up, statistical analysis, and lack of information regarding use of analgesic medications.

Iijima (2018) published a systematic review of MSC treatment for knee osteoarthritis, which included 35 studies.[10] Of these, only seven were RCTs. Meta-analysis results indicated that there was improvement in knee pain (SMD -1.45, 95% CI -1.94 to -0.96), cartilage quality (SMD -1.99, 95% CI -3.51 to -0.47), and self-reported function (SMD 1.50, 95% CI 1.09 to 1.92), however the authors stated that the evidence quality was “very low” to “low,” and emphasized the need for high-quality RCTs.

Another 2018 systematic review on stem cell therapy for articular cartilage repair noted similar concerns regarding the quality of the evidence.[11] The review included 46 studies that evaluated MSCs from a variety of sources, most of which were case reports and case series. The authors noted that among these, “18 studies erroneously referred to adipose tissue-derived stromal vascular fractions as "adipose-derived MSCs," 2 studies referred to peripheral blood-derived progenitor cells as "peripheral blood-derived MSCs," and 1 study referred to bone marrow aspirate concentrate as "bone marrow-derived MSCs."

Cui (2016) published a systematic review on 18 studies looking at the effect of MSC in treating patients with osteoarthritis.[12] MSC treatment in patients with KOA showed continual efficacy for 24 months compared with their pretreatment condition. Effectiveness of MSCs was improved at 12 and 24 months post-treatment, compared with at three and six months. There was no dose response association in the MSCs numbers. This review only included four randomized trials while the remaining 14 studies were non-randomized and had methodological limitations.

Xu (2015) published a meta-analysis on the effect of MSCs for articular cartilage degeneration treatment, including 11 controlled trials (n=558). No critical appraisal of the quality of the included studies was reported. MSC treatment significantly improved the American Orthopedic Foot and Ankle Society Scale (SMD 0.91, 95% confidence interval [CI], 0.52 to 1.29) and the Osteo-Arthritis Outcome Score (SMD 2.81, 95% CI 2.02 to 3.60).[13] Comprehensive evaluation indexes, such as the American Knee Society Knee Score System (SMD -0.12, 95% CI -1.02 to

0.78), the Hospital for Special Surgery Knee Rating Scale (SMD 0.24, 95% CI -0.56 to 1.05) and the International Knee Documentation Committee (SMD -0.21, 95% CI -0.77 to 0.34), were no different between MSC use and other treatments. The reviewers concluded that there was no obvious advantage regarding the application of stem cells to treat cartilage injury, compared with other treatments.

Filardo (2013) conducted a systematic review of mesenchymal stem cells for the treatment of cartilage lesions.[14] They identified 72 preclinical papers and 18 clinical reports. Of the 18 clinical reports, none were randomized, five were comparative, six were case series, and seven were case reports. In two clinical studies the source of MSCs was adipose tissue, in five it was bone marrow concentrate, and in 11 studies the source of MSCs was bone marrow-derived. The authors reached the following conclusion:

> "Despite the growing interest in this biological approach for cartilage regeneration, knowledge on this topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies. Many aspects have to be optimized, and randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments."

The source of MSCs may have an impact on outcomes, but this is not well understood, and the available literature uses multiple different sources of MSC. Because of the uncertainty over whether these products are equivalent, the summary of the key evidence to date is grouped by source of MSC.

Randomized Controlled Trials

Cartilage Defects: MSCs Expanded from Bone Marrow

Mautner (2023) compared multiple autologous and allogeneic cell-based therapies with gold-standard corticosteroid injection in 475 adults with OA of the knee in a single-blind phase 3 RCT.[15] Patients were randomized to one of two autologous cell therapies (bone marrow aspirate concentrate [BMAC] or stromal vascular fraction), allogeneic umbilical cord-derived MSCs, or intra-articular corticosteroid injection; the co-primary endpoints were changes from baseline in VAS and Knee injury and Osteoarthritis Outcome Score pain scores at 12-month follow-up. No significant differences in pain scores were noted in comparisons between corticosteroid injection and any of the cell therapy arms. The authors concluded that the study found no superiority of any of the cell therapies compared to corticosteroids at one year.

Wong (2013) reported on the use of cultured MSCs in 56 patients with osteoarthritis who underwent medial opening-wedge high tibial osteotomy and microfracture of a cartilage lesion.[16] Bone marrow was harvested at the time of microfracture and the MSCs were isolated and cultured. After three weeks, the cells were assessed for viability and delivered to the clinic, where patients received an intra-articular injection of MSCs suspended in hyaluronic acid (HA) or, for controls, intra-articular injection of HA alone. The primary outcome was the International Knee Documentation Committee (IKDC) score at six months, one year, and two years. Secondary outcomes were the Tegner and Lysholm scores through two years and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system by MRI at one year. All patients completed the two-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the IKDC (mean difference 7.65 on 0 to 100 scale, p=0.001), Lysholm (mean

difference, 7.61 on 0 to 100 scale, p=0.02), and Tegner (mean difference 0.64 on a 0 to 10 scale, p=0.02). Blinded analysis of MRI results found higher MOCART scores in the MSC group. The group treated with MSCs had a higher proportion of patients who had complete cartilage coverage of their lesions (32% vs 0%), greater than 50% cartilage cover (36% vs 14%) and complete integration of the regenerated cartilage (61% vs 14%).

A controlled, double-blind clinical trial was conducted with a group of 47 patients with radiographic and symptomatic knee osteoarthritis.[17] Three groups were randomized for intra-articular injections: autologous bone marrow-derived culture-expanded MSCs (n=16); autologous bone marrow-derived culture-expanded MSCs with platelet-rich plasma (PRP) (n=14); and corticosteroid (n=17). The results of the study show Knee Injury and Osteoarthritis Outcome Score (KOOS) is significantly improved at one month (p=0.003) with MSCs and by one year both MSCs and MSCS + PRP show the highest percentage of improvement.

Cartilage Defects: MSCs Concentrated from Bone Marrow

A small RCT published by Vega (2015) that assessed the efficacy of bone marrow derived MSCs as a treatment for knee osteoarthritis, randomizing 30 patients with chronic knee pain unresponsive to conservative treatments and showing radiological evidence of osteoarthritis.[18] Fifteen patients were treated with allogeneic bone marrow MSCs by intra-articular injection, while 15 controls received intra-articular hyaluronic acid (HA). Clinical outcomes were followed for one year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping. The MSC-treated patients displayed significant improvement in algofunctional indices versus the active controls. Quantification of cartilage quality by T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.

Cartilage Defects: Adipose-Derived MSCs

Kim (2023) reported a double-blind phase 3 RCT comparing a single intra-articular injection of autologous adipose tissue-derived MSCs with placebo in patients with knee OA (N=261).[19] Patients meeting American College of Rheumatology criteria for Kellgren-Lawrence grade 3 knee OA who had 100 mm VAS pain scores ≥50 and WOMAC functional impairment scores ≥40 despite >3 months of non-operative treatment were eligible for enrollment. All patients underwent abdominal subcutaneous lipoaspiration three weeks prior to assigned study injection (1:1 randomization to 1x108 autologous adipose tissue-derived MSCs [n=131] or a mixture of saline with autologous serum [n=130]). The co-primary endpoints were change in 100 mm VAS pain score and WOMAC function score from baseline to 6 months. In the primary analysis, patients assigned to adipose tissue-derived MSCs experienced significantly greater improvements than those assigned to placebo in both VAS pain score (25.2 ±24.6 vs 15.5 ±23.7; p=.004) and WOMAC function score (21.7 ±18.6 vs 14.3 ±19.2; p=.002) from baseline to 6 months. Six-month changes in patient-reported outcomes (KOOS, 36-Item Short Form Health Survey Score, and International Knee Documentation Committee subjective knee score) also reflected significant improvements in patients who received adipose tissue-derived MSCs compared with those who received placebo. Study limitations include that while patients were required to have received prior non-operative therapy for at least 3 months, specific prior treatments were not reported; it is unclear whether the use of a placebo comparator was more appropriate than an active comparator in this setting.

The literature on adipose-derived MSCs for articular cartilage repair is very limited, coming from two research groups in Korea. One of the groups appears to have been providing this treatment as an option for patients for a number of years and recently published a RCT that evaluated cartilage healing after high tibial osteotomy (HTO) in 52 patients with osteoarthritis of the medial compartment.[20] Patients were randomly assigned to HTO with application of platelet-rich plasma (PRP) or HTO with application of PRP plus MSCs. MSCs from adipose tissue were obtained through liposuction from the buttocks. The tissue was centrifuged and the stromal vascular fraction mixed with PRP for injection. A total of 44 patients completed second look arthroscopy and one- and two-year clinical follow-up. There were statistically significant differences for PRP only versus PRP+MSC on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for pain (74±5.7 vs. 81.2±6.9, p<0.001) and symptoms (75.4±8.5 vs. 82.8±7.2, p=0.006). There were also statistically significant differences on the final pain score for the PRP only versus PRP+MSC groups (16.2±4.6 vs. 10.2±5.7, p<0.001), but the Lysholm score, which is more scientifically proven, was not significantly different between the PRP only and PRP+MSC groups (80.6±13.5 vs. 84.7±16.2, all respectively, p=0.36). Articular cartilage healing was rated as improved with MSCs following video review of second-look arthroscopy; blinding of this measure is unclear. There are a number of limitations of this study, including the small sample size, short duration of follow-up, and significant improvements on only some of the outcomes. All of the significant differences in outcomes were modest in magnitude, and as a result, there is uncertainty regarding the clinical significance of the findings.

This group also published a trial comparing treatment with adipose-derived MSCs, fibrin glue, and microfracture to microfracture alone.[21] A total of 80 patients with a single International Cartilage Repair Society grade III/IV symptomatic cartilage defect on the femoral condyle were randomized to receive one of the treatments. The mean follow-up time was 27.4 months. At follow-up, the MSC + fibrin glue + microfracture group had significantly greater improvements in the Knee Injury and Osteoarthritis Outcome Score pain and symptom subscores than the microfracture alone group (p=0.034 and 0.005, respectively). There were no significant differences between groups for the activities of daily living, sports and recreation, or quality of live subscores. Second-look arthroscopies were performed in 57 of the 80 patients, with no significant differences between groups. The lack of blinding in this study limits the conclusions that can be drawn from its results.

More recently, Zaffagnini (2022) reported on results of an RCT that evaluated a single intra-articular injection of microfragmented adipose tissue or PRP in patients (N=118) with knee OA.[22] The primary outcomes were the IKDC subjective score and the KOOS pain subscore at 6 months. Overall, both treatments provided significant improvements from baseline in clinical outcomes, with no significant differences found between treatment groups. The IKDC scores significantly improved from baseline to 6 months, from 41.1 ± 16.3 to 57.3 ± 18.8 with microfragmented adipose tissue, and from 44.8 ± 17.3 to 58.4 ± 18.1 with PRP. The improvement in the KOOS pain subscore from baseline to 6 months was 58.4 ± 15.9 to 75.8 ± 17.4 with microfragmented adipose tissue and 63.5 ± 17.8 to 75.5 ± 16.1 with PRP. As a secondary outcome, more patients in the microfragmented adipose tissue group with moderate/severe knee OA reached the minimal clinically important difference for the IKDC score at 6 months compared with the PRP group (75.0% vs 34.6%, respectively; p=.005).

A multisite prospective double-blinded randomized placebo-controlled clinical trial was conducted in adult patients with symptomatic knee osteoarthritis.[23] The trial included 39 eligible patients injected with high-dose, low-dose, or placebo stromal vascular fraction medium obtained from liposuction for intra-articular administration of progenitor cells and

mesenchymal stem cells derived from adipose tissue. After six months, change in WOMAC score was 83.9%, 51.5%, and 25.0%, respectively, and at one year was 89.5%, 68.2%, and 0%, respectively. Significant changes when compared with placebo revealed a dose dependent improvement in osteoarthritis symptoms and pain at six months (high dose, p=0.04; low does, p=0.02) and at one year (high dose, p=0.006; low dose, p=0.009).

Cartilage Defects: MSCs from Peripheral Blood

A 2013 report described a small randomized controlled trial with autologous peripheral blood MSCs for focal articular cartilage lesions.[24] Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by five weekly injections of HA. Half of the patients were randomly allocated to receive injections of peripheral blood stem cells or no further treatment. There were baseline differences in age between the groups, with a mean age of 38 for the treatment group compared to 42 for the control group. The peripheral blood stem cells were harvested after stimulation with recombinant human granulocyte colony-stimulating factor, divided in vials, and cryopreserved. At six months after surgery, HA and MSC were re-administered over three weekly injections. At 18 months after surgery, second look arthroscopy on 16 patients in each group showed significantly (p=.022) higher histological scores (by about 10%) for the MSC group (1,066 vs. 957 by independent observers) while blinded evaluation of MRI showed a statistically significant (p=0.013) higher morphologic score (9.9 vs. 8.5). There was no difference in International Knee Documentation Committee (IKDC) scores between the two groups at 24 months after surgery. It is uncertain how differences in patient age at baseline may have affected the response to subchondral drilling.

Cartilage Defects: MSCs from Synovial Tissue

Akgun (2015) reported a small (n=14) investigator-blinded RCT that compared matrix-induced autologous MSCs from synovial tissue versus matrix-induced autologous chondrocyte implantation (MACI).[25] Both chondrocytes from cartilage and MSCs from synovia were harvested in an arthroscopic procedure, expanded in culture, and then cultured on a collagen membrane for two days. Implantation was performed with the cells facing the subchondral bone. Follow up evaluations were made through 24 months post-procedure. Outcomes on the KOOS subscales and the VAS pain score were statistically better in the MSC group than the MACI group ($p<0.05$) at the six-month follow up, although it is not clear if the difference observed would be considered clinically significant. Studies with larger samples sizes and follow-up supported by histological analyses are necessary to determine long-term outcomes of this treatment.

Cartilage Defects: MSCs from Umbilical Cord Blood

Lim (2021) reported on a RCT of 114 patients with large, full-thickness cartilage defects (International Cartilage Repair Society grade 4) treated with either a composite of umbilical cord-derived MSCs plus 4% hyaluronate (MSC-HA) or microfracture.[26] The study consisted of a 48-week phase 3 clinical trial and a 5-year follow-up study (64%). Of 114 patients randomized, 89 completed the phase 3 trial (78.1%) and 73 were enrolled in the follow-up study (64.0%). The primary outcome, proportion of participants with cartilage restoration equivalent to at least 1 grade improvement on the ICRS Macroscopic Cartilage Repair Assessment at 48-week arthroscopic evaluation, was 97.7% (42/43) in the MSC-HA group and 71.7% (33/46) in the microfracture group (odds ratio, 16.55; 95% CI, 2.06 to 133.03; P =.001). Both groups had significantly improved patient-reported pain scores (VAS pain, WOMAC, and IKDC scores) at 48 weeks versus baseline, but there was no significant difference between the

2 groups at this timepoint. From 36 to 60 months after intervention, the significant improvements from baseline were maintained in the MSC-HA group, whereas the improvements in VAS pain and WOMAC deteriorated in the microfracture group. This study had several limitations. There was no intervention group that received MSC alone, the comparator (microfracture) is not considered the standard of care for large, full-thickness cartilage defects, surgeons and participants were not blinded to treatment outcome, and there was high loss to follow-up. These limitations, along with a lack of improvement in patient-reported outcomes in the intervention group at 48 weeks, preclude drawing conclusions about the effectiveness of umbilical cord blood-derived MSCs in this population; higher quality evidence from RCTs is needed.

Section Summary

The evidence base on MSCs for cartilage repair is increasing, although nearly all studies to date have reported a variety of methods of MSC preparation. Some randomized studies have reported improvements in histologic, morphologic and functional outcomes, but others have found MSCs are not superior to standard treatment.. Meta-analyses have found reduction of pain in groups treated with MSCs, although high heterogeneity is noted. Long-term efficacy has not been established. Studies did not consistently distinguish between improvements due to MSCs and those due to pain medication. The method of preparation used in one positive study was to obtain MSCs from bone marrow at the time of microfracture, culture (expand) over a period of three weeks, and then inject into the knee in a carrier of HA. Another randomized trial, using MSCs from peripheral blood, found improvements in histologic and morphologic outcomes, but not functional outcomes, following stimulation with recombinant human granulocyte colony-stimulating factor. A third small RCT found that MSCs from synovial tissue and cultured in collagen resulted in outcomes at least as good as those following MACI.

FUSION AND NON-UNION

There is limited evidence on the use of allografts with stem cells for fusion of the extremities or spine or for the treatment of non-union. No RCTs for this indication were identified.

Eastlack (2014) reported outcomes from a series of 182 patients who were treated with anterior cervical discectomy and fusion using Osteocel Plus in a PEEK cage and anterior plating.[27] At 24 months, 74% of patients (180/249 levels treated) were available for follow-up. These patients had significant improvements in clinical outcomes; 87% of levels achieved solid bridging and 92% of levels had range of motion less than 3º. With 26% loss to follow-up at 24 months and lack of a standard of care control group, interpretation of these results is limited.

One retrospective series from 2009 was identified on the use of Trinity MSC bone allograft for revision surgery of the foot and ankle.[28] Twenty-three patients were included who had undergone revision foot and/or ankle surgery for residual malunion, non-union, or significant segmental bone loss. Patients were followed to the point of radiographic and clinical union, which occurred at a median of 72.5 days for 21 of the 23 patients (91.3%). However, these outcomes do not permit conclusions because of a lack of a control group for comparison with patients who received stem-cell therapy.

Section Summary

Current evidence is insufficient to determine whether the use of stem cell results in superior outcomes such as higher fusion rates, or lower rates of reoperations and adverse events.

MENISCECTOMY

Vangsness (2014) reported an industry-sponsored phase 1/2 randomized, double-blind, multicenter study of cultured allogeneic MSCs (Chondrogen™, Osiris Therapeutics) injected into the knee after partial meniscectomy.[29] The 55 patients were randomized to intra-articular injection of either 50´106 allogeneic MSCs, 150´106 allogeneic MSCs in HA, or HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from bone-marrow aspirates from unrelated donors. At two-year follow-up, three patients in the low-dose MSC group had significantly increased meniscal volume measured by MRI (with an a priori determined threshold of at least 15%) compared to none in the control group and none in the high-dose MSC group. There was no significant difference between the groups in the Lysholm Knee Scale. On subgroup analysis, patients with osteoarthritis who received MSCs had a significantly greater reduction in pain at two years compared with patients who received HA alone. This appears to be a post hoc analysis and should be considered preliminary. No serious adverse events were thought to be related to the investigational treatment.

Section Summary

Current evidence for the use of stem cells as an adjunct to meniscectomy is limited to a single preliminary RCT. The outcomes of this study must be validated in large, long-term, randomized controlled trials.

OSTEONECROSIS

Several randomized comparative trials have been identified that evaluated the use of MSCs for osteonecrosis of the femoral head.

Osteonecrosis: MSCs Expanded from Bone Marrow

Zhao (2012) reported a randomized trial that included 100 patients (104 hips) with early stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs versus core decompression (CD) alone.[30] At 60 months after surgery, two of the 53 hips (3.7%) treated with MSCs continued to have progressive disease and underwent vascularized bone grafting, compared with 10 of 44 hips (23%) in the decompression group who had disease progression and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). In addition, treatment with MSC improved Harris Hip scores compared to CD and decreased the volume of the necrotic lesion of the hips preoperatively classified at stage IC, IIB, and IIC ($p<0.05$, respectively; stage IIA, $P=0.06$, respectively).

Osteonecrosis: MSCs Concentrated from Bone Marrow

A 2017 randomized, double-blind trial was conducted using autologous bone marrow concentrate in 38 patients with stage three osteonecrosis.[31] A control group of core decompression plus saline injection was compared to patients receiving core decompression plus MSC implantation. The primary outcome was needing total hip replacement and secondary outcomes were clinical symptoms such as pain and functional ability. There was no difference between groups on any outcomes including total hip replacement requirements, clinical tests, or radiologic evidence.

Another small trial randomized 40 patients (51 hips) with early stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone.[32] Blinding of assessments in this small trial was not described. Harris

Hip Score (HHS) was significantly improved in the MSC group (scores of 83.65 and 82.42; p<0.05) compared with core decompression (scores of 76.68 and 77.39). Kaplan-Meier analysis showed improved hip survival in the MSC group (mean of 51.9 weeks) compared with the core decompression group (mean of 46.7 weeks). There were no significant differences between the groups in the radiographic assessment or MRI results. The conflicting report of improvement via HHS compared to no observable improvement via MRI, may point to the need for study blinding to control for confounding bias toward treatment.

Section Summary

Two small studies reported improvement in the Harris Hip Score in patients with osteonecrosis of the femoral head treated with core decompression and MSCs, although it was not reported if the patients or investigators were blinded to the treatment group. Hip survival was significantly improved following treatment with either expanded or concentrated MSCs. The effect appears to be larger with expanded MSCs compared with concentrated MSCs.However, a double-blind RCT found no difference between MSC treatment or saline injection, when combined with core decompression. Additional studies with a larger number of patients are needed to permit greater certainty regarding the effect of this treatment on health outcomes.

BONE FRACTURES

A systematic review by Yi (2022) explores the application potential of MSCs for healing bone fractures.[33] Of the 31 articles, 26 were preclinical studies (n = 913), and 5 were clinical trials (n = 335). Preclinically, MSCs therapy significantly augmented the progress of bone regeneration [(bone volume over tissue volume (MD7.35, p < 0.01)], despite some non-significant effects (on the callus index, bone strength, work to failure, and stiffness). Clinically, the MSC group had a significantly reduced incidence of poor recovery (odds ratio (OR) 0.30, p < 0.01); however, a significant decrease in healing time was not observed in the MSC group (MD 2.47, p = 0.26). The authors suggest that the patients have benefited from MSC administration but larger RCTs are needed to confirm these findings.

Section Summary

Current evidence for the use of stem cells for healing bone fractures is limited to a single systematic review. Larger RCTs are required to confirm the clinical and preclinical findings.

PRACTICE GUIDELINE SUMMARY

American College of Rheumatology and Arthritis Foundation

In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on osteoarthritis (OA) of the hand, hip, and knee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity in preparations and lack of standardization of techniques.[34] No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

American Academy of Orthopaedic Surgeons

A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint OA, endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA.[35] There was consensus from the panel that better standardization and high-quality evidence from

clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientific evidence to determine benefits and harms.The 2013 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review have indicated that “The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions. Demineralized Bone Matrix: Grade C (poor level of evidence).”[36]

SUMMARY

There is not enough research to know if or how well mesenchymal stem cells (MSCs), allograft bone products containing stem cells, or synthetic bone graft substitutes that must be combined with autologous bone marrow work to treat people with orthopedic conditions. No clinical guidelines based on research recommend MSC treatment, allograft bone products containing stem cells, or synthetic bone graft substitutes that must be combined with autologous bone marrow for people with orthopedic conditions. Therefore, use of stem cells for orthopedic applications is considered investigational.

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CODES

NOTE: There are no specific codes for orthopedic applications of stem cell therapy. The appropriate CPT code for reporting this procedure is 20999, or the code for an unlisted procedure of the body area on which the procedure is performed.

Codes	Number	Description
		Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
	0566T	Injection of cellular implant into knee joint using ultrasound guidance, unilateral
	0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
	0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
	0737T	Xenograft implantation into the articular surface
	20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)
	20999	Unlisted procedure, musculoskeletal system, general
	21899	Unlisted procedure, neck or thorax
	22899	Unlisted procedure, spine
	23929	Unlisted procedure, shoulder
	24999	Unlisted procedure, humerus or elbow
	25999	Unlisted procedure, forearm or wrist
	26989	Unlisted procedure, hands or fingers
	27299	Unlisted procedure, pelvis or hip joint
	27599	Unlisted procedure, femur or knee
	27899	Unlisted procedure, leg or ankle
	28899	Unlisted procedure, foot or toes
	29999	Unlisted procedure, arthroscopy
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous

Codes	Number	Description
	38241	Bone Marrow or blood-derived peripheral stem cell transplantation; autologous
HCPCS	None	

Date of Origin: *September 2011*

Regence

Medical Policy Manual Medicine, Policy No. 148

Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders

Effective: September 1, 2024

Next Review: February 2025
Last Review: August 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

Transcranial magnetic stimulation (TMS) is a noninvasive method of delivering electrical stimulation to the brain. The technique involves placement of a small coil over the scalp; a rapidly alternating current is passed through the coil wire, producing a magnetic field that passes unimpeded through the brain. In contrast to electroconvulsive therapy, transcranial magnetic stimulation does not require anesthesia and does not induce convulsions. Transcranial magnetic stimulation is being evaluated as a treatment of depression and other psychiatric/neurologic brain disorders.

MEDICAL POLICY CRITERIA

I. Transcranial magnetic stimulation (TMS) of the brain may be considered **medically necessary** as a treatment of *major depressive disorder* when either of the following criteria are met:

   A. As initial treatment of a depressive episode (up to 36 rTMS or iTBS treatment sessions, one session per day, including tapering) when all of the following criteria are met (1. - 5.):

1. Confirmed diagnosis of severe major depressive disorder (single or recurrent) when both of the following criteria are met (a. - b.):
    a. Diagnosis is confirmed by standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms; and
    b. Documentation is submitted of both the rating scale that was used and the score.
2. Age consistent with the device-specific FDA indication (see policy guidelines).
3. The TMS device is FDA cleared for use in major depressive disorder.
4. The TMS treatment of the brain is prescribed and supervised by a psychiatrist (MD or DO), psychiatric nurse practitioner or physician assistant/associate with appropriate supervision/collaboration (See policy guidelines).
5. One of the following conditions is present:
    a. Symptoms are ongoing despite treatment with the following psychopharmacologic regimens, and each has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated (see Policy Guidelines):
        i. Either of the following:
            a.) At least 3 antidepressant medications from at least 2 different classes in separate trials; or
            b.) At least 2 different antidepressant medications from at least 2 different classes in separate trials, plus failure with the addition of an augmenting agent to at least one of the failed antidepressants; and
        ii. At least four weeks' duration for one or more of the antidepressant agents (unless none of the agents was tolerated).
    b. History of response to TMS in a previous depressive episode (at least 3 months since the prior episode); or
    c. Both of the following criteria are met (i. - ii.):
        i. Patient is a candidate for electroconvulsive therapy (ECT); and
        ii. The patient does not have psychosis, acute suicidal risk, catatonia, significantly impaired essential function, or other condition for which ECT would be clinically superior to TMS.

B. Extension of initial therapy when both of the following criteria are met (1. - 2.):
1. The TMS is demonstrating meaningful improvements as documented by a 50% or greater improvement in standardized rating scales (see Policy Guidelines) that reliably measure depressive symptoms in the member's clinical status; and
2. There is reasonable expectation that continued treatment will produce improvement.

II. Transcranial magnetic stimulation (TMS) of the brain is considered **not medically necessary** as a treatment for major depressive disorder when Criterion I. above is not met.

III. Transcranial magnetic stimulation (TMS) of the brain is considered **investigational** as a treatment for all other indications.

IV. Accelerated protocols (more than one treatment session per day) for transcranial magnetic stimulation (TMS) of the brain is considered **investigational** for all indications. This includes the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol.

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

POLICY GUIDELINES

DEPRESSION RATING SCALES

Assessment tools to diagnose severe major depressive disorder may include, but are not limited to the following depression rating scales:

- Beck Depression Inventory (BDI): scores range from 0 to 63, higher scores represent more severe depression
- Inventory of Depressive Symptomatology Clinician-related (IDS-C): scores range from 0 to 84, higher scores represent more severe depression
- Quick Inventory of Depressive Symptomology Self-reported (QIDS-SR): scores range from 0 to 27, higher scores represent more severe depression
- Montgomery-Asberg Depression Rating Scale (MADRS): scores range from 0 to 60, higher scores represent more severe depression
- Patient Health Questionnaire (PHQ9): scores range from 0 to 27, higher scores represent more severe depression

PROVIDER TYPES

- A Nurse Practitioner is required to be qualified as a Psychiatric Mental Health Nurse Practitioner (PMHNP) or Advanced Registered Nurse Practitioner (ARNP) with national psychiatric PMHNP certification (e.g., PMHNP board certified).

- Physician Assistants/Associates (PA) are required to have a supervisory/collaborative agreement with a psychiatrist (MD or DO) who has training in TMS and provides direct patient care services with the same organization as the PA.

AGE LIMITATIONS FOR TMS DEVICES

TMS devices listed on this table have been approved for use in patients younger than 18 years of age for treatment of major depressive disorder. All other FDA approved devices are approved for use only in adults (>= 18 years of age).

Device name and Manufacturer	Approved Ages	FDA approval date
Neurostar® TMS therapy system (Neuronetics)	15- 25	March 2024

	Adult	2008

CONTRAINDICATIONS

Contraindications to TMS include:

- Seizure disorder or any history of seizure with increased risk of future seizure; OR
- Presence of acute or chronic psychotic symptoms or disorders (such as schizophrenia, schizophreniform or schizoaffective disorder) in the current depressive episode; OR
- Neurologic conditions that include epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the central nervous system (CNS); OR
- Significantly impaired essential function, defined as functions necessary to sustain life, such as feeding and hydrating oneself; OR
- Presence of an implanted magnetic-sensitive medical device located 30 centimeters or less from the TMS magnetic coil or other implanted metal items, including but not limited to a cochlear implant, implanted cardioverter defibrillator (ICD), pacemaker, deep brain stimulator, vagus nerve stimulator, or metal aneurysm clips or coils, staples, or stents.

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
- Confirmed diagnosis of severe major depressive disorder (single or recurrent) documented by standardized rating scales, including:
    - Standardized rating scale(s) used
    - Score
- Psychopharmacologic regimen history with documented response
- Name of FDA approved device to be used for TMS treatment
- Documentation of prescribing provider qualifications (MD or DO, psychiatric nurse practitioner or physician assistant with appropriate supervision/collaboration).
- Documentation of rTMS or iTBS protocol used

CROSS REFERENCES

1. Spravato, esketamine, Medication Policy Manual, Policy No. dru605

BACKGROUND

Transcranial magnetic stimulation (TMS), introduced in 1985 as a new method of noninvasive stimulation of the brain, involves placement of a small coil over the scalp, passing a rapidly alternating current through the coil wire, which produces a magnetic field that passes unimpeded through the scalp and bone, resulting in electrical stimulation of the cortex. TMS was initially used to investigate nerve conduction; e.g., TMS over the motor cortex will produce a contralateral muscular-evoked potential. The motor threshold (RMT), which is the minimum intensity of stimulation required to induce a motor response, is empirically determined for each

person by localizing the site on the scalp for optimal stimulation of a hand muscle, then gradually increasing the intensity of stimulation. The stimulation site for the treatment of depression is usually 5 cm anterior to the motor stimulation site.

In contrast to electroconvulsive therapy, TMS does not require general anesthesia and does not generally induce a convulsion. Interest in the use of TMS as a treatment for depression was augmented by the development of a device that could deliver rapid, repetitive stimulation. Imaging studies had shown a decrease in the activity of the left dorsolateral prefrontal cortex in depressed patients, and early studies suggested that high-frequency (e.g., 5-10 Hz) TMS of the left dorsolateral prefrontal cortex had antidepressant effects. Low frequency (1-2 Hz) stimulation of the right dorsolateral prefrontal cortex has also been investigated. The rationale for low-frequency TMS is inhibition of right frontal cortical activity to correct the interhemispheric imbalance. A combination approach (bilateral stimulation), or deep stimulation with an H1 coil, is also being explored, as is thetaburst stimulation.

Standard or conventional repetitive TMS (rTMS) protocols were initially approved by the FDA in 2008 and are typically delivered in one treatment per day for 20 - 30 sessions over six weeks with a taper of six sessions over three additional weeks. Thetaburst stimulation (iTBS) was first approved by the FDA in 2018 and delivers high frequency (50Hz) TMS. Accelerated TMS typically utilizes iTBS to deliver treatments over a shorter period, usually with ≥ 2 treatments per day.

Repetitive TMS (rTMS) is also being tested as a treatment for a variety of other disorders. In addition to the potential for altering interhemispheric imbalance, it has been proposed that high-frequency repetitive TMS may facilitate neuroplasticity.

Regulatory Status

The Food and Drug Administration (FDA) granted 510(k) approval for the following devices:

- Brainsway
    - In 2013 the BrainsWay™ H-Coil Deep TMS System (Brainsway, Ltd.) received FDA clearance for the treatment of depressive episodes in adult patients suffering from major depressive disorder who have failed to respond to antidepressant medications in their current episode of depression (K12228).
    - The Deep TMS System (Brainsway) was granted a de novo 510(k) classification by FDA (DEN170078) in August 2018. The new classification applies to this device and substantially equivalent devices of this generic type. The Brainsway Deep TMS system is cleared for treatment of adult patients with Obsessive-Compulsive Disorder (approved in 2019). FDA product code: QCI.
    - In 2019 and 2021 The BrainsWay Deep TMS System received FDA clearance for the treatment of depressive episodes and for decreasing anxiety symptoms for those who may exhibit comorbid anxiety symptoms in adult patients suffering from Major Depressive Disorder (MDD) and who failed to achieve satisfactory improvement from previous antidepressant medication treatment in the current episode (K210201, K220819).

- Cerena™ TMS device (Eneura Therapeutics) received de novo marketing clearance for the acute treatment of pain associated with migraine headache with aura in 2013. Warnings, precautions, and contraindications include the following:
    - The device is only intended for use by patients experiencing the onset of pain associated with a migraine headache with aura.
    - The device should not be used on headaches due to underlying pathology or trauma.
    - The device should not be used for medication overuse headaches.
    - The device has not been demonstrated as safe or effective when treating cluster headache or chronic migraine headache.
    - The device has not been shown to be effective when treating during the aura phase.
    - The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).
    - Safety and effectiveness have not been established in pregnant women, children under the age of 18, and adults over the age of 65.

- MagVita TMS Therapy System® (approved 2015) and MagVita TMS Therapy System w/Theta Burst Stimulation (approved 2018) are indicated for the treatment of Major Depressive Disorder in adult patients who failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

- NeuroStar® (formerly known as NeoPulse®) TMS Therapy system (Neuronetics, Inc.) received de novo clearance in 2008 for the treatment of major depressive disorder in adults who have failed a six-week course of one antidepressant medication. NeuroStar Advanced Therapy System (approved in 2022) is indicated as an adjunct for the treatment of adult patients who are suffering from Obsessive-Compulsive Disorder (OCD). In March 2024, the Neurostar® TMS therapy system was approved by the FDA for use in 15 - 25 year olds (K231926).

- Rapid^2 Therapy System from Magstim Company Limited (approved 2015) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

- SpringTMS® received FDA clearance for the treatment of migraines, with aura.

- Neurosoft TMS (TeleEMG) was approved by the FDA in 2016 for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

- Apollo TMS Therapy System (Mag & More, approved in 2018) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

- Nexstim Navigated Brain Therapy (NBT®) System 2 (approved in 2017) is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

- ALTMS Magnetic Stimulation Therapy System (also Blossom TMS Therapy System, approved in 2022) is indicated for the treatment of Major Depressive Disorder in adult patients, who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.
- The Magnus Neuromodulation System (MNS) with SAINT technology - model Number 1001K was FDA approved in 2022 for the treatment of Major Depressive Disorder (MD D) in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. (K220177)
- Horizon 3.0 TMS Therapy System Magstim is indicated for Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode, as well as an adjunct for the treatment of adult patients suffering from Obsessive-Compulsive Disorder (Cleared 1/13/2023 K222171).

The de novo 510(k) review process allows novel products with moderate or low-risk profiles and without predicates which would ordinarily require premarket approval as a class III device to be down-classified in an expedited manner and brought to market with a special control as a class II device.

EVIDENCE SUMMARY

Systematic reviews (SRs) and well-designed randomized controlled trials (RCTs) comparing active transcranial magnetic stimulation (TMS) to sham devices are needed in order to establish safety and efficacy of this treatment for any condition.

MAJOR DEPRESSIVE DISORDER (MDD)

Systematic Reviews and Technology Assessments

Cai (2023) published a SR and meta-analysis (MA) evaluating the effectiveness of accelerated intermittent theta burst stimulation (aiTBS) in MDD or bi-polar depression (BD).[1] Five double-blind randomized controlled trials (RCTs) with 239 MDD or BD patients with a major depressive episode were included. Active aiTBS overperformed sham stimulation in the study-defined response. The authors concluded that preliminary evidence that active aiTBS resulted in a greater response in treating major depressive episodes in MDD or BD patients than sham stimulation.

Qin (2023) published a SR of RCTs with meta-analysis evaluated efficacy and safety of bilateral theta-burst stimulation (TBS) as a type of repetitive TMS (rTMS) intervention for patients with mood disorders.[2] Analyses included six RCTs with 285 participants with major depressive disorder (MDD) (n = 233) or a depressive episode in the course of bipolar disorder (BD) (n = 52) who had undergone active bilateral TBS (n = 142) versus sham stimulation (n = 143). Active bilateral TBS outperformed sham stimulation with respect to study-defined improvements (55.1 % versus 20.3 %, 4 RCTs, n = 152, 95%CI: 1.63 to 4.39, $p < 0.0001$; $I2 = 0$ %) and remission rates (37.2 % versus 14.3 %, 2 RCTs, n = 85, 95%CI: 1.13 to 5.95, $p = 0.02$; $I2 = 0$ %) in MDD patients but not those with bipolar or unipolar mixed depression. Superiority of active bilateral TBS over sham stimulation was confirmed for improvements in depressive symptoms at post-bilateral TBS assessments and 8-week follow-ups in patients with either MDD or mixed depression (all $p < 0.05$). Discontinuation rates due to any reason

and adverse events (i.e., headache, dizziness) were similar between TBS and sham stimulation groups with MDD or mixed depression (all p > 0.05). The authors conclude that bilateral TBS targeting the dorsolateral prefrontal cortex (DLPFC) appears to be a well-tolerated form of rTMS that has substantial antidepressant effects, particularly in patients with MDD.

Neuteboom (2023) published a SR evaluating the efficacy, safety and tolerability of accelerated intermittent theta burst stimulation (aiTBS) in patients with MDD.[3] aiTBS was defined as at least three iTBS treatments sessions per day, during at least four days for one week. Six articles from five unique studies met eligibility criteria; two open-label studies and three RCTs [two double blind and one quadruple blind]. Response rates directly after treatment ranged from 20.0% to 86.4% and remission rates ranged from 10.0 to 86.4%. Four weeks after treatment response rates ranged from 0.0% to 66.7% and remission rates ranged from 0.0% to 57.1%. Three articles described a significant reduction in suicidality scores. aiTBS was well tolerated and safe, with no serious adverse events reported. The included studies had small samples sizes and differed in frequency, intersession interval, neuro localization and stimulation intensity. Replication studies and larger RCTs are warranted to establish efficacy, safety and long-term effects.

A systematic review conducted by Voigt (2021) focused on theta burst stimulation for treatment-resistant depression (TRD).[4] The reviewers included eight RCTs comparing theta burst stimulation to sham treatment and one comparing theta burst stimulation to conventional rTMS. As measured by the HAM-D, theta burst stimulation was superior to sham on response (RR 2.4; 95% CI 1.27 to 4.55; p=0.007; I^2 = 40%). There was no statistically significant difference between theta burst stimulation and conventional rTMS (RR 1.02; 95% CI 0.85 to 1.23; p=0.80; I^2 = 0%). There was no difference between theta burst stimulation and rTMS in the incidence of adverse events.

Chu (2020) published an SR on theta-burst stimulation for major depression. A total of 10 studies met inclusion criteria. Six, including 294 participants, were RCTs, and four, including 297 participants, were uncontrolled. According to the meta-analysis, the overall effect size of response rate was 0.38 (95% confidence interval [CI] 0.29 to 0.48) and the overall effect size of remission rate was 0.20 (95% CI 0.13 to 0.29).

In 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) published an updated review of rTMS for depression, previously published in 2015.[5] The report addressed the clinical safety and effectiveness of TMS for treatment-resistant depression and the cost-effectiveness. This summary will focus on the safety and effectiveness review. The review includes three SRs (the Health Quality Ontario SR described below and two more recent SRs) and five RCTs on the safety and effectiveness of rTMS. Two of the SRs included only sham comparators, while the third included pharmacological, ECT, and sham comparators. One SR reported separately on unilateral and bilateral stimulation, although both resulted in greater rates of response and remission (with weighted mean differences [WMDs] of 3.36 and 2.67 for unilateral and bilateral, respectively). The second and third SRs did not do separate analyses of unilateral and bilateral rTMS. The second reported a difference in Montgomery-Asberg Depression Rating Scale (MADRS) score of -3.6 points (95% credible interval [CrI], -7.6 to 0.3) between rTMS and sham and the third reported a WMD in HDRS scores between rTMS and sham of 2.31 points (95% CI 1.19 to 3.43, p<0.001) in favor of rTMS. In the analysis of rTMS versus ECT in the third SR, the WMD in HDRS scores was 5.97 (95% CI 10.94 to 11.0) in favor of ECT, with a 72% higher response

rate and 44% higher remission rate. The review concluded that the effect of rTMS would be considered clinically relevant in two systematic reviews, but not in the third. Additionally, the review stated that based on one SR, the benefit of ECT versus rTMS would be considered clinically relevant.

Hung (2020) performed an SR evaluating the use of deep TMS for treatment-resistant depression.[6] A total of 15 studies met inclusion criteria, including three RCTs and 12 uncontrolled studies. Results of the meta-analysis including all 15 studies indicated that dTMS significantly improved the depressive (Hedges' g=-1.323, 95% CI -1.651 to -0.995, p<0.001) and anxiety symptoms (Hedges' g=-1.282, 95% CI -1.514 to -1.051, p<0.001) in patients with treatment-resistant depression. A subgroup analysis was performed of RCTs versus uncontrolled studies that indicated there was a larger effect size in the uncontrolled studies (-1.461 for uncontrolled studies vs -0.756 for RCTs).

In 2019, Voigt published an SR that reviewed the efficacy of repetitive TMS (rTMS) in non-treatment resistant patients with major depressive disorder.[7] Ten studies were included in the analysis. The quality of these studies was assessed with GRADE and CEBM. Only one study was a double-blind RCT (quality rating 1B). This RCT compared medication resistant patients (two or more medication trials) with non-medication resistant patients (one unsuccessful medication trial). The likelihood of responding to rTMS was four times higher in the group with only one unsuccessful medication trial before rTMS compared to the group that received two or more unsuccessful trials (p=0.021). Of the remainder of the studies, four were RCTs. They were all single-center RCTs conducted in China and all had a quality rating of 1B. Two addressed treatment of the first episode of depression. One reported significantly greater numbers of early improvers in rTMS plus antidepressant compared to sham plus antidepressant at two weeks (p=0.031) but not four weeks (p=0.586). The other reported that the rate of relapse/recurrence at 12 months was significantly lower in rTMS plus antidepressant compared to antidepressant alone (p=0.033). Two RCTs addressed treatment naïve patients. One reported significantly greater response and remission rates in active versus sham rTMS (both in combination with antidepressant; p<0.05). The other reported a significantly greater number of patients achieving a ≥50% reduction in HAMD-17 score in the active versus sham rTMS (both in combination with antidepressant; p<0.05). Limitations of this analysis were heterogeneity of the included studies and a lack of risk of bias assessment.

Martin (2017) published an SR that evaluated the cognitive effects of rTMS used for the treatment of depression. Eighteen studies were included in the analysis.[8] Using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials, the authors determined that the majority of studies had a low risk of bias across most standard criteria, but had an unclear risk of bias for allocation concealment and selective reporting of results. One study, which was not randomized, had a high risk of selection bias. Measures of attention and working memory, processing speed, executive function, and learning and memory were examined. Significant differences were found between rTMS and sham for the Trail Making Test Parts A and B, measures of attention/working memory and processing speed. A lack of significant differences was found for the remainder of measures analyzed.

Kedzior (2017) published an SR assessing cognitive outcomes following high-frequency rTMS versus electroconvulsive therapy (ECT).[9] Due to high heterogeneity with respect to cognitive assessment, no meta-analyses were performed. Cognitive functioning was assessed in six studies including 111 high-frequency rTMS-treated and 94 ECT-treated patients. All but one

study reported similar acute cognitive impairments were reported following ECT and high-frequency rTMS. Three studies reported outcomes that favored ECT over high-frequency rTMS based on acute mood outcomes. The review concluded that more studies are needed to be able to reliably compare the effects of these treatments on cognitive outcomes.

In 2016, the Health Quality Ontario published a meta-analysis of left DLPFC rTMS for treatment-resistant depression (TRD).[10] Reviewers included 23 RCTs (n=1156 patients) that compared rTMS with sham and six RCTs (n=266 patients) that compared rTMS with ECT. In 16 studies, patients received rTMS in addition to antidepressant medication. Seven studies used intensities of less than 100% motor threshold and the definition of remission in the included studies varied (from ≤7 to ≤10 on the HAM-D). A meta-analysis showed a statistically significant improvement in depression scores when compared with sham, with a weighted mean difference (WMD) of 2.31. However, this was smaller than the prespecified clinically important difference of 3.5 points on the HAM-D, and the effect size was small (0.33; 95% confidence interval [CI], 0.17 to 0.5; p<0.001). Subgroup analysis showed a larger and clinically significant treatment effect in the rTMS studies using 20 Hz with shorter train duration compared with other rTMS techniques (WMD=4.96; 95% CI 1.15 to 8.76; p=0.011). Secondary analyses showed rTMS demonstrated statistically greater rate of response among 20 studies (pooled relative risk, 1.72; 95% CI 1.13 to 2.62; p=0.11) as well as statistically greater rate of remission among 13 studies (pooled relative risk=2.20; 95% CI 1.44 to 3.38, p<0.001).

For the six trials that compared rTMS with ECT, the WMD of 5.97 was both statistically and clinically significant in favor of ECT. The relative risk for remission and response rates favor ECT but was not statistically significant. Remission and relapse rates at the six-month follow-up were reported in two studies including 40 and 46 subjects, comparing rTMS and ECT. While one study reported slightly higher remission rate for ECT (27.3%) compared with rTMS (16.7%), the other study did not find significant difference between ECT and rTMS for mean depression scores at three or six months, but did note relapses were less frequent for ECT. Statistical comparisons were either not significant or not available, limiting the interpretation of these findings. The authors concluded there is little data to evaluate the long-term effects of rTMS and that ECT was more effective in improving depression.

Kedzior (2016) published a SR that evaluated cognitive function i.e. memory, attention, and psychomotor coordination after dTMS, using the H-coil system for patients with major psychiatric disorders.[11] Thirteen studies were included, with most being of poor quality. Patients had either unipolar or bipolar depression or schizophrenia and showed short-term improvements. Although short-term cognitive function improved, more long-term sham-controlled studies are needed beyond the daily stimulation phase.

In 2014, the Washington State Health Care Authority conducted a Technology Assessment and updated review of the current literature comparing TMS to sham and ECT.[12] The review included the AHRQ assessment noted below plus three additional RCTs. The WA TEC review came to the following conclusions:

> Although the three RCTs published after the AHRQ report did not consistently detect statistically significant differences between rTMS and sham stimulation, the overall body of evidence is consistent with regard to direction of the results. A small quantity of data suggested that the durability of effect, i.e., the continued advantage of active rTMS over

sham rTMS, may not last beyond two or three weeks after the end of treatment; rTMS may serve primarily to accelerate recovery (low-quality evidence).

In addition, the WA TEC assessment concluded that a review of five RCTs, “suggested that rTMS may be as effective as ECT under certain circumstances, but under other circumstances, ECT may be superior; this evidence is based on low quality evidence because of unexplained inconsistency in study results.”

Randomized Controlled Trials

Wang (2023) published a RCT to explore the effect of rTMS on brain-derived neurotrophic factor (BDNF) levels and cognitive function in the treatment of middle-aged and elderly MDD.[13] The patients (n=120) were randomly divided into control group (n = 60, patients received simple oral treatment with escitalopram and sham rTMS) and study group (n = 60, patients received oral treatment with escitalopram combined with rTMS) according to the random number table method. We compared the clinical efficacy, serum BDNF levels, and cognitive function between the two groups. After treatment, the HAMD-17 score in the study group was lower than that in the control group [13.00 (12.00-16.00) vs 17.00 (15.00-19.00), $p < .05$], and the RBANS score was higher than that in the control group [166.00 (161.25-171.75) vs 133.00 (130.00-136.75), $p < .05$]. The total effective rate of the research group was 95.0%, which was higher than the 82.0% of the control group ($p < .05$). The serum BDNF levels [36.00 (33.00-38.00) vs 30.00 (28.00-32.00), $p < .05$] and MoCA scores [24.00 (22.00-26.75) vs 23.00 (21.00-25.00), $p < .05$] of the study group were higher than those of the control group. There were no significant adverse reactions during the treatment of both groups. The authors concluded that compared with oral escitalopram alone, repeated transcranial magnetic stimulation in the treatment of middle-aged and elderly patients with major depressive disorder can further improve the efficacy, and can more effectively improve the BDNF level and cognitive function, with ideal safety.

Zangen (2023) published a prospective, multicenter, randomized to evaluate if Deep TMS targeting the medial prefrontal cortex (MPFC) is noninferior to targeting the lateral prefrontal cortex (LPFC) and whether electrophysiological or clinical markers for patient selection can be identified.[14] They enrolled 169 patients with MDD for whom antidepressants failed in the current episode. Patients were randomized to receive 24 Deep TMS sessions over 6 weeks, using either the H1 coil or the H7 coil. The primary efficacy endpoint was the change from baseline to week 6 in Hamilton Depression Rating Scale scores. Clinical efficacy and safety profiles were similar and not significantly different between groups, with response rates of 60.9% for the H1 coil and 64.2% for the H7 coil. Moreover, brain activity measured by EEG during the first treatment session correlated with clinical outcomes in a coil-specific manner. This study provides a treatment option for MDD, using the H7 coil, and initial guidance to differentiate between patients likely to respond to LPFC versus MPFC stimulation targets. This study needs validation by additional research.

Bulteau (2022) published a RCT comparing rTMS with iTBS in participants (n=54) with treatment resistant depression.[15] The protocols were as follows: for rTMS: 110% of RMT; 10 Hz pulses; 20-min session; 4 s per train; 28-s intertrain interval; 1600 pulses per day (40 trains of 40 pulses each). For iTBS: 80% of RMT; 50 Hz pulses; 600 pulses per day. In both trial arms, participants had one session each weekday for 4 weeks, for a total of 20 sessions. A total of 54 completed the stimulation sessions (10 Hz rTMS: 27 [90%]; iTBS: 27 [90%]. Response rates were 36.7% and 33.3%, and remission rates were 18.5% and 14.8%, in the iTBS and 10 Hz rTMS groups respectively. Both groups showed a similar significant reduction

in depression scores and quality of life improvement at six months. The authors reported that they did not find any clinical predictive factor of therapeutic response for either modality. Two adverse effects of moderate to severe intensity were reported: asthenia (10 Hz rTMS: 2 [6%]; iTBS: 4 [13%]) and headaches (10 Hz rTMS: 1 [3%]; iTBS: 5 [17%]). Fisher's exact test detected no significant difference between groups for asthenia (OR: 0.47; 95% CI: 0.0394 to 3.600; p = 0.6708) or headaches (OR: 0.1769; 95% CI: 0.0035 to 1.7331; p = 0.1945). Limitations include a small sample size, possibility of unblinding and a few patients received lamotrigine (off label use) which may modify TMS affects.

The STAR*D study and recent update by Rush (2020) has demonstrated that patients with a major depressive episode who have failed to respond to their initial pharmacologic treatment show less and less response and remission rates with subsequent medication trials.[16, 17] Rush stated that after non-efficacy with an initial failed SSRI trial, only *21%* of patients achieved remission and *58%* of patients achieve no meaningful benefit with a second step switch to another antidepressant. Over four levels of treatment, 1/3 of patients will not respond. In the Deep TMS pivotal trial, patients were shown to have a remission rate of *32.6%* vs 14.6% sham and a response rate of 38.4% vs. 21.4% sham after the initial 4 weeks (20 sessions).[18] Patients who failed 1 or 2 medications had a remission rate of *36.6%* vs 16.7% while patients who failed 3+ medications had a remission rate of *28.9%* vs. 12.2% in the sham treatment. Additionally, approximately 64% of the acute phase (initial 20 sessions) non-responders, achieved remission during the continuation phase (24 sessions over 12 weeks).

Blumberger (2018) published a multicenter, randomized noninferiority trial (THREE-D) comparing 10 Hz rTMS with intermittent theta burst stimulation (iTBS).[19] Between 2013 and 2016, 414 patients with treatment-resistant major depressive disorder were enrolled and randomized to four to six weeks of MRI-guided rTMS (n=205) or iTBS (n=209). Treatment resistance was defined as failure to tolerate two or more antidepressant trials of adequate dose and duration or no clinical response to an adequate dose of an antidepressant. Patients who failed more than three antidepressant trials of adequate dosage were excluded from the study. Patients could alter their medication through the trial. Treatment with rTMS (37 minutes) and iTBS (3 minutes) was delivered five times a week for four to six weeks. The primary outcome measure was the 17-item HAM (HAM-17), for which scores for patients treated with rTMS improved by 10.1 points and scores for patients treated with iTBS improved by 10.2 points, indicating noninferiority of iTBS (adjusted difference, 0.103; lower 95% CI -1.16; p=0.001). Treatment with iTBS resulted in a higher self-rated intensity of pain (mean score, 3.8; SD=2.0) than treatment with rTMS (mean score, 3.4; SD=2.0; p=0.011). Headache was the most common treatment-related adverse event for both groups (rTMS 131/204 [64%]; iTBS 136/208 [65%]). Serious adverse events were noted in patients treated with rTMS (n=1; myocardial infarction) and iTBS (n=3; agitation, worsening suicidal ideation, worsening depression); there was no significant difference in the number of adverse events in the two groups. The study was limited by absence of a treatment group with placebo.

Several RCTs not discussed above or included in the above systematic reviews also had significant limitations which did not allow reliable conclusions to be made about the effectiveness of TMS as a treatment for depression. Limitations of individual studies and the body of the literature as a whole include one or more of the following:

- Standardized optimal treatment parameters for TMS have not been established. Studies varied with respect to frequency, location, intensity, and duration. Many studies did not mention repeat treatments using TMS after their intervention phase or in the follow-up

assessments.[20-27]

- There were significant (greater than 10%) or unclear loss to follow-up and/or poorly defined intention-to-treat (ITT) analyses.[20-26, 28, 29]
- Use of co-therapies such as antidepressants, unequal distribution of co-therapies between treatment and sham groups, sham devices in which potential for some therapeutic effect was possible, and mental health counseling were allowed but not quantified in the results, potentially confounding the findings.[20-25, 28, 30-32]
- Follow-up of all study subjects was over a short period of time, less than six months, so durability of the results is unknown.[20-30, 32-35]
- Study populations were small, less than 100 patients total, making results unreliable and difficult to apply to patients requiring treatment in the general population.[20-25, 27-30, 32-34, 36-43]
- Statistical power calculations were inadequate or unclear, and/or the study failed to enroll a sufficient number of participants in order to have adequate statistical power to reliably detect differences between the treatment groups.[27]
- Randomization methods were not clearly stated or weak methods of randomization were used (e.g. one provider randomly assigned patients to groups using their own personal judgment).[21-23, 27, 28, 30, 33, 34]
- Strict inclusion/exclusion criteria were used which were not representative of patients requiring treatment in the general population, for example, a mild to moderate level of depression or illness, no comorbidities (or only a few that were well controlled), and treatment resistance to standard therapies to name a few.[20-23, 25, 28, 30, 34]
- Studies used previously published unreliable data for new and/or further analyses.[44, 45]

Adolescents

There are currently no TMS devices with FDA approval for use in adolescents, but research in this population is ongoing.

Zheng (2023) published a systematic review of randomized controlled trials (RCTs) to explore the therapeutic effects and safety of active low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) versus sham LF-rTMS in children and adolescent patients with first-episode and drug-naïve (FEDN) major depressive disorder (MDD).[46] A systematic search of the literature yielded 442 references, of which 3 RCTs (130 children and adolescents with FEDN MDD, 50.8% male, and mean age range from 14.5 to 17.5 years) met the inclusion criteria. Among the two RCTs (66.7%, 2/3) examining the effects of LF-rTMS on study-defined response and remission and cognitive function, active LF-rTMS was more efficacious than sham LF-rTMS in terms of study-defined response rate and cognitive function (all $p < 0.05$) but not regarding study-defined remission rate (all $p > 0.05$). The authors reported that LF-rTMS could benefit children and adolescents with FEDN MDD in a relatively safe manner, although further studies are warranted.

Majumder (2021) performed a systematic review of the safety and efficacy of rTMS in adolescents and children (ages 10 and over) with major depressive disorder.[47] A total of 18 publications, including case reports, met inclusion criteria. Most studies included treatment-resistant depression, defining it as one, two or several failed antidepressant trials depending on the study. The multi-subject trials allowed comorbid anxiety disorder, dysthymia, attention deficit hyperactivity disorder (ADHD) but excluded schizophrenia, bipolar disorder, substance use disorder, post-traumatic stress disorder (PTSD), intellectual disability, pervasive developmental disorders, and eating disorders. There was heterogeneity in inclusion criteria,

number of rTMS sessions, and various other parameters. No meta-analysis was completed due to heterogeneity. Overall, the included studies indicated that in children and adolescents rTMS is safe but did not show that it is superior to placebo as a stand-alone treatment for resistant depression. The results were more promising for rTMS as an add-on treatment.

The only RCT included in the above systematic review was performed by Croarkin (2021), which TMS for adolescents with treatment-resistant depression.[48] Individuals aged 12 to 21 years with treatment-resistant depression (defined as an antidepressant treatment record level of 1 to 4 in a current episode of depression) were randomized to receive active NeuroStar TMS monotherapy (n=48) or sham TMS (n=55). Treatment was delivered daily for 30 days. At the end of treatment, there was no statistically significant difference in improvement in the least-squares mean (SE) HAM-D-24 between groups (active -11.1 [2.03]; sham -10.6 [2.00]; p= 0.8; difference [95% CI], - 0.5 [-4.2 to 3.3]). There were also no statistically significant differences between groups in response rates (active 41.7%; sham 36.4%; p=0.6) or remission rates (active 29.2%; sham 29.0%; p=0.95).

Durability of rTMS

Systematic Reviews

Kedzior (2015) examined the durability of the antidepressant effect of high-frequency rTMS on the left DLPFC in the absence of maintenance treatment.[49] Included were 16 double-blind, sham-controlled randomized trials (total n=495 patients). The range of follow-up was 1 to 16 weeks, but most studies only reported follow-up to two weeks. The overall effect size was small with a standardized mean difference (SMD; Cohen's d) of -0.48, and the effect sizes were lower in RCTs with 8 to 16 weeks of follow-up (d=-0.42) than with 1 to 4 weeks of follow-up (d=-0.54). The effect size was larger when an antidepressant medication was initiated concurrently with rTMS (five RCTs, d=-.56) than when patients were on a stable dose of medication (nine RCTs, d=-0.43) or were unmedicated (two RCTs, d=-0.26).

Observational Studies

Dunner (2014) reported a one-year follow-up with maintenance therapy from a large multicenter observational study (42 sites) of rTMS for patients with TRD.[50] A total of 257 patients agreed to participate in the follow-up study of 307 who were initially treated with rTMS. Of them, 205 completed the 12-month follow-up, and 120 patients had met the Inventory of Depressive Symptoms-Self Report response or remission criteria at the end of treatment. Ninety-three (36.2%) of the 257 patients who enrolled in the follow-up study received additional rTMS (mean, 16.2 sessions). Seventy-five (62.5%) of the 120 patients who met response or remission criteria at the end of the initial treatment phase (including a two-month taper phase) continued to meet response criteria through a one-year follow-up.

A variety of tapering schedules are being studied. For example, Richieri (2013) used propensity-adjusted analysis of observational data and found that patients who had rTMS tapered over 20 weeks (from three times per week to once a month) had a significantly reduced relapse rate than patients who had no additional treatment (37.8% vs 81.8%).[51] Connolly (2012) reported that in the first 100 cases treated at their institution, the response rate was 50.6% and the remission rate was 24.7%.[52] At six months after the initial rTMS treatment, 26 (62%) of 42 patients who received tapered maintenance therapy (from two sessions per week for the first three weeks to monthly) maintained their response. In another study, Janicak (2010) evaluated patients who met criteria for a partial response during either a

sham-controlled or an open-label phase of a prior study were tapered from rTMS and simultaneously started on maintenance antidepressant monotherapy.[31] During the 24-week follow-up, 10 of 99 patients relapsed, 38 had symptom worsening, and of these 32 (84%) had symptomatic benefit with adjunctive rTMS.

Section Summary

There are a large number of sham-controlled randomized trials and meta-analyses of these RCTs evaluating the use of rTMS for depression. The meta-analyses found a clinical benefit associated with rTMS for TRD, with improved response rates and remission rates compared with sham. There is some evidence that rTMS, when given in conjunction with the initiation of pharmacologic therapy, improves the response rate compared with pharmacologic therapy alone, while the effect of rTMS is less robust when it is given in combination with a stable dose of antidepressant medication. There is limited evidence to compare the effects of these treatments on cognition, although the adverse events of rTMS appear to be minimal. While the most recent meta-analyses have found that the effect of rTMS is smaller than the effect of ECT on TRD, given that rTMS does not require general anesthesia or induce seizures and some individuals may not elect ECT, the balance of incremental benefits and harms associated with rTMS may be reasonable compared with ECT.

BIPOLAR DISORDER

Systematic Review

Konstantinou et al (2022) conducted a systematic review of 31 RCTs of rTMS for the treatment of bipolar disorder; meta-analysis was not performed.[53] Most included studies were in the setting of bipolar depression (n=24). Only 8 studies had a low risk of bias. Overall, rTMS seems safe and well-tolerated but efficacy results are mixed and there is no consensus about the optimal rTMS regimen. The authors noted limitations of the available literature including heterogeneity among studies, differences in sham treatments, and small sample sizes. They also stated that adequately powered sham-controlled studies are needed to verify the efficacy of rTMS in patients with bipolar disorder.

Tee (2020) conducted a systematic review of sham-controlled RCTs of rTMS for bipolar disorder.[54] A total of 11 RCTs met inclusion criteria, of which seven included only patients with bipolar depression, three included only patients with bipolar mania, and one included both unipolar and bipolar depression. Of the 345 included bipolar patients, 257 were treated for bipolar depression, 85 for mania, and 2 for mixed episodes. Risk of bias was assessed with the Cochrane Risk of Bias Tool. Of the studies of bipolar depression, one study was classified as good quality, two were classified as fair quality, and five were classified as poor quality. Of the studies of bipolar mania, one study was classified as fair quality and two were classified as poor quality. Results of the meta-analysis showed a statistically significant improvement in depressive symptoms in rTMS-treated versus sham-treated patients (standardized mean difference = 0.302, 95% CI 0.055 to 0.548, p=0.016). There was no statistically significant heterogeneity. There was also a statistically significant difference between groups in favor of rTMS for remission rate (risk difference = 0.14, p<0.05). There were no significant differences between groups for patients treated for bipolar mania. No serious adverse events were reported.

Randomized Controlled Trials

Torres (2023) published a randomized sham-controlled trial where 16 patients received active Intermittent theta burst stimulation (iTBS) to the Left Dorsolateral Prefrontal Cortex (DLPF) and 15 patients received sham stimulation across four weeks.[55] No significant improvements were observed in any cognitive variables in the active relative to the sham group; however, there was a trend for increased left hippocampal volume in the former. Left hippocampal volume increases were associated with improvements in nonverbal memory in the active group. Larger studies are required to determine the effects of iTBS for bipolar disorder.

Tavares (2017) published a randomized sham-controlled trial that examined the safety and efficacy of deep (H1-coil) TMS (dTMS) for treatment-resistant bipolar depression patients.[56] Fifty patients were randomized to 20 sessions of active or sham dTMS over the left dorsolateral prefrontal cortex. Two patients in the sham and five patients in the active group dropped out during the study. Assessments using the 17-item Hamilton Depression Rating Scale (HDRS-17) were completed at baseline, week four (end of treatment), and week eight. Patients were also assessed using the dTMS adverse effects questionnaire and the Young Mania Rating Scale, which would identify treatment-emergent mania switch. Changes in HDRS-17 from baseline (25.32 and 25.8 in sham and dTMS groups, respectively) were statistically superior in the active versus sham dTMS group at the end of treatment (difference at four weeks favoring dTMS=4.88; 95% CI 0.43 to 9.32, p=0.03) but not at follow-up (difference favoring dTMS=2.76; 95% CI 1.68 to 7.2, p=0.22). Response and remission rates were not significantly different between groups. No incidences of treatment-emergent mania were reported.

McGirr (2016) performed a meta-analysis to assess the efficacy of TMS for bipolar depression.[57] The analysis included randomized, double-blind, sham-controlled trials of rTMS involving five or more sessions that randomized patients with bipolar depression to both active and sham rTMS arms. Many of the studies did not include enough patients with bipolar depression to analyze them separately within the study. Data from a total of 19 studies were included. Study quality was not evaluated. There was high methodological heterogeneity, but there was no statistical evidence of heterogeneity. A funnel plot revealed an asymmetrical distribution. According to the meta-analysis, significantly more patients who received active rTMS achieved clinical response at study end compared to those who received sham rTMS (47/106, 44.3%, vs. 19/75, 25.3%; RD=0.18, 95% CI: 0.06 to 0.30, p<0.01).

Fitzgerald (2016) published a two arm parallel design RCT evaluating rTMS for patients with refractory bipolar depression.[58] Forty-nine patients participated in the study and received rTMS or sham stimulation. The authors concluded there was no difference in depression between the groups. The study was limited in size.

BIPOLAR DEPRESSION

Randomized Controlled Trials

Nahas (2003) performed an RCT and carried out the following left prefrontal rTMS study to determine the safety, feasibility, and potential efficacy of using TMS to treat the depressive symptoms of bipolar affective disorder (BPAD).[59] They enrolled 23 depressed BPAD patients (12 BPI depressed state, nine BPII depressed state, two BPI mixed state). Patients were randomly assigned to receive either daily left prefrontal rTMS (5 Hz, 110% motor threshold, 8

sec on, 22 sec off, over 20 min) or placebo each weekday morning for 2 weeks. The authors failed to find a statistically significant difference between the two groups in the number of antidepressant responders (>50% decline in HRSD or HRSD <10 - 4 active and 4 sham) or the mean HRSD change from baseline over the 2 weeks (t = -0.22, p = 0.83). The authors concluded that further studies are needed to fully investigate the potential role, if any, of TMS in BPAD depression.

Myczkowski (2018) performed an RCT to evaluate the cognitive effects of H1-coil (deep) transcranial magnetic stimulation (TMS) in patients with treatment-resistant bipolar depression.[60] Fourty-three patients were randomized to receive 20 sessions of active (55 trains, 18 Hz, 120% resting motor threshold intensity) or sham rTMS within a double-blind, sham-controlled trial. : Cognitive improvement was shown for all cognitive domains. It occurred regardless of intervention group and depression improvement. For the language domain, greater improvement was observed in the sham group over time. No correlations between depression (at baseline or during treatment) and cognitive improvement were found. The authors comment that Putative pro-cognitive effects of rTMS in BD were not observed and thus should be further investigated.

Zengin (2022) performed an RCT to is to investigate the efficacy and safety of Transcranial magnetic stimulation (TMS) treatment, a non-invasive brain stimulation technique, on depressive symptoms in treatment-resistant bipolar depression (TRBD).[61] The study included 29 patients between the ages of 18-65, with bipolar disorder depressive episode. Patients were divided into two groups double-blind-randomly, 20 sessions of TMS and 20 sessions of sham TMS were applied crossover. In both groups, the severity of depression was decreased significantly according to HAM-D and BDI scores after the procedure. As well as active stimulation, some positive placebo effects were observed with sham stimulation. But the decreases seen in HAM-D and BDI scores and response to the treatment were higher during the weeks when the groups received active stimulation (respectively p=0.000, p=0.001, p=0.005). The authors concluded that TMS treatment is an effective and safe treatment for patients with treatment-resistant bipolar depression.

Mallik (2023) published an RCT for to study the effect of novel continuous theta burst stimulation (cTBS) targeting right dorsolateral prefrontal cortex in a randomized rater blinded placebo control design.[62] Nineteen patients aged 18 to 59 years (baseline Hamilton Depression Rating Scale [HAM-D] 17 severity score >18) were randomly allocated to active cTBS (n = 11) and sham cTBS (n = 9) groups using block randomization method. They received 15 cTBS sessions (burst of 3 pulses delivered at 50 Hz, repeated every 200 ms at 5 Hz, 600 pulses per session), 3 sessions per day (total of 1800 pulses) for 5 days in a week at 80% resting motor threshold. On repeated measures analysis of variance, a significant within-group time effect (from pretreatment to 2 weeks after TBS) for HAM-D (F = 15.091, P < 0.001), Beck Depression Inventory (F = 22.376, P < 0.001), Hamilton Anxiety Rating Scale (F = 18.290, P < 0.001), Changes in Sexual Functioning Questionnaire (F = 9.281, P = 0.001), and World Health Organization's abbreviated quality of life assessment (F = 24.008, P < 0.001). The authors concluded that although safe and well tolerated, the therapeutic efficacy of intensive intermittent TBS in acute-phase bipolar depression is inconclusive.

POST TRAUMATIC STRESS DISORDER AND ANXIETY

Systematic Reviews

Cui (2019) included 21 studies (n=1481 patients) in a meta-analysis of rTMS plus drug therapy compared to drug therapy alone for the treatment of generalized anxiety disorder.[63] Results of the analysis showed that rTMS improved anxiety symptoms as measured by the Hamilton Anxiety Scale, (standardized mean difference = −0.68, 95% CI −0.89 to −0.46). The conclusions that could be drawn from the body of evidence were limited by significant heterogeneity across studies, and the authors concluded that additional high-quality studies are needed to confirm the results.

An SR by Cirillo (2019) evaluated the safety and efficacy of TMS as a treatment for anxiety and trauma-related disorders.[64] The authors identified 17 studies that met inclusion criteria. Nine were for post-traumatic stress disorder (PTSD) (six double-blind, randomized, sham-controlled, one open-label, and two retrospective), four were for generalized anxiety disorder (two double-blind, randomized, sham-controlled, and two uncontrolled open-label), two were for specific phobias (one double-blind, randomized, sham-controlled, and single-blind, randomized, sham-controlled), and two were for panic disorder (both double-blind, randomized, sham-controlled). According to the meta-analysis including all nine PTSD studies, the overall effect size for PTSD was -0.88 (95% CI -1.42 to -0.34), favoring TMS. According to the meta-analysis for generalized anxiety disorder, which included all four studies meeting inclusion criteria, the effect size for generalized anxiety disorder was −2.06 (95%CI −2.64 to −1.48), favoring TMS. No meta-analyses were performed for panic disorder and specific phobia due to an insufficient number of studies and patients.

Trevizol (2016) published a SR to evaluate the effects of rTMS on PTSD.[65] The five studies included showed rTMS statistically superior to sham stimulation (standard mean difference [SMD] =0.74; 95% CI 0.06 to 1.42), although heterogeneity of the trials was high. Despite improvements, the authors concluded this SR was limited in size and additional RCTs are needed to determine clinical impact.

Randomized Control Trials

Yuan (2023) published a RCT comparing the two forms of TMS (iTBS and rTMS) in 75 participants with post-traumatic stress disorder (PTSD).[66] Participants were randomly assigned to groups in a ratio of 1:1:1, receiving either 10 Hz rTMS, iTBS, or sham-controlled iTBS. Participants in the two treatment groups underwent 15 therapies which consisted of 1800 pulses and targeted the right dorsolateral prefrontal cortex (DLPFC). The main outcomes included changes in scores on the Posttraumatic Stress Disorder Checklist (PCL-C) and the Post-Traumatic Growth Inventory (PTGI). After intervention, the PCL-C and PTGI scores in iTBS and rTMS groups were significantly different from those in sham-controlled iTBS group. No significant differences in PCL-C and PTGI were found between the two active treatment groups. They concluded that ITBS, with a shorter treatment duration, can effectively improve the symptoms of PTSD, with no significant difference in effect from that of rTMS. Future studies are needed to further elucidate the mechanisms, optimize the parameters and investigate the therapeutic potential and efficacy of iTBS in PTSD.

Isserles (2021) reported a multisite randomized sham-controlled trial of deep TMS combined with exposure therapy for the treatment of PTSD.[67] A total of 125 patients were randomly assigned to receive deep TMS or sham during 12 sessions administered over four weeks. The primary endpoint was change in five-week Clinician-Administered PTSD Scale for DSM-5 score. While both groups improved significantly, the improvement in the sham group was

significantly greater than the improvement in the active treatment group (20.52 vs. 16.32; p=0.027). This remained true at the nine-week follow-up (p=0.024).

SCHIZOPHRENIA

Systematic Reviews and Technology Assessments

Marzouk (2019) published an SR evaluating the use of TMS for positive symptoms in schizophrenia.[68] Thirty studies met the inclusion criteria, of which 25 investigated auditory verbal hallucinations. Twelve studies reported significant beneficial effects of TMS while 18 reported no significant beneficial effects. The SR concluded that further research with larger sample sizes is needed.

A 2019 SR published by Limori evaluated the effect of rTMS on cognitive function when used for depression, schizophrenia, and Alzheimer's disease.[69] A total of 31 studies met inclusion and exclusion criteria, of which 15 were conducted in patients with depression, 11 in patients with schizophrenia, and 5 in patients with Alzheimer's disease. Six studies reported positive effects of rTMS on executive function while the rest reported no significant cognitive effects. A small number of studies also reported positive effects on verbal memory, working memory, and attention. No studies reported adverse cognitive effects. Conclusions were limited by heterogeneity between studies in terms of cognitive measures applied, stimulation parameters, and participants.

He (2017) published a meta-analysis of the effects of 1-Hz (low frequency) and 10-Hz rTMS (high frequency) for auditory hallucinations and negative symptoms of schizophrenia, respectively.[70] For 1-Hz rTMS, 13 studies were included. Compared with sham, the rTMS group showed greater improvement in auditory hallucinations (SMD = -0.29; 95% CI -0.57 to -0.01). However, significant heterogeneity between the studies was found (p=0.06). In the seven studies included for 10-Hz rTMS, the overall effect size for improvement in negative symptoms was -0.41 (95% CI -1.16 to -0.35); again, there was significant heterogeneity between studies (p<0.001). The study was further limited by the small number of articles included and by the unavailability of original data for some studies.

Dollfus (2016) published a SR to evaluate the impact of the placebo effect in studies involving rTMS on visual hallucinations for patients with schizophrenia.[71] Twenty-one articles with 303 patients were reviewed. The authors concluded that the placebo in rTMS studies cause bias and that the design or such studies should be carefully evaluated.

A 2015 Cochrane SR included 41 studies with a total of 1473 participants.[72] Based on very low-quality evidence, there was a significant benefit of temporoparietal TMS compared to sham for global state (seven RCTs) and positive symptoms (five RCTs). The evidence on cognitive state was equivocal. For prefrontal rTMS compared to sham, the evidence on global state and cognitive state was of very low quality and equivocal. The authors concluded that there is insufficient evidence to support or refute the use of TMS to treat symptoms of schizophrenia, and although there is some evidence to suggest that temporoparietal TMS may improve certain symptoms such as auditory hallucinations and positive symptoms of schizophrenia, the results were not robust enough to be unequivocal.

A 2011 BCBSA TEC Assessment evaluated TMS as an adjunct treatment for schizophrenia.[73] Five meta-analyses were reviewed, along with RCTs in which measurements were carried out beyond the treatment period. A meta-analysis of the effect of TMS on positive symptoms of

schizophrenia (hallucinations, delusions, and disorganized speech and behavior) did not find a significant effect of TMS. Four meta-analyses that looked specifically at auditory hallucinations showed a significant effect of TMS. It was noted that outcomes were evaluated at the end of treatment, and the durability of the effect was unknown. The Assessment concluded that the available evidence is insufficient to demonstrate that TMS is effective as a treatment of schizophrenia.

Randomized Controlled Trials

Several additional small, single center RCTs of rTMS for the treatment of schizophrenia have been published since the systematic reviews described above.[74-78] These studies were limited by their small sample sizes (28 to 50), very high loss to follow-up, and inadequate duration of followup. Due to these limitations, these studies do not provide sufficient evidence to draw conclusions about the effectiveness of the technology in patients with schizophrenia.

Section Summary

The evidence on TMS for the treatment of auditory hallucinations in schizophrenia consists of a number of small RCTs. Evidence to date shows small to moderate effects on hallucinations when measured at the end of treatment, but evidence suggests that TMS does not produce a durable treatment effect in patients with schizophrenia.

OBSESSIVE COMPULSIVE DISORDER

Systematic Reviews

Grassi (2023) systematic review and meta-analysis of the available open and sham-controlled trials for the treatment of obsessive compulsive disorder (OCD) focused on neural pathways and protocols.[79] The primary analysis included a pairwise meta-analysis (over 31 trials), and subgroup analyses were performed for each targeted brain area. Meta-regression analyses explored the possible moderators of effect size. The pairwise meta-analysis showed a significant reduction in OCD symptoms following active rTMS (g = -0.45 [95%CI: -0.62, -0.29]) with moderate heterogeneity (I2 = 34.9%). Subgroup analyses showed a significant effect of rTMS over the bilateral pre-SMA (supplementary motor area), the DLPFC (dorsolateral prefrontal cortex), the ACC/mPFC (anterior cingulate cortex and medial prefrontal cortex), and the OFC (orbitofrontal cortex). No moderators of the effect size emerged. All the TMS protocols were well tolerated and no serious side effects occurred with mild and transient headache as the most frequently reported side effect. Limitations to the studies include small sample size, heterogeneity of TMS protocols and devices. Future studies should define the sufficient number of sessions and stimuli for each patient as well as define clinical features or biomarkers to predict the most promising TMS target for a single patient. In addition, defining strategies to augment the TMS effects should be investigated.

Pellegrini (2022) attempts to explain some of this heterogeneity in trails for testing the efficacy of r-TMS as a treatment for OCD by comparing the efficacy of r-TMS in patients with or without resistance to treatment with selective serotonin reuptake inhibitors (SSRI), defined using standardized criteria.[80] Twenty-five independent comparisons (23 studies) were included. Overall, r-TMS showed a medium-sized reduction of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (Hedge's g: -0.47; 95%CI - 0.67 to -0.27) with moderate heterogeneity (I2 = 39.8%). Subgroup analysis found that those studies including patients non-resistant to SSRI (stage 1) (g: -0.65; 95%CI -1.05 to -0.25, k = 7) or with low SSRI-resistance

(stage 2) (g:-0.47; 95%CI -0.86 to -0.09, k = 6) produced statistically significant results with low heterogeneity, while studies including more highly resistant patients at stage 3 (g: -0.39; 95%CI: -0.90 to 0.11, k = 4) and stage 4 (g: -0.36; 95%CI: -0.75 to 0.03, k = 8) did not. The authors conclude that r-TMS is an effective treatment for OCD, but largely for those not resistant to SSRI or failing to respond to only one SSRI trial. As a consequence, r-TMS may be best implemented earlier in the care pathway.

Fitzsimmons (2022) reported results of a systematic review and pairwise/network meta-analysis of randomized, sham-controlled studies of rTMS for obsessive compulsive disorder (OCD).[81] A total of 21 studies including 662 participants met inclusion criteria. Studies were generally small and there was heterogeneity in study protocols. Overall, rTMS for OCD was found to be efficacious across all protocols according to the pairwise meta-analysis (Hedges' g=-0.502 [95%CI -0.708 to -0.296]). rTMS remained efficacious in analyses where stimulation protocols were clustered only by anatomical location, including both dorsolateral prefrontal cortex (dlPFC) stimulation and medial frontal cortex stimulation, and in analyses of each unique combination of frequency and location separately, including low frequency (LF) pre-supplementary motor area (preSMA) stimulation, high frequency (HF) bilateral dlPFC stimulation, and LF right dlPFC stimulation.

Suhas (2021) conducted a network meta-analysis [NMA] to compare the efficacy of all interventions in SRI-resistant OCD from published RCTs from all modalities of treatments; pharmacological, psychological, neuromodulation, neurosurgery including deep brain stimulation.[82] 55 RCTs examining 19 treatments or placebo involving 2011 participants were included in the NMA. Ondansetron [Standardized mean difference -2.01 (95% CI -3.19, -0.83)], deep TMS [- 1.95 (-3.25, -0.65)], therapist administered Cognitive Behavioral Therapy [CBT-TA] [-1.46 (-2.93, 0.01)] and aripiprazole [-1.36 (-2.56, -0.17)] were ranked as the best four treatments on using the Surface Under the Cumulative Ranking [SUCRA] percentage values (85.4%, 83.2%, 80.3%, 67.9% respectively). The authors concluded that deep TMS, ondansetron, CBT, and aripiprazole may be considered a first-line intervention for SRI-resistant OCD in adults. The small number of subjects in individual studies, higher confidence interval limits, and wider prediction interval for most agents warrant a cautious interpretation.

Pereyra (2021) conducted a systematic review and meta-analysis of rTMS in the treatment of OCD.[83] All RCTs in the analysis (n=26) had a low risk of bias. A random effects model was used to compare pre- and post-stimulation YBOCS scores, with effect sizes reported as Hedges' g. The analysis found that rTMS had a significant effect on YBOCS scores compared to sham (effect size, 0.64; 95% CI, 0.39 to 0.89; p<.0001). Raw mean difference in standardized mean difference for the primary outcome (YBOCS score) between treatments was 4.04 (95% CI, 2.54 to 5.54; p<.001). The effect size was still significant when 2 dominant trials were removed. Effect sizes with rTMS appeared to be significant until 4 weeks after treatment, and low- and high-frequency rTMS had similar efficacy to each other. The authors performed several subgroup analyses (cortical target, stimulation frequency, total pulses per session, total duration of treatment) but none of the effect sizes were significant between rTMS and sham.

Liang (2021) conducted a systematic review and meta-analysis of different TMS modalities for the treatment of OCD.[84] Three of the five protocols assessed were significantly more efficacious than sham TMS, and all treatment strategies were similar to sham TMS regarding tolerability. Transcranial magnetic stimulation was not more effective than sham TMS, but there was direct evidence from only one RCT for this comparison (Carmi, 2019, discussed in

the next section).[85] The overall quality of the evidence was rated very low for efficacy and low for tolerability, and the reviewers concluded that high quality RCTs with low selection and performance bias are needed to further verify the efficacy of specific rTMS strategies for OCD treatment.

Zhou (2017) published an SR that analyzed 20 sham-controlled studies with 791 patients examining the effect of rTMS on obsessive-compulsive disorder (OCD).[86] Treatments targeted the bilateral DLPFC, left DLPFC, right DLPFC, supplementary motor area (SMA), and the orbitofrontal cortex. The majority of studies did not use intention to treat analyses and only three studies assessed the effectiveness of the blinding procedures used. Results of a meta-analysis indicated a large effect size for therapeutic effect (g=0.71; 95%CI 0.55 to 0.87; p<0.001). Significant improvements over sham treatment were seen for rTMS targeting the supplementary motor area, left dorsolateral prefrontal cortex (DLPFC), bilateral DLFPC, and right DLPFC, excluding the orbitofrontal cortex. High-frequency and low-frequency treatments were significantly better than sham treatment, with no differences found between frequencies.

A systematic review by Trevizol (2016) included 15 RCTs (total n=483) that compared active with sham rTMS for obsessive-compulsive disorder (OCD).[87] All studies were sham-controlled and double-blinded. Sample sizes in the trials ranged from 18 to 65 patients. Mean age of participants was 31.9 (SD = 7.6) years. The duration of the studies was between one and six weeks. Seven studies used low-frequency stimulation and eight studies used high-frequency stimulation. The cortical regions varied among the studies, targeting the supplementary motor area, orbitofrontal cortex, or left, right, or bilateral DLPFC. The researchers calculated the YBOCS score. Response rates were not reported. The pooled mean difference between groups on the YBOCS was 2.94 (95% CI 1.26 to 4.62), translating to a small to moderate effect size for active stimulation of 0.45 (95% CI 0.20 to 0.71). Individual adverse effects were not assessed due to a lack of reporting in the primary studies, but there was no difference between groups in the dropout rate. Intervention protocols were heterogeneous across the studies, but regression analysis did not identify any treatment protocol or other variables as predictors of TMS response.

Randomized Controlled Trials

Ozer (2024) published a double blind, placebo controlled RCT evaluating high-frequency deep transcranial magnetic stimulation (dTMS) targeting the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) with an H-coil compared to a sham coil treatment in patients (n = 29) with OCD.[88] Patients in the active TMS group (n = 14) underwent stimulation of the mPFC and ACC twice daily at a frequency of 20 Hz for three weeks, using a double-cone coil. The same procedure was applied to the sham control group (n = 15) using a placebo coil. Throughout the study, the patients continued their antidepressant and/or antipsychotic treatments at the same dose. Following treatment, the active TMS group exhibited a more significant reduction in Yale-Brown Obsessive-Compulsive Scale scores (pre-treatment: 25.36 ± 5.4, post-treatment: 18.43 ± 6.86) and Hamilton Anxiety Rating Scale scores (pre-treatment: 10.6 ± 3.5, post-treatment: 6.7 ± 2.7) compared to the sham TMS group. However, there was no statistically significant reduction in symmetry-related obsessive-compulsive symptoms in the TMS group compared to the sham TMS group.

Jiang (2023) investigated whether an accelerated high-dose theta burst stimulation (ahTBS) protocol significantly improves the efficacy of OCD compared to traditional 1-Hz repetitive transcranial magnetic stimulation (rTMS) in the routine clinical setting.[89] Patients diagnosed

with OCD (n = 45) were randomized into two groups and treated with ahTBS or 1-Hz rTMS for 5 days. Patients were assessed at baseline at the end of treatment using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). After 5 days of treatment, there was a significant decrease in Y-BOCS scores in both groups ($p < 0.001$), and the difference between the two groups was not statistically significant (group × time interaction, $F = 1.90$, $p=0.18$). There was also no statistically significant difference in other secondary outcome indicators, including depression, anxiety symptoms, and response rate. Neuropsychological testing showed no negative cognitive side effects of either treatment. Limitations include small sample size, possible medication interference with TMS treatment, lack of sham control and high loss to follow-up.

Roth (2021) published the efficacy of Deep transcranial magnetic stimulation (dTMS) with the H7-coil was for obsessive-compulsive disorder (OCD) based on multicenter sham-controlled studies.[90] The primary outcome measure was response, defined by at least a 30% reduction in the Yale Brown Obsessive Compulsive Scale (YBOCS) score from baseline to endpoint. Secondary outcome measures included first response, defined as the first time the YBOCS score has met response criteria, and at least one-month sustained response. Twenty-two clinical sites with H7-coils provided data on details of treatment and outcome (YBOCS) measures from a total of 219 patients. First response was achieved in average after 18.5 sessions (SD = 9.4) or 31.6 days (SD = 25.2). Onset of sustained one-month response was achieved in average after 20 sessions (SD = 9.8) or 32.1 days (SD = 20.5). Average YBOCS scores demonstrated continuous reduction with increasing numbers of dTMS sessions. The authors reported that the majority of OCD patients benefitted from dTMS, and the onset of improvement usually occurs within 20 sessions.

A more recent RCT, Carmi (2019) was addressed in the 2021 Liang systematic review, above.[85] The trial was submitted to FDA as part of the de novo classification request, to establish a reasonable assurance of safety and effectiveness of the deep TMS device for OCD.[85] Adults ages 22 to 68 years with a diagnosis of OCD as a primary disorder, who were receiving treatment in an outpatient setting, and have a YBOCS score >20 were included. In addition, patients were either in maintenance treatment with a therapeutic dosage of a serotonin reuptake inhibitor (SRI) for at least two months before randomization or, were in maintenance treatment on cognitive-behavioral therapy (CBT) and had failed to respond adequately to at least one past trial of an SRI. A total of 99 patients were randomized to active treatment or sham. The primary outcome was the difference between groups in the mean change from baseline to six weeks on the YBOCS. Secondary outcomes included the response rate (defined as a 30% or greater improvement from baseline on the YBOCS), the Clinical Global Impression of Improvement (CGI-I), the Clinical Global Impression of Severity (CGI-S), and the Sheehan Disability Scale, a patient-reported measure of disability and impairment. Results at 10 weeks were also reported as secondary outcomes.

The primary efficacy analysis used a modified intention to treat analysis (n=94), excluding five patients who were found to not meet eligibility criteria following randomization. There was a greater decrease from baseline in the active treatment group (-6.0 points) than the sham group (-2.8 points), translating to a moderate effect size of 0.69. At six weeks, the response rate was 38.1% in the active treatment group compared to 11.1% in the sham group ($p=0.003$). The FDA review provides data from the ITT analysis of the mean change in YBOCS score (n=99). In the ITT data set, the YBOCS score decreased by -6.0 points (95% CI -3.8 to -8.2) in the active group and by -4.1 points (95% CI -1.9 to -6.2) in the sham group. Although the decreases were both statistically significant from baseline, the difference of 1.9 points between

the treatment arms was not statistically significant (p=0.0988). Results on the secondary outcomes were mixed. More patients in the active treatment group were considered improved based on the Clinical Global Impression of Improvement (CGI-I) and the Clinical Global Impression of Severity (CGI-S) at six weeks, but there was no significant difference between groups on the Sheehan Disability Scale. The number of adverse events and dropouts were similar between groups (73% vs. 69% for adverse events and 12.5% vs. 12.0% for dropouts, for TMS and sham, respectively).

Additional small, single center RCTs of rTMS for the treatment of OCD have been published since the systematic reviews described above.[91] These studies were limited by their small sample sizes (under 50), very high loss to follow-up, and inadequate duration of followup.

OTHER PSYCHIATRIC DISORDERS

Systematic Reviews

Smith (2023) published a SR and meta-analysis examining the use of TMS in the treatment of pediatric and young adult autism spectrum disorder in intellectually capable persons (IC-ASD).[92] Sixteen studies were identified and twelve were included in the meta-analysis. Seven were open-label or used neurotypical controls for baseline cognitive data, and nine were controlled trials. In the latter, waitlist control groups were often used over sham TMS. Only one study conducted a randomized, parallel, double-blind, and sham controlled trial. Favorable safety data was reported in low frequency repetitive TMS, high frequency repetitive TMS, and intermittent theta burst studies. Compared to TMS research of other neuropsychiatric conditions, significantly lower total TMS pulses were delivered in treatment and neuronavigation was not regularly utilized. The meta-analysis results report improvement in cognitive outcomes (pooled Hedges' g = 0.735, 95% CI = 0.242, 1.228; p = 0.009) and primarily Criterion B symptomology of IC-ASD (pooled Hedges' g = 0.435, 95% CI = 0.359, 0.511; p < 0.001) with low frequency repetitive TMS to the dorsolateral prefrontal cortex. The authors conclude that TMS may offer a promising and safe treatment option for pediatric and young adult patients with IC-ASD. Future work should include use of neuronavigation software, theta burst protocols, targeting of various brain regions, and robust study design before clinical recommendations can be made.

Westwood (2021) published an SR and meta-analysis of noninvasive brain stimulation for the treatment of attention-deficit/hyperactivity disorder (ADHD).[93] A total of 18 studies met inclusion criteria, of which four addressed rTMS and 14 addressed tDCS. The meta-analysis showed no statistically significant improvements following rTMS or tDCS in any measures.

A 2020 SR on noninvasive brain stimulation for alcohol craving published by Mostafavi identified 34 eligible studies, of which 23 addressed rTMS and 11 addressed tDCS.[94] Twenty-seven of the studies included a control group. According to the meta-analysis, the pooled standardized mean differences in alcohol cravings based on tDCS or rTMS treatment were not statistically significant (- 0.13 [-0.34 to 0.08] and - 0.43 [-1.02 to 0.17], respectively).

A 2018 SR published by Barahona-Corrêa assess the use of rTMS for the treatment of Autism Spectrum Disorder (ASD).[95] A total of 23 studies met inclusion criteria, including four case-reports, seven non-controlled clinical trials, and 12 controlled clinical trials. The controlled trials compared the effects of real TMS with waiting-list controls (n=6) or sham-treatment (n=6). Four of the controlled trials were not randomized. Meta-analyses indicated moderate, statistically significant effects on repetitive and stereotyped behaviors, social behavior, and number of

errors in executive function tasks. However, most studies had a moderate to high risk of bias and outcomes were not reported long-term.

A 2014 Cochrane review identified two RCTs with a total of 40 patients that compared low frequency rTMS with sham rTMS for the treatment of panic disorder.[96] The larger of the two studies was a randomized, double-blind, sham-controlled trial in 21 patients with panic disorder with comorbid major depression. Response was defined as a 40% or greater decrease on the Panic Disorder Severity Scale and a 50% or greater decrease on HAM-D. After four weeks of treatment, the response rate for panic was 50% with active rTMS and 8% with sham. The study had a high risk of attrition bias. The overall quality of evidence for the two studies was considered to be low, and the sample sizes were small, precluding any conclusions about the efficacy of rTMS for panic disorder.

Additional SRs have been published exploring the efficacy of TMS for a variety of psychiatric disorders like borderline personality disorder and addiction.[97-100] All of these SRs had one or more significant methodological limitations, including but not limited to small patient populations, short follow-up times, continued use of concurrent therapies, and/or significant loss to follow-up in the included studies, heterogeneous treatment parameters between studies, and limited management of study bias and conflict of interest. Generally, the authors agreed that larger, long-term RCTs are needed, along with better defined optimal treatment parameters for administering TMS.

Randomized Controlled Trials

A number of additional RCTs explored the efficacy of TMS for a variety of mental health disorders other than depression, including, but not limited to, bipolar mania, panic disorder, alcohol dependence, and ADHD. Many of these studies are preliminary (feasibility) studies and/or have serious methodological limitations that render outcomes unreliable. Some limitations of these studies include:

- Poorly defined or unmet endpoints[101-106]
- Significant or unclear loss to follow-up and poorly defined intention-to-treat (ITT) analyses[103, 105, 107-109]
- Lack of long-term follow up[101-115]
- Small patient populations[101-111, 116-126]
- Lack of standardized optimal treatment parameters[101-104, 106-110, 116, 127-129]
- Use of co-therapies[101-111]
- Strict inclusion/exclusion criteria which were not representative of patients requiring treatment in the general population[101-104, 107, 110, 111, 116]

Section Summary

Current evidence is insufficient to determine the efficacy of TMS in patients with the psychiatric disorders discussed here. Well-designed RCTs are needed which address the methodological limitations of current studies, noted above.

NEURODEGENERATIVE DISEASES:

Xiu (2024) evaluated the efficacy of HF-rTMS in improving global cognitive function rehabilitation in elderly patients with mild to moderate Alzheimer’s Disease (AD) in a SR with meta-analysis.[130] Seventeen RCTs, with a total of 1161 elderly patients with mild to moderate

AD, were included in the meta-analysis. Compared to the control group, HF-rTMS could increase MMSE (mean difference [MD] = 3.64; 95%CI 1.86-5.42; p < 0.0001), MoCA (MD = 3.69; 95%CI 1.84-5.54; p < 0.0001), P300 amplitude (MD = 1.09; 95%CI 0.45-1.72; p = 0.0008), and total effective rate scores (MD = 3.64; 95% CI 2.14-6.18; p < 0.00001) while decreasing ADAS-Cog (MD = - 3.53; 95%CI - 4.91- - 2.15; p < 0.00001) and P300 latency scores (MD = - 38.32; 95%CI - 72.40- - 4.24; P = 0.03). The authors concluded that HF-rTMS could improve the global cognitive function of elderly patients with mild to moderate AD.

Huang (2024) published a SR with meta-analysis evaluating the efficacy of repeated transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) using neuropsychological assessments as a potential treatment option for Alzheimer's disease (AD).[131] A total of 17 eligible studies were included. Repetitive TMS improved cognition of patients with AD (immediate post-treatment WMD of MMSE score: 2.06, p < 0.00001; short-term follow-up WMD of MMSE score: 2.12, p = 0.006; WMD of ADAS-Cog score in single-arm studies: -4.97, p = 0.001). DBS did not reverse the progression of cognitive decline (WMD of ADAS-Cog score in single-arm studies: 7.40, p < 0.00001). Furthermore, tDCS demonstrated no significant efficacy in improving cognition in random clinical trials or single-arm studies.

Miller (2023) published a SR to evaluate the efficacy and moderators of repetitive transcranial magnetic stimulation (rTMS) targeted over the dorsolateral prefrontal cortex (DLPFC) as an intervention to treat cognitive decline in people with age-related neurodegenerative diseases. [132] Sixteen studies involving 474 participants met the inclusion criteria, of which eight studies measured global cognitive function. The results from the random-effects meta-analysis showed rTMS significantly improved global cognitive function relative to control groups shown by a large, significant effect size (g = 1.39, 95% CI, 0.34-2.43; p = 0.017). No significant effects were found between subgroups or for individual cognitive domains. The authors concluded that high-frequency rTMS, targeted over the DLPFC, appears to improve global cognitive function in people with age-related neurodegenerative diseases. This research is limited by the small number of studies with high between -study heterogeneity.

Teselink (2021) performed an SR and meta-analysis of non-invasive brain stimulation for Alzheimer’s disease and mild cognitive impairment.[133] A total of 19 studies measuring cognition and nine measuring neuropsychiatric symptoms met inclusion criteria. There was no evidence of publication bias. Overall, noninvasive stimulation was found to significantly improve global cognition (p=0.001) and neuropsychiatric symptoms (p=0.019) compared to sham stimulation. According to subgroup analyses, these effects were driven by TMS treatment in Alzheimer’s disease and there was no significant effect of tDCS or in dementia patients. A meta-regression analysis showed Meta-regression showed that age was significantly associated with global cognition response (p=0.02). There was substantial heterogeneity across all subgroup analyses and meta-regressions (all $I^2 > 50\%$).

Wang (2020) published an SR and meta-analysis of rTMS and tDCS for the behavioral and psychological symptoms of dementia.[134] A total of 10 studies were identified. Seven of the studies included patients with Alzheimer’s disease. The meta-analysis included both forms of stimulation and the results indicated that stimulation resulted in a statistically significant improvement in the behavioral and psychological symptoms of dementia immediately following stimulation (SMD, 0.31; 95% CI 0.10 to 0.52; p=0.005). The improvement was not statistically significant at the last follow-up visit for stimulation overall (0.15; 95% CI - 0.11 to 0.41; p=0.25), but was statistically significant in the subgroup analysis for rTMS (0.57; 95% CI 0.18 to 0.96;

p=0.004). The subgroup analysis for Alzheimer's disease patients did not indicate any significant differences from the group overall.

Vacas (2018) published an SR and meta-analysis of rTMS and tDCS for the behavioral and psychological symptoms of dementia.[135] Three RCTs and two open-label clinical trials of rTMS were identified as well as two RCTs of tDCS. A meta-analysis with four RCTs did not show significant efficacy of noninvasive brain stimulation techniques, but a meta-analysis of the rTMS RCTs alone showed a statistically significant positive effect on behavioral and psychological symptoms of dementia (overall effect = -0.58; 95% CI -1.02 to -0.14; I^2 = 0%). The adverse effects reported were mild and not clinically relevant.

A 2017 SR published by Cheng analyzed studies that used rTMS for patients with mild to moderate Alzheimer's disease.[136] Seven RCTs (including 107 active and 87 sham rTMS patients) were included in a meta-analysis analyzing a primary outcome of cognitive function as measured by the Mini-Mental State Examination or the Alzheimer's Disease Assessment Scale-cognitive subscale. Active rTMS was found to be significantly more effective than sham for improving cognition.

CEREBRAL PALSY

Systematic Reviews

No SRs were identified.

Randomized Control Trials

Gupta (2016) published a RCT that evaluated motor function, after rTMS for cerebral palsy (CP) patients.[137] Forty-one spastic CP children who completed the study and were randomly assigned to receive physical therapy (n=12) alone, 5hz rTMS followed by physical therapy (n=15), or 10hz rTMS, (n=14) followed by physical therapy for 20 days. The gross motor function measure (GMFM) test was applied at baseline and after 20 treatments. Although the study showed improved motor function for the rTMS plus physical therapy groups, the authors concluded the results should not be interpreted as a final outcome, especially with previous studies showing lack of progress from this treatment. Larger studies evaluating long-term effects are needed.

EPILEPSY

Systematic Reviews

A meta-analysis conducted by Mishra and colleagues (2020) included seven RCTs that compared rTMS with sham or placebo controls in patients with epilepsy.[138] Two of the included studies showed statistically significant reductions in the seizure rate from baseline, three trials failed to show any statistically significant difference in seizure frequency, and two had unclear results due to inadequate power. In a meta-regression, when adjusted for other potential variables such as the type of coil used, stimulation frequency, and the total duration of the active intervention, seizure frequency worsened by 2.00 ± 0.98 (p=0.042) for each week of lengthening of the posttreatment follow-up period. These results suggested that rTMS exerted only a short-term effect. The reviewers concluded that although the procedure may be a therapeutic alternative for patients with drug-resistant epilepsy, further RCTs using standardized protocols and with adequate sample sizes and duration are still needed.

Walton (2021) published an update to a Cochrane SR that included eight RCTs to evaluate the effects of rTMS on health outcomes for patients with drug-resistant epilepsy.[139] All studies were randomized and seven were blinded. However, a meta-analysis could not be conducted due to differences in the design, interventions, and outcomes of the studies. Therefore, a qualitative synthesis was performed. For the outcome of seizure rate, two studies showed a significant reduction and six studies did not. Of the four studies evaluating the mean number of epileptic discharges, three showed a statistically significant reduction in discharges. Adverse effects were uncommon and mild, involving headache, dizziness, and tinnitus. There were no significant changes in medication use. The authors noted low quality of evidence and that more studies are needed to evaluate reduction in seizure activity, quality of life, and adverse outcomes.

Pereira (2016) published an update to a 2007 SR that evaluated the safety of rTMS for patients with epilepsy and how well the procedure was tolerated.[140] Sixteen new studies were identified totaling 48, for this SR. The authors concluded the risk of increased seizure activity with rTMS was small and adverse events for patients with epilepsy were similar to healthy patients. They also questioned data control, stated results should be interpreted with caution and more studies are needed.

Randomized Control Trials

No RCTs were identified since the publication of the above SRs.

FIBROMYALGIA

Systematic Review

Su (2021) conducted a meta-analysis of 18 RCTs (n=643) with rTMS in patients with fibromyalgia.[141] Reduction in disease influence according to the Fibromyalgia Impact Questionnaire showed a significant effect of rTMS (SMD, -0.7; 95% CI -1.173 to -0.228). The effect of rTMS on disease influence, pain, depression, and anxiety lasted for at least 2 weeks after the last session. Older patients were most likely to experience reduced Fibromyalgia Impact Questionnaire scores. The authors concluded that larger RCTs are needed to confirm these findings.

Sun (2022) performed a systematic review and meta-analysis of the effectiveness of rTMS for fibromyalgia.[142] A total of 14 studies, including 433 participants, met inclusion criteria. The mean study quality was rated 8.5/10 on the PEDro scale. The analysis found that rTMS resulted in a greater improvement than sham treatment in the Numerical Pain Rating Scale (NPRS) (standardized mean difference = -0.49; 95% CI -0.86 to 0.13; p=0.0008) and the Fibromyalgia Impact Questionnaire (FIQ) (standardized mean difference = -0.50, 95% CI -0.75 to -0.25; p=0.0001). No significant differences between groups were identified for the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) anxiety score, Pain Catastrophizing Scale (PCS), or Fatigue Severity Scale (FSS).

In 2017, Saltychev and Laimi published a meta-analysis of rTMS for the treatment of patients with fibromyalgia.[143] The meta-analysis included seven sham-controlled double-blinded RCTs with low risk of bias. The sample size of the trials ranged from 18 to 54. Five of the studies provided high-frequency stimulation to the left primary motor cortex, the remaining two were to the right DLPFC or left DLPFC. The number of sessions ranged from 10 to 24, and follow-up ranged from immediately after treatment to three months after treatment. In

the pooled analysis, pain severity decreased after the last simulation by 1.2 points (95% CI -1.7 to -0.8) on a 10-point numeric rating scale, while pain severity measured at one week to one month after the last simulation decreased by 0.7 points (95% CI -1.0 to -0.3 points). Both were statistically significant but not considered to be clinically significant, with a minimal clinically important difference of 1.5 points.

Kninik (2016) published a SR that determined the effects repetitive transcranial magnetic stimulation (rTMS) versus a sham stimulation had on fibromyalgia, depression and/or quality of life.[144] The SR included five RCTs of moderate quality. The authors concluded that rTMS had a superior effect on quality of life after 30 days, but more studies are needed to determine why and how rTMS impacts health outcomes and what treatment protocols are appropriate.

A 2012 SR included four studies on transcranial direct current stimulation (tDMS) and five on TMS for treatment of fibromyalgia pain.[145] Four of the five TMS studies were double-blind RCTs, however the fifth included study was a case series of four patients who were blinded to treatment. Quantitative meta-analysis was not conducted due to variability in brain site, stimulation frequency/intensity, total number of sessions, and follow-up intervals. Results of four out of five of these studies reported significant decreases in pain and greater durability of pain reduction was observed overall, with stimulation of the primary motor cortex compared to the dorsolateral prefrontal cortex. However, all five TMS trials used in this analysis were limited by small sample size (n ≤ 40), continued use of concomitant medications and four had short-term follow-up (≥ 8 weeks) which preclude the ability to reach conclusions regarding the ability of TMS to effect pain reduction scores in patients suffering with fibromyalgia.

Randomized Controlled Trials

No sham-controlled RCTs were identified since the publication of the above SRs that evaluated the safety and efficacy of TMS for fibromyalgia.

Section Summary

Additional studies are needed to establish effective treatment parameters in a larger number of subjects and to evaluate the durability of tDMS or TMS treatment effect in patients with fibromyalgia.

HEADACHES/MIGRAINES

Systematic Reviews and Technology Assessments

Saltychev (2022) conducted a systematic review and meta-analysis of 8 RCTs from 2004-2021 that studied that compared rTMS to sham stimulation in patients with migraine (n=339).[146] All RCTs used high-frequency rTMS to the left dorsolateral prefrontal cortex and all studies except 1 included patients with chronic migraine. The treatment duration was three to 12 sessions over three to eight days. All studies except 1 had a low risk of bias and the risk of publication bias was nonsignificant. Results for the frequency of migraine days per month and the intensity of migraine pain both favored rTMS; however, the authors stated that the difference in migraine pain intensity was clinically insignificant.

A 2020 the Canadian Agency for Drugs and Technologies in Health (CADTH) rapid response report evaluated the use of non-invasive nerve stimulation for migraine pain.[147] The six included publications assessed a variety of stimulation methods, including but not limited to

TMS, tDCS, and trigeminal nerve stimulation. The review concluded that the evidence is limited in quality and quantity. Based on the limited evidence identified, the review concluded that there is a lack of evidence of the effectiveness of non-invasive nerve stimulation for migraine pain.

Feng (2019) performed an SR of non-invasive brain stimulation (rTMS and transcranial direct current stimulation [tDCS]) for the treatment of migraine.[148] Nine RCTs met inclusion criteria, of which five used rTMS and four used tDCS. Several studies overlapped with the WA HCA technology assessment below. Results of a meta-analysis of outcomes following excitatory stimulation of the primary motor cortex of migraine patients showed a significant reduction in headache intensity (Hedges' g = -0.94; 95% CI -1.28 to -0.59; p<0.001, I^2 =18.39%) and frequency (Hedges' g=-0.88; 95% CI -1.38 to -0.38; p=0.001, I^2 = 57.15%). Stimulation of the dorsolateral prefrontal cortex also showed a significant effect on headache intensity (Hedges' g=-1.14; 95% CI -2.21 to -0.07; p=0.04, I^2 =61.86%), but did not significantly alter the frequency of headaches.

In 2017, the Washington State Health Care Authority (WA HCA) published a technology assessment of treatments for chronic migraine and chronic tension-type headache. [148, 149] The authors identified two small RCTs that evaluated the efficacy of TMS for the treatment of chronic migraine using a sham control. One RCT was considered to be at moderately low risk of bias and the other moderately high risk of bias due to multiple methodological concerns. One of the RCTs found that at four weeks post-treatment, TMS resulted in statistically significant improvement in outcomes compared to sham (low quality of evidence). With regard to safety, this study reported no statistical difference between the TMS and sham group in frequency of study withdrawal due to adverse events, but more TMS-treated patients experienced discomfort compared to sham. In the other RCT, eight weeks-results were reported. At this time-point, no statistical differences were reported between TMS and sham for reduction in migraine attacks or reduction in migraine days and no differences were reported in the frequency of minor adverse events or study withdrawal due to adverse events. The assessment authors concluded that the data in the second RCT was of insufficient quality to draw conclusions.

A 2019 SR published by Stilling evaluated the use of TMS and tDCS for the treatment of headache.[150] A total of 34 studies met inclusion criteria, including 16 rTMS, 6 TMS, and 12 tDCS studies. The quality of the studies was assessed using GRADE and ranged from very low to high. rTMS was found to be the most promising, but few studies reported changes from active treatment greater than sham.

Lan (2017) performed a meta-analysis that included five RCTs and 313 migraine patients.[151] Only one study was identified that assessed the efficacy of TMS on migraine with aura. This study found a significant effect of TMS after the first attack. The remaining four RCTs assessed the effect of TMS on chronic migraine. These studies were found to have statistically significant heterogeneity. The analysis showed no significant effect of TMS on chronic migraine.

Randomized Control Trials

A 2019 RCT published by Granato evaluated the effects of high-frequency rTMS in patients with chronic migraine and medication overuse headache.[152] Of the 26 patients enrolled, 14 completed the study. Half of these received high-frequency rTMS and half received sham treatment. Outcome measures were changes in headache days (HD), headache hours (HH)

and symptomatic drug intake (SDI). These were recorded for 30 days before the beginning of stimulation and during the three following months. There were reductions in all measures in both groups but no significant differences between groups.

Leung (2015) published an RCT that evaluated how rTMS improved headaches for military patients with mild traumatic brain injury (MTBI).[153] Twenty-four patients received rTMS or sham rTMS at the left motor cortex (LMC). Patients were evaluated one week and one-month post treatment. Although the authors concluded rTMS is an effective treatment for MTBI headaches, this study did not evaluate whether the outcomes were sustained long-term.

Rapinesi (2016) published an RCT that evaluated the impact of dTMS on chronic migraines (CM).[154] Fourteen treatment-resistant patients were randomized to receive add-on high-frequency dTMS (n=7) or standard abortive or preventive antimigraine treatment (n=7). Twelve sessions were received over one-month time. Depression symptoms were evaluated during treatment and one month later. Although the authors concluded add-on dTMS is effective in decreasing the intensity and frequency of migraines, this study was limited in size and did not evaluate long-term effects.

PAIN

Systematic Reviews

Che (2021) reported the results of a systematic review of rTMS over the DLPFC for the treatment of chronic and provoked pain.[155] A total of 26 studies met inclusion criteria. A publication bias was identified in the studies of provoked pain but not for chronic pain conditions. Overall, no significant effect was found for TMS across chronic pain conditions. However, there was a significant short-term analgesia effect in neuropathic pain conditions (SMD = -0.87). There was an overall pain reduction identified in the midterm (SMD = -0.53, 24.6 days average) and long-term (SMD = -0.63, three months average) post DLPFC stimulation across pain conditions, but not within specific chronic pain conditions.

A 2019 SR by Ramger analyzed the efficacy of non-invasive brain stimulation for the treatment of central post-stroke pain.[156] Six studies met inclusion criteria. These included one RCT of direct current stimulation and five studies of TMS (three within-subject randomized cross-over studies, one case series, and one prospective cohort). Only one of the cross-over studies was rated as “good/excellent” quality, while the remainder of included studies were rated as “fair” or “poor”. Four studies reported significant decreases in VAS ($p<0.05$). Overall, the authors concluded that there may be a beneficial effect of non-invasive brain stimulation for central post-stroke pain, but that the evidence is limited.

An SR published by Hamid (2019) evaluated the efficacy of TMS for chronic pain. Twelve RCTs met inclusion criteria.[157] Risk of bias was assessed for the included studies and ranged from low to high. Limitations of the studies include that not all clearly specify sham blinding, inconsistent reporting of the type of control, and heterogeneity in treatment protocols. A meta-analysis demonstrated a statistically significant improvement in pain measured by the pain VAS associated with rTMS ($p<0.001$).

Randomized Control Trials

Attal (2021) conducted a multicenter sham-controlled randomized trial of rTMS for neuropathic pain.[158] A total of 152 patients were randomized to receive rTMS to the primary

motor cortex (M1; n=49), rTMS to the dorsolateral prefrontal cortex (DLPFC; n=52), or sham rTMS (n=48). The primary end point was the comparison between active M1-rTMS, active DLPCF-rTMS and sham-rTMS for the change over the 25 weeks (Group × Time interaction) in average pain intensity (from 0 no pain to 10 maximal pain) on the Brief Pain Inventory in patients who received at least one rTMS session (modified intention-to-treat population). Compared to sham, M1-rTMS significantly improved pain intensity, pain relief, sensory dimension of pain, self-reported pain intensity and fatigue, Patient and Clinician Global Impression of Change (PGIC and CGIC). DLPFC-rTMS did not result in outcomes that were significantly different than sham. rTMS to either brain region resulted in no differences from sham for quality of pain, mood, sleep, or quality of life. The most commonly reported side effect was headache, which did not occur at significantly different rates between groups.

Ambriz-Tututi (2016) published a RCT that evaluated the impact of rTMS on patients with chronic low back pain.[159] Eighty-two patients received rTMS, sham stimulation, or physical therapy (PT) for one week and were evaluated with the visual analogue scale (VAS), Short Form McGill pain questionnaire (SF-MPQ), and the Short Form 36 Health Survey. The authors concluded long-term reduction of pain in the rTMS group, but there was no apparent long-term outcome documented.

Malavera (2016) published a randomized, double-blinded, parallel group, single-center RCT to evaluate the impact of rTMS on phantom limb pain (PLP), for land mine victims.[160] Fifty-four patients received rTMS (n=27) or sham stimulation (n=27) five days a week for two weeks and were evaluated 15 and 30 days after treatments. The rTMS group showed significant PLP improvement up to 15 days after treatment, but as the authors noted the study was limited in size and may not have included enough assessment data, nor were the long-term effects evaluated.

Additional studies are not discussed here due to methodological limitations, including low patient numbers and lack of long-term follow-up.[161]

PARKINSON’S DISEASE

Systematic Reviews

Li (2022) conducted a meta-analysis of 32 sham-controlled RCTs of rTMS in patients with Parkinson disease and motor dysfunction (n=1048 patients).[162] Motor dysfunction was assessed using the United Parkinson's Disease Rating Scale part III score. Overall, rTMS had a significant effect on motor symptoms compared to sham (SMD, 0.64; 95% CI, 0.47 to 0.80; p<.0001; I2=64%). High-frequency rTMS to the primary motor cortex was the most effective intervention. Significant benefit of rTMS was also demonstrated for akinesia, rigidity, and tremor.

2022 systematic review and meta-analysis by Cheng evaluated the efficacy of TBS on motor and nonmotor symptoms of Parkinson’s disease.[163] A total of eight studies met inclusion criteria. Of these, two evaluated only in the “off” medicine status (under the anti-Parkinsonism medicine withdrawal status for at least 12 hours), two evaluated only in the “on” anti-Parkinsonism medicine state, and four assessed both the “on” and “off” medicine states. According to the meta-analysis, TBS significantly improved the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score compared to sham in the “off” medicine state (SMD = -0.37; 95% CI -0.65 to -0.09; p<0.01; I^2 = 19%) but not the “on” medicine state (SMD = -0.06; 95% CI -0.37 to 0.25; p=0.69; I^2 = 0%). Statistically significant effects were also reported for

improved slowing of gait in the “off” medicine status (SMD = -0.37; 95% CI -0.71 to -0.03; p = 0.03; I^2 = 0%) and therapeutic effect on PD depression (mean difference = -2.93; 95% CI -5.52 to -0.33; p=0.03). The authors concluded that large, high-quality RCTs are needed to confirm these findings.

Jiang (2020) performed a systematic review and meta-analysis of the effect of rTMS on cognitive function in Parkinson’s disease patients.[164] A total of 14 studies (173 participants) met inclusion criteria. Significant effects of rTMS were identified for the mini-mental state examination (MMSE) for the global cognitive outcome, and executive function. No significant effects were identified for the rest of the cognitive domains (memory, attention, and language ability).

A 2019 SR by Kim evaluated the effect of non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, for freezing of gait in parkinsonism.[165] Seven studies met inclusion criteria. A meta-analysis was performed on the data from the 102 included patients. It showed a significant improvement in freezing of gait questionnaire scores (SMD=0.28; 95% CI 0.01 to 0.55) and turning time (SMD = 0.30; 95% CI 0.02 to 0.58). The effect size was greater when only Parkinson’s disease patients were included.

Qin (2018) published a meta-analysis of RCTs examining high-frequency rTMS for Parkinson’s disease (PD).[166] The primary outcome measure was changes in depressive symptoms in Parkinson’s disease patients and the secondary outcome was changes in motor symptoms. Nine RCTs, with data from 332 participants, were analyzed. Results were reported as mean difference (MD) or standard mean difference (SMD). For the primary outcome, changes in depressive symptoms, rTMS was not better than sham-rTMS (SMD =-0.33, 95% CI -0.83 to 0.17) or selective serotonin re-uptake inhibitors (SSRIs) (SMD =0.07, 95% CI -0.52 to 0.18). The changes in motor symptoms were greater, both compared to sham-rTMS (MD =-2.80, 95% CI -5.45 to -0.15) and SSRIs (MD =-2.70, 95% CI -4.51 to -0.90).

Wagle (2016) published a SR that evaluated how rTMS improved motor symptoms in patients with Parkinson’s disease.[167] Twenty-one clinical trials with an active and control arm were reviewed. The authors concluded that rTMS can improve motor function as an adjunct therapy, but had insufficient data to evaluate specific clinical conditions related to Parkinson’s disease i.e. dyskinesia, bradykinesia, and gait. Larger studies are needed to evaluate clinical features that will have a positive long-term response.

A 2015 SR included 20 sham-controlled RCTs with a total of 470 patients with PD.[168] Sample sizes ranged from 8 to 102. The total effect size of rTMS on Unified Parkinson’s Disease Rating Scale (UPDRS) part III score was 0.46, which is considered a small to medium effect size, and the mean change in the UPDRS-III score (-6.42) was considered to be a clinically important difference. The greatest effect on motor symptoms was from high frequency rTMS over the primary motor cortex (standardized mean difference [SMD] of 0.77, p<0.001) and low-frequency rTMS over other frontal regions (SMD: 0.50, p=0.008). High frequency rTMS at other frontal regions and low frequency rTMS over the primary motor cortex did not have a statistically significant benefit. The largest study (described below) included in the SR was an exploratory, multicenter, double-blind trial that randomized 106 patients to eight weeks of 1-Hz rTMS, 10 Hz rTMS, or sham stimulation over the supplementary motor area.[169] At nine weeks, all groups showed a similar amount of improvement. It cannot be determined from these results if the negative results of the largest trial are due to a lack of effect of rTMS on motor

symptoms in general or to the location of stimulation. Additional study with a larger number of subjects and longer follow-up is needed to determine if high frequency rTMS over the primary motor cortex improves motor symptoms in patients with Parkinson disease.

A SR from 2009 included 10 RCTs with a total of 275 patients with PD.[170] Seven of the studies were double-blind, one was not blinded and two of the studies did not specify whether the raters were blinded. In studies that used high frequency TMS there was a significant improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) with a moderate effect size of -0.58. For low frequency TMS the results were heterogeneous and did not significantly reduce the UPDRS. The analyzed studies varied in outcomes reported, TMS protocol, patient selection criteria, demographics, stages of Parkinson's disease and duration of follow-up, which ranged from immediate to 16 weeks after treatment

Randomized Controlled Trials

He (2021) conducted a randomized sham-controlled study on the effect of iTBS on mild cognitive impairment in Parkinson's disease.[171] A total of 35 PD patients were randomly assigned to receive iTBS (n=20) or sham (n=15) over the left dorsolateral prefrontal cortex for 10 consecutive weekdays. Statistically significant differences in improvement in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Montreal Cognitive Assessment (MoCA) were reported immediately post-intervention for both the iTBS and sham groups and at the three-month follow-up for only the iTBS group ($p<0.05$).

Cohen (2018) reported a double-blind, randomized, sham-controlled study to assess repetitive deep TMS for PD.[172] Forty-eight patients were randomized to sham or real repetitive deep TMS to the primary motor cortex and prefrontal cortex. The primary outcome measures were the total and motor scores of the Unified Parkinson's Disease Rating Scale, and secondary measures were rating of depression and quantitative motor tasks. Both groups improved significantly over the trial period. There was no significant effect of treatment. Side effects were reported to be more common in the repetitive deep TMS group. These effects were transient and reported to be tolerable.

Makkos (2016) published a double-blinded placebo-controlled RCT to determine if rTMS can improve depression for patients with PD.[173] Forty-six patients with mild to moderate depression received rTMS (n=23) or sham stimulation (n=23) for 10 days. Patients were evaluated by the Montgomery-Åsberg Depression Rating Scale at baseline, one day into treatment and 30 days after treatment. The authors concluded results were promising for the rTMS group, but rTMS trials should further evaluate the effects of rTMS on PD patients with severe depression.

A 2013 exploratory multicenter double-blind trial randomized 106 patients to eight weeks of 1 Hz TMS, 10 Hz TMS, or sham stimulation over the supplementary motor area.[169] At nine weeks all groups showed a similar amount of improvement. At the 20-week follow-up only the 1 Hz group showed a significant improvement (6.84 points) in the primary outcome measure, the UPDRS. There was no significant improvement in other outcome measures.

In 2012, Benninger reported a double-blind sham-controlled RCT of brief (six sec) very high frequency (50 Hz) TMS over the motor cortex in 26 patients with mild to moderate Parkinson's disease.[174] Eight sessions of 50 Hz TMS did not improve gait, bradykinesia, or global and motor scores on the UPDRS compared to the sham-treated group. Activities of daily living

were significantly improved a day after the intervention, but the effect was no longer evident at one month after treatment. Functional status and self-reported well-being were not affected by the treatment. No adverse effects of the very high frequency stimulation were identified.

In another study from 2012, Yang randomized 20 patients with Parkinson's disease to 12 brief sessions (six min) of high frequency (5-Hz) TMS or sham TMS over the leg area of the motor cortex followed by treadmill training.[175] Blinded evaluation showed a significant effect of TMS combined with treadmill training on neurophysiological measures, and change in fast walking speed and the timed up and go task. Mean treadmill speed improved to a similar extent in the active and sham TMS groups.

Section Summary

The current evidence is mixed regarding the treatment benefits of TMS in patients with Parkinson's disease. Additional well-designed, RCTs, which control for treatment effect and include a larger number of subjects and longer follow-up, is needed to determine if TMS improves motor symptoms in patients with Parkinson's disease.

STROKE REHABILITATION

Systematic Reviews

Ahmed (2023) completed a SR with network meta-analysis (NMA) to compare the efficacy of non-invasive brain stimulation (NiBS) including transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), theta-burst stimulation (TBS), and transcutaneous vagus nerve stimulation (taVNS) in upper limb stroke rehabilitation.[176] A total of 87 RCTs (3750 participants) were included. Pairwise meta-analysis showed that all NiBS except continuous TBS (cTBS) and cathodal tDCS were significantly more efficacious than sham stimulation for motor function (standardized mean difference [SMD] range 0.42-1.20), whereas taVNS, anodal tDCS, and both low and high frequency rTMS were significantly more efficacious than sham stimulation for ADLs (SMD range 0.54-0.99). The NMA showed that taVNS was more effective than cTBS (SMD:1.00; 95% CI (0.02-2.02)), cathodal tDCS (SMD:1.07; 95% CI (0.21-1.92)), and physical rehabilitation alone (SMD:1.46; 95% CI (0.59-2.33)) for improving motor function. The taVNS ranked highest in improving motor function (SMD: 1.20; 95% CI (0.46-1.95)) and ADLs (SMD:1.20; 95% CI (0.45-1.94)) after stroke. After taVNS, excitatory stimulation protocols (intermittent TBS, anodal tDCS, and HF-rTMS) are most effective in improving motor function and ADLs after acute/sub-acute (SMD range 0.53-1.63) and chronic stroke (SMD range 0.39-1.16).

Chen (2023) published a SR with meta-analysis to summarize the current effectiveness of noninvasive brain stimulation (NIBS) in the treatment of post-stroke sensory dysfunction.[177] A total of 14 RCTs were included (combined n = 804). Moderate-quality evidence suggested that NIBS significantly improved sensory function after stroke, and significant effects were observed up to one year after the intervention. In subgroup analysis, treatment with transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) was significantly more effective than controls for recovery of sensory function in stroke patients. Stimulation of the primary motor cortex (M1), primary somatosensory cortex (S1) or M1 + S1 stimulation sites significantly improved sensory function. NIBS for sensory dysfunction showed significant therapeutic potential in patients with different stages of stroke. No significant effects were observed in subjects with less than 10 NIBS stimulations.

Significant therapeutic effects were observed with either high-frequency or low-frequency rTMS.

Qiao (2022) performed a meta-analysis of RCTs that assessed the effect of rTMS in 433 patients with post-stroke dysphagia.55, Twelve trials that used dysphagia severity rating scales (Dysphagia Grade and Penetration Aspiration Scale) were included. The specific controls used in each study were not specified. Study characteristics included duration of treatment of 1 to 10 days, stimulation frequency of 1 to 10 Hz, and duration of stimulation of 5 to 20 minutes. The analysis favored rTMS (SMD, -0.67; 95% CI -0.88 to -0.45; p<.001; I2=42%). Subgroup analyses identified treatment duration >5 days and rTMS during the subacute phase after stroke as potential situations with greater clinical benefit, but there was no difference in efficacy according to stimulation frequency, location, or duration of each stimulation. The authors noted that publication bias was present and there may be limited clinical applicability of the dysphagia rating scales.

Xie (2021) published an SR and network meta-analysis of rTMS for lower extremity motor function recovery in stroke patients.[178] A total of 18 RCTs met inclusion criteria. The meta-analysis indicated high-frequency rTMS was superior to sham in promoting lower extremity motor function recovery. Based on the five relevant studies, the meta-analysis also indicated that high-frequency rTMS resulted in higher amplitudes of motor evoked potentials than low-frequency rTMS or sham stimulation.

Dionísio (2018) published an SR on the efficacy of rTMS for recovery of nonmotor functions following stroke.[179] A total of 38 studies met the inclusion criteria on the topics of aphasia, dysphagia, neglect, and visual extinction. No meta-analysis was completed. Most of the included studies had small patient numbers. The authors concluded that the variability that was present in terms of patient selection, treatment protocols, and outcome measures, limits the conclusions that can be drawn.

Zhang (2017) published an SR and meta-analysis evaluating the effects of rTMS on upper-limb motor function after stroke.[180] A search for studies published before October 2016 was performed, yielding 34 RCTs with a total of 904 participants (range, 6 to 108 participants). Pooled estimates found improvement with rTMS for both short-term (SMD=0.43; p<0.001) and long-term (SMD=0.49; p<0.001) manual dexterity. Of the 28 studies reporting on adverse events, 25 studies noted none. Mild adverse events, such as headache and increased anxiety were reported in three studies. The review was limited by variation in TMS protocols between studies.

Sebastianelli (2017) published an SR including 67 studies on the use of low-frequency rTMS of the unaffected hemisphere in stroke patients.[181] No meta-analyses were included. The SR concluded that rTMS applied to the unaffected hemisphere following stroke appears to be safe and has potential to be a useful adjuvant strategy for neurorehabilitation but that further research is needed.

McIntyre (2017) published an SR on the use of rTMS for spasticity post-stroke. Ten studies met the inclusion criteria, two of which were RCTs.[182] The RCTs were rated on the Physiotherapy Evidence Database with scores of eight to nine. Meta-analyses were conducted separately for the uncontrolled studies and the RCTs. Whereas the uncontrolled pre-post studies found significant improvements in spasticity, the RCTs did not.

A 2017 SR published by Fan included 12 studies total examining the effect of noninvasive brain stimulation in the recovery of unilateral neglect in poststroke patients.[183] Eleven RCTs were included in the meta-analysis. Techniques of noninvasive brain stimulation included transcranial direct current stimulation, theta-burst TMS, and rTMS. The quality of included RCTs was good to excellent, with PEDro scores of eight or nine in seven studies and six to eight in the remainder. A moderate degree of heterogeneity was identified in rTMS and cTBS studies. The meta-analysis showed a significant effect of rTMS immediately following treatment and at follow-up.

In 2016, Graef reported a meta-analysis of rTMS combined with upper-limb training for improving function after stroke.[184] Included were 11 sham-controlled randomized trials with 199 patients that evaluated upper-limb motor/functional status and spasticity; eight RCTs with sufficient data were included in the meta-analysis. These studies were considered to have a low-to-moderate risk of bias. In the overall analysis, there was no benefit of rTMS on upper-limb function or spasticity (SMD=0.03; 95% CI -0.25 to 0.32).

Liao (2016) published a SR that evaluated the impact of rTMS on dysphagia in stroke patients.[185] Six RCTs with a total of 163 patients were reviewed. The authors concluded that patients had improved, four weeks after treatment with low or high frequency rTMS. High frequency rTMS may be more beneficial than low frequency rTMS. This SR did not include long-term outcomes.

A 2015 meta-analysis by Li included four RCTs on rTMS over the right pars triangularis for patients (n=137) with aphasia after stroke.[186] All of the studies used double-blinding, but therapists were not blinded. Every study used a different outcome measure, and the sample sizes were small (range from 12 to 40). Meta-analysis showed a medium effect size for naming (p=0.004), a trend for a benefit on repetition (p=0.08), and no significant benefit for comprehension (p=0.18). Additional study in a larger number of patients is needed to determine with greater certainty the effect of this treatment on aphasia after stroke.

A 2014 meta-analysis by Le assessed the effect of rTMS on recovery of hand function and excitability of the motor cortex after stroke.[187] Eight RCTs with a total of 273 participants were included in the review. The quality of the studies was rated moderate to high, although the size of the studies was small. There was variability in the time since stroke (five days to 10 years), in the frequency of rTMS applied (1 Hx to 25 Hx for one sec to 25 mins per day), and the stimulation sites (primary motor cortex or premotor cortex of the unaffected hemisphere). Meta-analysis found a positive effect on finger motor ability (four studies, n=79, standardized mean difference of 0.58) and hand function (three studies, n=74, standardized mean difference of -0.82), but no significant change in motor evoked potential (n=43) or motor threshold (n=62).

A 2013 Cochrane review included 19 trials with a total of 588 participants on the effect of TMS for improving function after stroke.[188] The two largest trials included in the review showed that TMS was not associated with a significant improvement in the Barthel Index score. Four trials (n=73) found no significant effect for motor function. Subgroup analysis for different stimulation frequencies or duration of illness also did not show a significant benefit of rTMS when compared to sham rTMS or no treatment. The review concluded that current evidence does not support the routine use of TMS for the treatment of stroke.

Randomized Controlled Trials

Dai (2023) published a single-blinded, randomized controlled trial, to evaluate the effectiveness of 10-Hz cerebellar rTMS in poststroke dysphagia (PSD) patients with infratentorial stroke (IS).[189] Patients (n = 42) with PSD with subacute in infratentorial stroke (IS) were allocated to three groups: bilateral cerebellar rTMS (biCRB-rTMS), unilateral cerebellar rTMS (uniCRB-rTMS), or sham-rTMS. The stimulation parameters were 5 trains of 50 stimuli at 10 Hz with an interval of 10 s at 90% of the thenar resting motor threshold (RMT). The Functional Oral Intake Scale (FOIS) was assessed at T0 (baseline), T1 (day 0 after intervention), and T2 (day 14 after intervention), whereas the Dysphagia Outcome and Severity Scale (DOSS), Penetration Aspiration Scale (PAS), and neurophysiological parameters were evaluated at T0 and T1. Significant time and intervention interaction effects were observed for the FOIS score ($F = 3.045$, $p = 0.022$). The changes in the FOIS scores at T1 and T2 were both significantly higher in the biCRB-rTMS group than in the sham-rTMS group ($p < 0.05$). The uniCRB-rTMS and biCRB-rTMS groups demonstrated greater changes in the DOSS and PAS at T1, compared with the sham-rTMS group ($p < 0.05$). Bilateral corticobulbar tract excitability partly increased in the biCRB-rTMS and uniCRB-rTMS groups at T1, compared with T0. The percent changes in corticobulbar tract excitability parameters at T1 showed no difference among three groups.

Zhong (2023) published an RCT to evaluate the effect of high-frequency cerebellar rTMS on poststroke dysphagia.[190] This was a randomized, sham-controlled, double-blind trial. A total of eighty-four study participants were randomly assigned into the cerebellum and control groups. The cerebellum group received bilateral 10Hz rTMS treatment of the pharyngeal motor area of the cerebellum. The control group was administered with sham rTMS of the pharyngeal motor area of the cerebellum. All patients underwent the same conventional swallowing rehabilitation training after the intervention 5 days a week for a total of 10 days. The interaction between time and intervention had a significant effect on PAS ($P<0.001$) and Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS) ($P<0.001$). Compared to the control group, the cerebellum group exhibited significantly improved clinical swallowing function scores (PAS: $P=0.007$, FEDSS: $P=0.002$). Bilateral cerebellar rTMS is a potential new neurorehabilitation technique for post-stroke dysphagia. The authors comment on the need for more studies investigating the therapeutic mechanism for cerebellar rTMA.

Wang (2020) conducted an RCT to determine the efficacy of high-frequency TMS over the contralesional motor cortex for motor recovery in severe hemiplegic stroke patients. Patients with ischemic or hemorrhagic stroke in the territory of the middle cerebral artery were randomized to receive 10 Hz rTMS (n=15), 1 Hz rTMS (n=15) or sham (n=15). Treatment was applied over the contralesional motor cortex (M1) prior to physiotherapy daily for two weeks. Clinical efficacy was assessed by the FMA score (a standardized motor impairment scale) and the Barthel Index (BI; a measure of daily life ability). According to a repeated-measures mixed analysis of variance, all patients had a significant recovery from impairment and improvement in activities of daily living postintervention compared to pre-treatment. There were no statistically significant differences between the 1 Hz rTMS group and the sham group. The 10 Hz rTMS group FMA and BI scores were significantly higher than the 1 Hz rTMS group and the sham group ($p<0.05$ and $p<0.005$, respectively). Neurophysiological measures and muscle activation were also improved in all groups, but significantly greater in the 10 Hz rTMS group ($p<0.05$ for both).

An RCT published by Ren (2019) assessed the use of rTMS over the right pars triangularis of the posterior inferior frontal gyrus (pIFG) and the right posterior superior temporal gyrus (pSMG) for the treatment of poststroke global aphasia. A total of 45 patients were

randomized to receive one of three treatments: rTMS over the right triangular part of the pIFG, rTMS over the right pSTG, or sham stimulation. Outcomes reported were aphasia quotient (AQ) scores obtained from the Chinese version of the Western Aphasia Battery (WAB), spontaneous speech, auditory comprehension, and repetition. These were measured at baseline and immediately after three weeks (15 days) of experimental treatment. There were statistically significant increases in the right pSTG rTMS group compared to sham for auditory comprehension, repetition, and AQ ($p<0.05$). There were statistically significant increases in the pIFG rTMS group compared with sham for repetition, spontaneous speech, and AQ ($p<0.05$).

Choi (2018) examined the effects of high frequency rTMS on hemiplegic shoulder pain in patients with chronic stroke.[191] A total of 24 chronic stroke patients with chronic hemiplegic shoulder pain were randomly assigned to receive real rTMS (10 sessions of high-frequency stimulation) or sham rTMS. Pain was evaluated using the Numeric Rating Scale (NRS) at one day and one, two, and four weeks after treatment. Additional measures were changes the Motricity Index (MI-UL) and modified Brunnstrom Classification (MBC), which were used to evaluate changes in upper-limb motor function. There was a significant improvement in the NRS score at all time points in the real rTMS but not sham group. No significant changes were observed in the measures of upper-limb motor function.

Forogh (2017) performed a randomized double-blind sham-controlled trial on TMS for stroke recovery.[192] Twenty-six patients were evaluated. Patients received five days of low-frequency rTMS or sham rTMS. Follow-up was conducted at 12 weeks. Static postural stability, balance, muscle strength, and motor recovery were assessed. Significant differences between real and sham treatment groups were observed for static postural stability, balance, and muscle strength. There was significant improvement in muscle recovery compared to baseline in the real rTMS group. However, the groups were different in this measure at baseline, and they were not significantly different at three or 12 weeks.

Huang (2017) reported results of an RCT on the use of rTMS for the recovery of lower extremities after stroke.[193] Thirty-eight subacute stroke patients with significant leg disabilities received real or sham rTMS followed by 45 minutes of physical therapy for three weeks. Real rTMS consisted of 15 minutes of 1-Hz treatment over the contralesional motor cortex representing the quadriceps muscle. Recovery in ambulation, balance, motor functions, and activities of daily living were assessed. No significant differences between groups were identified.

Guan (2017) performed a prospective, double-blind, randomized, sham-controlled study to assess the effectiveness of rTMS on motor recovery after stroke.[194] Forty-two were assessed and found eligible for the study and following dropout during the study, 27 were included in the final analysis. Patients were randomized to receive real or sham high-frequency rTMS treatment. Treatment consisted of 10 consecutive days of 5 Hz rTMS applied to the ipsilesional M1. Motor functional scores, including the National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), Fugl-Meyer Assessment Upper Limb/Lower Limb (FMA-UL/LL), modified Rank Score (mRS), and the resting motor threshold (RMT) of the hemiplegic limb, were assessed. At one month following treatment, there were significant differences in score improvement from baseline in HIHSS, BI, and FMA-UL. At three months, six months, and one year the only score for which a significant difference in improvement was seen was FMA-UL, representing a lasting improvement in upper extremities function.

Additional RCTs of the efficacy of TMS for post-stroke recover have been published that are preliminary (feasibility) studies and/or have serious methodological limitations, such as very small patient populations or lack of a sham control, that render outcomes unreliable.

Section Summary

Evidence consists of a number of RCTs and SRs of the effect of TMS on recovery from stroke. Results are conflicting, and efficacy may depend on the location of the stroke and frequency of the TMS. Additional study is needed to determine whether TMS facilitates standard physiotherapy in patients with stroke.

TINNITUS

Systematic Reviews

The Washington HTA published a technology assessment in 2020 that reviewed non-invasive, non-pharmacological treatments for tinnitus. The authors identified a total of 10 parallel-assignment RCTs and 9 crossover RCTs from 19 publications describing results of rTMS stimulation interventions compared to sham stimulation. Intervention protocols were heterogeneous. Most of the 18 RCTs reporting measures of tinnitus distress or disability did not report a significant difference between active and sham rTMS. No significant differences between groups were reported for depression, anxiety, and sleep outcomes in the five RCTs reporting on psychological measures or quality of life in the one reporting RCT. A total of 14 studies reported on adverse events. In five, no adverse events were reported and in three, results were not reported by group. Of the six studies that reported differences by group, three reported similar incidence between groups, two reported higher incidence of adverse events in the active rTMS group and one reported a higher incidence of adverse events in the sham rTMS group.

Randomized Control Trials

In 2017, Sahlsten published a prospective randomized placebo-controlled study to investigate the effects of rTMS using electric field navigation for tinnitus.[196] Thirty-nine patients were randomized to receive 10 sessions of 1 Hz rTMS or placebo targeted to the region of the left auditory cortex corresponding to tonotopic representation of tinnitus pitch. Primary outcomes were tinnitus intensity represented by the visual analogue scores (VAS 0-100), annoyance and distress, and the Tinnitus Handicap Inventory (THI). These were evaluated immediately following treatment and one, three, and six months later. All measures tested decreased significantly in both groups. No significant differences between groups were reported.

Landgrebe (2017) reported a multicenter randomized, sham-controlled trial that investigated the efficacy and safety of rTMS for chronic tinnitus.[197] A total of 163 patients were randomized to receive real or sham rTMS. Treatment consisted of 10 sessions of 1 Hz to the left temporal cortex. Tinnitus questionnaire scores were taken at baseline and at the end of treatment. The primary outcome was change in this score and secondary outcome measures were depression and quality of life. There were no significant differences in any measures between groups at the end of the trial.

Lehner (2016) published a two-arm parallel group RCT that evaluated 74 patients who received ten sessions of triple-site stimulation (n=25), single-site stimulation (n=24) or placebo (n=25).[198] Patients answered a tinnitus questionnaire day one and 12 and at follow-up three and six months later. The authors concluded rTMS reduces tinnitus severity in both

groups the single and triple site groups, with no differences between them. Larger RCTs are needed to determine long-term effects, objective outcomes and appropriate treatment protocols.

OTHER MEDICAL INDICATIONS

SRs and RCTs have been published exploring the efficacy of TMS for a variety of central nervous system-related disorders such as central pain related to spinal cord injury, dysphagia, blepharospasm, amyotrophic lateral sclerosis (ALS), multiple sclerosis, chronic pain, substance abuse, burning mouth syndrome, phantom limb sensations, cravings, traumatic brain injury, concussion, symptom management in breast cancer, and treatment of obesity.[176, 199-268] All of these studies had one or more significant methodological limitations, including but not limited to small patient populations, short follow-up times, heterogeneous treatment parameters, continued use of concurrent therapies, and/or significant loss to follow-up. Generally, the authors agreed that larger, long-term RCTs are needed, along with better defined optimal treatment parameters for administering TMS.

PRACTICE GUIDELINE SUMMARY

MOVEMENT DISORDER SOCIETY

The Movement Disorder Society (MDS) published an evidence-based review of treatments for motor (updated in 2018) and non-motor (updated in 2019) symptoms of Parkinson's disease.[269, 270] The reviews found insufficient evidence to make adequate conclusions on the efficacy of rTMS for the treatment of motor symptoms or depression in Parkinson's disease. The MDS did note that evidence regarding TMS treatment of depression in the general population is growing; therefore, it concludes that the practice implication is "possibly useful."

In 2008, the society also conducted a literature review describing current management practices for tic disorder and noted that study results regarding the use of TMS as a treatment for tics varied.[271]

AMERICAN PSYCHIATRIC ASSOCIATION

In 2018, the American Psychiatric Association published consensus recommendations on rTMS for the treatment of depression.[272] The guidelines state, "Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant `therapy." The recommendations include information on the following variables: clinical environment, operator requirements, documentation, coils, cortical targets, coil positioning methods, determination of motor threshold, number of treatment sessions for acute treatment, and allowable psychotropic medications during TMS treatment.

The APA's guidelines on the treatment of patients with obsessive-compulsive disorder (2007, reaffirmed in 2012) state that "findings of the four published trials of repetitive TMS (rTMS) are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice."

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology published an evidence-based practice guideline in 2016 on the treatment of restless legs syndrome (RLS) in adults.[273] It stated, “For patients or clinicians wanting to use nonpharmacologic approaches to treat RLS…clinicians may consider prescribing near-infrared spectroscopy (NIRS) or repetitive transcranial magnetic stimulation (rTMS) (where available) (Level C).” This recommendation is based on one Class II study.

DEPARTMENT OF VETERANS AFFAIRS/DEPARTMENT OF DEFENSE

The 2022 Veteran's Affairs/Department of Defense guideline for management of major depressive disorder recommends offering rTMS to patients who have experienced partial response or no response to an adequate trial of 2 or more pharmacologic treatments (strength of recommendation: weak).[274] Recommended options for the second treatment attempt after the initial therapy tried include switching to another antidepressant or adding augmentation therapy with a second-generation antipsychotic. The recommendation for rTMS was graded as weak due to limitations of the available literature including small study effects, high rates of discontinuation, lack of allocation concealment, and the practical limitations of the need for daily treatment and lack of widespread access to facilities that offer this therapy. The guideline also concluded that there is limited evidence to recommend for or against theta-burst stimulation for treatment of depression.

In 2019, the Department of Veterans Affairs (VA)/Department of Defense (DoD) published an update to its 2010 evidence-based clinical practice guideline for the management of stroke rehabilitation.[275] The guideline includes the following recommendation regarding TMS:

> There is insufficient evidence to recommend for or against repetitive transcranial magnetic stimulation to improve upper or lower extremity motor function. (Recommendation rating: Neither For Nor Against; Reviewed, New-added)

A clinical practice guideline on the primary care management of headache published in 2020 by the VA/DoD states that there is insufficient evidence to recommend for or against Transcranial magnetic stimulation for headache (Recommendation rating: Neither For nor Against; Reviewed, New-added).[276]

A clinical practice guideline on management and rehabilitation of post-acute mild traumatic brain injury published in 2021 by the VA/DoD recommends against the use of rTMS for the treatment of symptoms attributed to mild traumatic brain injury (Recommendation rating: Weak Against; Reviewed, New-added).[277]

SUMMARY

It appears that transcranial magnetic stimulation (TMS) delivered as repetitive TMS (rTMS) or Theta Burst TMS (iTBS) may improve depression for some people with major depressive disorder. Despite the weaknesses in the published clinical evidence and limited guideline support, TMS has become a recognized standard of care for treatment resistant major depressive disorder. Therefore, TMS may be considered medically necessary for up to 36 sessions, one session per day as a treatment of major depressive disorder when policy criteria are met. Additional sessions may be considered medically necessary when continuation criteria are met.

Transcranial magnetic stimulation (TMS) is not clinically indicated for major depressive disorder except in the clinical scenarios addressed in the criteria. Therefore, TMS is considered not medically necessary when Criterion I. is not met.

There is not enough research to show that transcranial magnetic stimulation (TMS) improves health outcomes for any condition other than major depressive disorder. Therefore, TMS is considered investigational as a treatment of all other conditions.

There is not enough evidence to show that treatment using an accelerated transcranial magnetic stimulation (TMS) protocol is superior to conventional protocols to improves health outcomes. Therefore, the use of accelerated TMS protocols is considered investigational for all indications. This includes the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol.

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CODES

Codes	Number	Description
CPT	0858T	Externally applied transcranial magnetic stimulation with concomitant measurement of evoked cortical potentials with automated report
	0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission,

Codes	Number	Description
		generation of the target, motor threshold–starting location, neuronavigation files and target report, review and interpretation
	0890T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day
	0891T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day
	0892T	Accelerated, repetitive high-dose functional connectivity MRI–guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent motor threshold redetermination with delivery and management, per treatment day
	90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
	90868	;subsequent delivery and management, per session
	90869	;subsequent motor threshold re-determination with delivery and management
HCPCS	None	

Date of Origin: *April 2002*

Regence

Medical Policy Manual Medicine, Policy No. 150

Coverage of Treatments Provided in a Clinical Trial

Effective: February 1, 2025

Next Review: November 2025
Last Review: December 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

Effective January 1, 2014, the Affordable Care Act (ACA) requires group health plans or a health insurance issuer offering group or individual health insurance coverage to provide coverage for routine patient costs associated with participating in an approved clinical trial. This policy is written to assist in applying Sec. 2709 of the ACA, Coverage for Individuals Participating in Approved Clinical Trials.

MEDICAL POLICY CRITERIA

Routine patient costs associated with approved clinical trials may be considered **medically necessary** for qualified individuals with respect to treatment of cancer or other life threatening disease or condition, when the Affordable Care Act definitions for clinical trial participation are met.

- See Background for definitions.
- See Policy Guidelines for clinical trial registry resource.

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

POLICY GUIDELINES

ClinicalTrials.gov includes a registry of publicly and privately supported clinical studies.

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. Pertinent History and Physical, including specific diagnosis and treatment history
2. Clinical trial name and the NCT number
3. Phase of the trial
4. Currently planned, requested interventions
5. Anticipated possible interventions

CROSS REFERENCES

1. COVID-19 Testing, Laboratory, Policy No. 74

BACKGROUND

DEFINITIONS[1]

- Routine patient costs
    - Routine patient costs *include* all items and services consistent with the coverage provided in the plan (or coverage) that is typically covered for a qualified individual who is not enrolled in a clinical trial.
    - Routine patient costs *do not include* the investigational item, device, or service, itself; items and services that are provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient; or a service that is clearly inconsistent with widely accepted and established standards of care for a particular diagnosis.

- Approved clinical trial

  An approved clinical trial is defined as a phase I, phase II, phase III, or phase IV clinical trial that is conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition, and that is described by any of the following:

    - The study or investigation is approved or funded by one or more of the following:
        - The National Institutes of Health
        - The Centers for Disease Control and Prevention
        - The Agency for Health Care Research and Quality
        - The Centers for Medicare & Medicaid Services
        - A cooperative group or center of any of the above four entities or the Department of Defense or the Department of Veterans Affairs
        - A qualified non-governmental research entity identified in the guidelines issued by the National Institutes of Health for center support grants

        - The Department of Veterans Affairs, the Department of Defense or the Department of Energy if the study or investigation has been reviewed and approved through a system of peer review that the Secretary determines to be comparable to the system of peer review of studies and investigations used by the National Institutes of Health, and assures unbiased review of the highest scientific standards by qualified individuals who have no interest in the outcome of the review; OR
    - The study or investigation is conducted under an investigational new drug application reviewed by the Food and Drug Administration; OR
    - The study or investigation is a drug trial that is exempt from having such an investigational new drug application.

- Life-threatening condition

  A life-threatening condition is defined as any disease or condition from which the likelihood of death is probable unless the course of the disease or condition is interrupted.

- Qualified individual

  A participant who is a beneficiary in a health plan who is eligible to participate in an approved clinical trial according to the trial protocol with respect to treatment of cancer or another life-threatening disease or condition and either:

    - The referring health care professional is a participating health care provider and has concluded that the individual's participation in such trial would be appropriate based upon the individual meeting the clinical trial eligibility requirements; or
    - The participant or beneficiary provides medical and scientific information establishing that the individual's participation in such trial would be appropriate based upon the individual meeting the clinical trial eligibility requirements.

REFERENCES

1. Affordable Care Act, Section 2709. [cited 11/24/2024]. 'Available from:' http://www.hhs.gov/sites/default/files/ppacacon.pdf.

CODES

Codes	Number	Description
		Services provided as part of a phase I clinical trial
	S9990	Services provided as part of a phase II clinical trial
		Services provided as part of a phase III clinical trial

Date of Origin: *November 2013*

Regence

Medical Policy Manual Medicine, Policy No. 151

Confocal Laser Endomicroscopy

Effective: November 1, 2024

Next Review: July 2025
Last Review: September 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

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows *in vivo* microscopic imaging of cells during endoscopy. CLE is proposed for a variety of purposes, especially as a real-time alternative to histology during colonoscopy and for targeting areas to undergo biopsy in patients with inflammatory bowel disease and Barrett esophagus.

MEDICAL POLICY CRITERIA

Use of confocal laser endomicroscopy is considered **investigational** for all indications.

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

CROSS REFERENCES

1. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
2. In Vivo Analysis of Colorectal Polyps, Medicine, Policy No. 104

BACKGROUND

CLE involves using light from a low-power laser to illuminate tissue and, subsequently, the same lens detects light reflected from the tissue through a pinhole. The term confocal refers to having both illumination and collection systems in the same focal plane. Light reflected and scattered at other geometric angles that is not reflected through the pinhole is excluded from detection, which dramatically increases the special resolution of CLE images.

Endoscope-based and probe-based systems have been cleared by the U.S. Food and Drug Administration (FDA). Endoscope-based systems incorporate a confocal probe onto the tip of a conventional endoscope. Image collection scan rates vary by device. Probe-based systems place a probe through the biopsy channel of a conventional endoscope. Depth of imaging and field of view varies by device. As pointed out in review articles, the limited viewing area emphasizes the need for careful conventional endoscopy to target the areas for evaluation. Both CLE systems are optimized using a contrast agent. The most widely used agent is intravenous fluorescein, which is FDA-approved for ophthalmologic imaging of blood vessels when used with a laser scanning ophthalmoscope.

Unlike techniques such as chromoendoscopy, which are primarily intended to improve the sensitivity of colonoscopy, CLE is unique in that it is designed to immediately characterize the cellular structure of lesions. CLE can thus potentially be used to make a diagnosis of polyp histology, particularly in association with screening or surveillance colonoscopy, which could allow for small hyperplastic lesions to be left in place rather than removed and sent for histologic evaluation. This would reduce risks associated with biopsy and reduce the number of biopsies and histologic evaluations. Another key potential application of CLE technology is targeting areas for biopsy in patients with Barrett esophagus undergoing surveillance endoscopy. This is an alternative to conducting random biopsies during surveillance and has the potential to reduce the number of biopsies and/or improve the detection of dysplasia. Other potential uses of CLE under investigation include better diagnosis and differentiation of conditions such as gastric metaplasia, lung cancer, and bladder cancer.

As noted previously, limitations of CLE systems include a limited viewing area and depth of view. An additional limitation is the lack of standardized systems for classifying lesions viewed with CLE devices. Although there is not currently an internationally accepted classification system for colorectal lesions, two systems have been developed that have been used in a number of studies conducted in different countries. These are the Mainz criteria for endoscopy-based CLE devices and the Miami classification system for probe-based CLE devices.[1] Lesion classification systems are less developed for non-gastrointestinal lesions viewed by CLE devices, e.g., those in the lung or bladder. Another potential limitation of CLE is the learning curve for obtaining high-quality images and classifying lesions. Although several recent studies have found that the ability to acquire high-quality images and interpret them accurately can be learned relatively quickly, these studies were limited to colorectal applications of CLE.[2, 3]

Regulatory Status

Several CLE devices have been cleared for marketing by the FDA. These include:

Cellvizio® (Mauna Kea Technologies): This device consists of a confocal laser system, proprietary software, a flat-panel display and miniaturized fiber optic probes. Since 2006, Mauna Kea has received ten FDA approvals for Cellvizio® systems, most recently in May 2016

(FDA no.'s: K160416, K150831, K151593, K141358, K133466, K132389, K123676, K122042, K120208, K111047, and K061666).

EC-3870CLIK Confocal Video Colonoscope (Pentax Medical Company): This is an endoscopy-based CLE system which consists of the EC-3870CLIK, Confocal Video Colonoscope (K042741) and the ISC-1000 Pentax Confocal Laser System (K042740). The device must be used with a Pentax Video Processor. According to FDA materials, the intended use of the device is to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract.

EVIDENCE SUMMARY

COLORECTAL LESIONS

Ideally, the evaluation of the safety and efficacy of confocal laser endomicroscopy (CLE) as a diagnostic tool would be based on randomized controlled trials (RCTs) comparing CLE to conventional diagnostic methods, such as biopsy with histology for analysis of colorectal lesions. The evidence for the use of CLE is best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. Validation of the clinical use of any diagnostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting abnormal histology that is present or in excluding an abnormality that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Multiple studies have evaluated the diagnostic accuracy of CLE for patients undergoing screening or surveillance colonoscopy. Several systematic reviews of studies evaluating the diagnostic accuracy of CLE compared to a reference standard have been published. Descriptions of several systematic reviews and representative diagnostic accuracy studies are included below.

Systematic Reviews

A 2018 systematic review by Lord analyzed the diagnostic accuracy of several optical imaging techniques for in vivo lesion characterization in colonic inflammatory bowel disease (IBD).[4] A total of 22 studies were identified assessing performance of virtual chromoendoscopy, dye-based chromoendoscopy, magnification endoscopy, and confocal laser endomicroscopy. A bivariate meta-analysis was performed. Pooled sensitivities of real-time CLE, magnification endoscopy, virtual chromoendoscopy, and dye-based chromoendoscopy were 91% (95%CI 66% to 98%), 90% (95%CI 77% to 96%), 86% (95%CI 62% to 95%), and 67% (95%CI 44% to 84%), respectively. Pooled specificities were 97% (95%CI 94% to 98%), 87% (95%CI 81% to 91%), 87% (95% CI 72% to 95%), 86% (95%CI 72% to 94%), for the same methods, respectively. The authors concluded that real-time CLE is highly accurate for differentiating neoplastic from non-neoplastic lesions in patients with colonic IBD, but also note that most

CLE studies were performed by single expert users within tertiary centers, which may confound results.

In 2013, Su reviewed studies on the efficacy of CLE for discriminating colorectal neoplasms from non-neoplasms,[5] Studies needed to use histologic biopsy as the reference standard and in which the pathologist and endoscopist were blinded to each other's findings. Included studies also used a standardized CLE classification system. Patient populations included individuals at increased risk of colorectal cancer due to personal or family history, patients with previously identified polyps, and/or patients with IBD. Two reviewers independently assessed the quality of individual studies using the modified Quality Assessment Of Diagnostic Accuracy Studies (QUADAS) tool, and studies considered to be at high risk of bias were excluded from further consideration. A total of 15 studies with 719 adult patients were found to be eligible for the systematic review. All were single-center trials and two were available only as abstracts. In all the studies, suspicious lesions were first identified by conventional white-light endoscopy with or without chromoendoscopy and then further examined by CLE. A pooled analysis of the 15 studies found an overall sensitivity of CLE of 94% (95% CI 0.88 to 0.97) and specificity of 95% (95% CI 0.89 to 0.97), compared to histology. Six of the studies included patients at increased risk of colorectal cancer (CRC) who were undergoing surveillance endoscopy, five studies included patients with colorectal polyps and four studies included patients with IBD. In a predefined subgroup analysis by indication for screening, the pooled sensitivity and specificity for surveillance studies was 94% (95% CI, 90% to 97%) and 98% (95% CI 97% to 99%), respectively. For patients presenting with colorectal polyps, the pooled sensitivity of CLE was 91% (95% CI 87% to 94%) and specificity was 85% (95% CI 78% to 90%). For patients with IBD, the pooled sensitivity was 83% (95% CI 70% to 92%) and specificity was 90% (95% CI 87% to 93%). In other predefined subgroup analyses, the summary sensitivity and specificity was significantly higher ($p<0.001$) in studies of endoscopy-based CLE (97% and 99%, respectively) than studies of probe-based CLE (87% and 82%, respectively). In addition, the summary sensitivity and specificity was significantly higher ($p<0.01$) with real-time CLE in which the macroscopic endoscopy findings were known (96% and 97%, respectively) than with blinded CLE in which recorded confocal images were subsequently analyzed without knowledge of macroscopic endoscopy findings (85% and 82%, respectively).

Another systematic review was published in 2013 by Dong.[6] The investigators included studies that assessed the diagnostic accuracy of CLE compared with conventional endoscopy. They did not explicitly state that the reference standard was histologic biopsy, but this was the implied reference standard. A total of six studies were included in a meta-analysis. All of the studies were prospective, and at least five included blinded interpretation of CLE findings (in one study, it was unknown whether interpretation was blinded). In a pooled analysis of data from all six studies, the sensitivity was 81% (95% CI 77% to 85%) and the specificity was 88% (95% CI 85% to 90%). The authors also conducted a subgroup analysis by type of CLE used. When findings from the two studies on endoscopy-based CLE were pooled, the sensitivity was 82% (95% CI 69% to 91%) and the specificity was 94% (95% CI 91% to 96%). Two studies may not have been a sufficient number to obtain a reliable estimate of diagnostic accuracy. When findings from the 4 studies on probe-based endoscopy were pooled, the sensitivity was 81% (95% CI 76% to 85%) and the specificity was 75% (95% CI 69% to 81%).

A 2013 systematic review by Wanders searched for studies that reported diagnostic accuracy of studies on any of several new technologies used to differentiate between colorectal neoplasms and non-neoplasms.[7] To be included in the review, studies needed to use the technology to differentiate between non-neoplastic and neoplastic lesions and to use

histopathology as the reference standard. Blinding was not an inclusion criterion. Eleven eligible studies were identified that included an analysis of CLE. A pooled analysis of study findings yielded an estimated sensitivity of 93.3% (95% CI 88.4 to 96.2) and a specificity of 89.9% (95% CI 81.8% to 94.6%). A meta-analysis limited to the five studies that used endoscopy-based CLE found a sensitivity of 94.8% (95% CI 90.6% to 98.92%) and a specificity of 94.4% (95% CI 90.7% to 99.2%). When findings of the six studies on probe-based CLE were pooled, the sensitivity was 91.5% (86.0% to 97.0%) and the specificity was 80.9 (95% CI 69.4% to 92.4%).

Nonrandomized Studies

Ohmiya (2017) evaluated the ability of CLE to differentiate among ulcerative colitis (UC)-associated neoplasia (differentiated type or undifferentiated type), sporadic adenoma, and circumscribed regenerative lesions.[8] The authors examined 12 patients with suspected UC-associated neoplasia with probe-based CLE and compared findings with pathological diagnoses determined by magnifying chromoendoscopy with crystal violet and narrow band imaging. Sensitivity, specificity, and accuracy of CLE were 100%, 83%, and 92%, respectively. The authors stated that CLE was helpful in evaluating suspected UC-associated neoplasia, but it is limited by the small sample size.

In 2017, Kim evaluated probe-based CLE for feasibility and safety in evaluating colorectal submucosa following removal of colorectal neoplasms.[9] Colorectal submucosa were classified as negative or indicative of carcinoma infiltration. The results were compared to pathological findings. The sensitivity, specificity, and accuracy of the classifications were 91.7, 86.8, and 88.0 %, respectively. The authors concluded that CLE is useful but that large-scale prospective studies are needed.

In a 2012 study by Shadid two methods of analyzing CLE images, real-time diagnosis and blinded review of video images after endoscopy (known as “offline” diagnosis), were compared.[10] The study included 74 patients with a total of 154 colorectal lesions. Eligibility criteria were similar to the Buchner study (see above); the included patients undergoing surveillance or screening colonoscopy. Patients underwent white-light colonoscopy and identified polyps were also evaluated with virtual chromoendoscopy and probe-based CLE. Intravenous fluorescein sodium was administered after the first polyp was identified. At the time of examination, an endoscopist made a real-time diagnosis based on CLE images. Based on that diagnosis, the patient underwent polypectomy, biopsy or endoscopic mucosal resection, and histopathologic analysis was done on the specimens. The CLE images were then de-identified and then reviewed offline by the same endoscopist at least one month later. At the second review, the endoscopist was blinded to the endoscopic and histopathologic diagnosis. Of the 154 polyps, 74 were found by histopathologic analysis to be non-neoplastic and 80 were neoplastic (63 tubular adenomas, 12 tubulovillous adenomas, three mixed hyperplastic-adenoma polyps and two adenocarcinomas). Overall, there was not a statistically significant difference in the diagnostic accuracy of real-time CLE diagnosis and blinded offline CLE diagnosis (i.e., confidence intervals overlapped). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for real-time CLE diagnosis was 81%, 76%, 87%, and 79%, respectively. For offline diagnosis, these numbers were 88%, 77%, 81% and 85%, respectively. However, in the subgroup of 107 smaller polyps, less than 10 mm in size, the accuracy of real-time CLE was significantly lower than offline CLE. For the smaller polyps, sensitivity, specificity, PPV and NPV of real-time CLE was 71%, 83%, 78%, and 78% and for offline CLE was 86%, 78%, 76%, and 87%, all respectively. For larger polyps, in

contrast, there was a nonsignificant trend in favor of better diagnostic accuracy with real-time compared to offline CLE.

A 2011 study by Hlavaty included patients with ulcerative colitis or Crohn disease.[11] Thirty patients were examined with standard white-light colonoscopy, chromoendoscopy and an endoscopy-based CLE system. An additional 15 patients were examined only with standard colonoscopy. All lesions identified by white-light colonoscopy or chromoendoscopy were examined using CLE to identify neoplasia using the Mainz classification system. Suspicious lesions underwent biopsy and, additionally, random biopsies were taken from four quadrants every 10 cm per the standard surveillance colonoscopy protocol. All specimens underwent histologic analysis by a gastrointestinal pathologist who was blinded to the CLE diagnosis. Diagnostic accuracy of CLE was calculated for examinable lesions only. Compared to histologic diagnosis, the sensitivity of CLE for diagnosing low-grade and high-grade intraepithelial neoplasia was 100%, the specificity was 98.4%, the PPV was 66.7%, and the NPV was 100%. However, whereas CLE was able to examine 28 of 30 (93%) flat lesions, it could examine only 40 of 70 (57%) protruding polyps. Moreover, 6 of 10 (60%) dysplastic lesions, including three of five low-grade and high-grade intraepithelial neoplasms were not evaluable by CLE. It is also worth noting that the diagnostic accuracy of chromoendoscopy was similar to that of CLE. The sensitivity, specificity, PPV and NPV of chromoendoscopy was 100%, 97.9%, 75%, and 100%, respectively.

A 2011 study by Xie included 116 consecutive patients who had polyps found during CLE; one patient was excluded from the analysis. All patients had an indication for colonoscopy (19 were undergoing surveillance postpolypectomy, two had a family history of colorectal cancer, three had IBD and 91 were seeking a diagnosis). All patients first underwent white-light colonoscopy. Endoscopy-based CLE was used on the first polyp identified during withdrawal of the endoscope (i.e., one polyp per patient was analyzed). Intravenous fluorescein sodium was used. Real-time diagnosis of the polyp was performed based on criteria used at the study center (which is adapted from the Mainz classification system). The polyps were biopsied or were removed and histopathologic diagnosis was determined. Real-time CLE diagnosis correctly identified 109 of 115 (95%) adenomas or hyperplastic polyps. Four adenomas were misdiagnosed by CLE as hyperplastic polyps (two were tubulous adenomas and two were tubulovillous adenomas) and two hyperplastic polyps were misdiagnosed as adenomas. The overall sensitivity, specificity, PPV, and NPV of CLE diagnosis was 93.9% (95% CI 85.4% to 97.6%), 95.9% (95% CI 86.2% to 98.9%), 96.9% (95% CI 89% to 99%), and 94.8% (95% CI 89.1% to 97.6%), respectively. For polyps less than 10 mm, the CLE diagnosis had a sensitivity of 90.3% and specificity of 95.7%, and for polyps 10 mm and larger, sensitivity was 97.1% and specificity was 100%.[12]

In 2010, Buchner published findings on 75 patients who had a total of 119 polyps.[13] Patients were eligible for study participation if they were undergoing surveillance or screening colonoscopy or undergoing evaluation of known or suspected polyps identified by other imaging modalities or endoscopic resection of larger flat colorectal neoplasia. White-light colonoscopy was used as the primary screening method. When a suspicious lesion was identified, it was evaluated by virtual chromoendoscopy system and a probe-based CLE system. Intravenous fluorescein sodium was administered after the first polyp was identified. Following the imaging techniques, the appropriate intervention, i.e., polypectomy, biopsy, or endoscopic mucosal resection, of lesions were performed and all resected specimens underwent histopathologic analysis by a pathologist blinded to CLE information. Confocal images of the 199 polyps were evaluated after all procedures were completed; the evaluator

was blinded to histology diagnosis and endoscopic appearance of the lesion. Diagnosis of confocal images used modified Mainz criteria; polyps were classified as benign or neoplastic. According to histopathologic analysis, there were 38 hyperplastic polyps and 81 neoplastic lesions (58 tubular adenomas, 15 tubulovillous adenomas and 4 adenocarcinomas). CLE correctly identified 74 of 81 neoplastic polyps (sensitivity, 91%; 95% CI 83% to 96%). In addition, CLE correctly identified 29 of 38 hyperplastic polyps (specificity, 76%; 95% CI, 60% to 89%). In contrast, virtual chromoendoscopy correctly identified 62 neoplastic polyps (sensitivity, 77%; 95% CI 66% to 85%) and 27 hyperplastic polyps (specificity, 71%; 95% CI 54% to 85%).

Section Summary

Multiple studies have evaluated the accuracy of confocal laser endoscopy compared with histopathology for diagnosing colorectal lesions. In three published systematic reviews, pooled estimates of overall sensitivity of CLE ranged from 81% to 94% and pooled estimates of specificity ranged from 88% to 95%. Although the reported diagnostic accuracy tended to be relatively high, it is not clear whether the accuracy is high enough to replace biopsy/polypectomy and histologic analysis.

BARRETT ESOPHAGUS

The ideal study would determine whether CLE with targeted biopsy can distinguish Barrett's Esophagus (BE) without dysplasia from BE with low- and high-grade dysplasia. In addition, study results would need to determine if CLE with target biopsy led to fewer biopsies of benign tissue compared to surveillance with random biopsies. The ideal study to address the above questions would include an unselected clinical population of patients with BE presenting for surveillance and would randomly assign patients to CLE with targeted biopsy or a standard biopsy protocol without CLE. Relevant outcomes include diagnostic accuracy for detecting dysplasia, the detection rate for dysplasia, and the number of biopsies. Several studies with most or all of these elements of study design were identified, including randomized controlled trials (RCTs).

Systematic Reviews

In 2017, Xiong published a systematic review and meta-analysis to assess the accuracy of within-patient comparisons of narrow band imaging and CLE for the diagnosis of high-grade dysplasia and esophageal adenocarcinoma in BE patients.[14] The quality of studies was assessed using the QUADAS-2 tool. A total of five studies with 251 patients were included in the meta-analysis. The pooled sensitivities were not significantly different, with values of 62.8% (95% CI 0.56 to 0.69, I2=94.6%) for narrow band imaging and 72.3% (95% CI 0.66 to 0.78, I2=89.3%) for CLE. Pooled specificities were also not significantly different (narrow band imaging 85.3% [95% CI 0.84 to 0.87, I2=92.1%] vs CLE 83.8% [95% CI 0.82 to 0.85, I2=96.8%]). The pooled additional detection rate of CLE compared to narrow band imaging for per-lesion detection of neoplasia was 19.3% (95% CI 0.05 to 0.33, I2=74.6%).

In 2016, Xiong published a meta-analysis of prospective studies evaluating the diagnostic accuracy of CLE in patients with BE and using histopathologic analysis as the criterion standard.[15] Studies were not required to compare CLE to standard four-quadrant biopsy. Fourteen studies were included. Three were reported to have a high risk of bias and the rest a low risk of bias. There was no statistically significant publication bias. In a pooled analysis of seven studies (n=473 patients) reporting a per-patient analysis, the sensitivity of CLE for

detecting neoplasia was 89% (95% CI, 82% to 94%) and the specificity was 83% (95% CI 78% to 86%). The pooled positive and negative likelihood ratios were 6.53 (95% CI, 3.12 to 13.4) and 0.17 (95% CI 0.11 to 0.29, respectively). Reviewers did not report PPV or NPV. Sensitivity and specificity were similar to those reported below in the 2014 meta-analysis by Gupta. Limitations to this analysis include heterogeneity of the results and a lack of relationship between the diagnostic odds ratio and the characteristics of the studies.

Gupta (2014) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of the CLE-based targeted biopsies in detecting high grade dysplasia (HGD)/adenocarcinoma compared with four-quadrant random biopsies.[16] All the studies that compared the diagnostic yield from CLE-based targeted biopsies to detect HGD/adenocarcinoma with a gold standard of histopathology were included and a meta-analysis was carried out to estimate the pooled sensitivity, specificity, and positive and negative likelihood. Seven studies with 345 patients and 3080 lesions were included in the meta-analysis. All the studies had reported per-lesion analyses; however, only four of the seven studies had data reported on per-patient analyses. 'Per-lesion' analysis for the diagnosis of HGD/adenocarcinoma yielded a pooled sensitivity and specificity of 68% (95% CI of 64-73%) and 88% (95% CI 87 to 89%), respectively. The pooled positive and negative likelihood ratios were 6.56 (95% CI 3.61 to 11.90) and 0.24 (95% CI 0.09 to 0.63), respectively. Similar numbers were calculated on the basis of 'per-patient' basis, which showed a pooled sensitivity and specificity of 86% (95% CI 74 to 96%) and 83% (95% CI 77 to 88%), respectively. The pooled positive and negative likelihood ratios were 5.61 (95% CI 2.00 to 15.69) and 0.21 (95% CI 0.08 to 0.59), respectively. Authors noted that CLE, by providing targeted biopsies, has a good diagnostic accuracy in identifying HGD/EAC; however, the overall prevalence of HGD/EAC in the studies included was much higher than what would be seen in clinical practice and these results should be interpreted with caution. Due to its relatively low sensitivity and negative predictive value, CLE may currently not replace standard biopsy techniques for the diagnosis of HGD/EAC in Barrett's esophagus.

In 2013, a meta-analysis by Wu of observational studies and RCTs focused on the diagnostic accuracy of CLE for detecting neoplasia in BE patients.[17] In a pooled analysis of data from four studies that reported per-patient accuracy of CLE, the pooled sensitivity for detection of neoplasia was 89% (95% CI 0.80% to 0.95%), and the pooled specificity was 75% (95% CI 69% to 81%). Seven studies reported per-location accuracy of CLE. The pooled sensitivity for CLE was 70% (95% CI 65% to 74%) and the pooled specificity was 91% (95% CI 90% to 92%). This study did not address other outcomes such as number of biopsies and did not compare CLE for detection of neoplasia in patients with BE with white-light endoscopy.

Randomized Controlled Trials

In 2013, Canto published findings from a single-blind multicenter RCT conducted at academic centers with experienced endoscopists.[18] The trial included consecutive patients undergoing endoscopy for routine surveillance of BE or for suspected or known neoplasia. Patients were randomized to high-definition white-light endoscopy with random biopsy (n=98) or white-light endoscopy with endoscopy-based CLE and targeted biopsy (n=94). In the white-light endoscopy-only group, four-quadrant random biopsies were taken every one to two cm of the entire length of the BE for patients undergoing surveillance and every one cm in patients with suspected neoplasia. In the CLE group, biopsy specimens were obtained only when there was CLE evidence of neoplasia. The final pathology diagnosis was the reference standard. A per-patient analysis of diagnostic accuracy for diagnosing BE-related neoplasia found a sensitivity

of 40% with white-light endoscopy alone and 95% with white-light endoscopy plus CLE. Specificity was 98% with white-light endoscopy alone and 92% with white-light endoscopy plus CLE. When the analysis was done on a per-biopsy specimen basis, when CLE was added, the sensitivity was substantially higher and the specificity was slightly lower. The median number of biopsies per patient was significantly higher in the white-light endoscopy group compared with the group that also received CLE (4 vs 2, p<0.001). The investigators conducted an analysis of the number of cases in which CLE resulted in a different diagnosis. Thirty-two of 94 (34%) patients in the white-light plus CLE group had a correct change in dysplasia grade after CLE compared to the initial endoscopic findings. Six of the 32 (19%) patients had lesions and the remaining 26 did not. In 21 of the 26 patients without lesions, CLE changed the plan from biopsy to no biopsy. The remaining 62 of 94 (65%) patients in the white-light endoscopy plus CLE group had concordant diagnoses with the two techniques. The study was conducted at academic centers and used endoscopy-based CLE. Findings may not be generalizable to other clinical settings or to probe-based CLE.

In 2011, Sharma published an international, multicenter RCT that included 122 consecutive patients presenting for surveillance of BE or endoscopic treatment of high-grade dysplasia or early carcinoma.[19] This study was described in the systematic review and meta-analysis described by Gupta in the previous section. Patients were randomly assigned to receive, in random order, both standard white-light endoscopy and narrow-band imaging. Following these two examinations, which were done in a blinded fashion, the location of lesions was unblinded and, subsequently, all patients underwent probe-based CLE. All examinations involved presumptive diagnosis of suspicious lesions. Also, in both groups, after all evaluations were performed, there were biopsies of all suspicious lesions, as well as biopsies of random locations (four quadrants every two cm). Histopathologic analysis was the reference standard. Twenty-one patients were excluded from the analysis. Of the remaining 101 patients, 66 (65%) were found on histopathologic analysis to have no dysplasia, four (4%) had low-grade dysplasia, six (6%) had high-grade dysplasia and 25 (25%) had early carcinoma. The sensitivity of CLE with white-light endoscopy for detecting high-grade dysplasia or early carcinoma was 68.3% (95% CI, 60.0% to 76.7%), which was significantly higher than white-light endoscopy alone; 34.2% (95% CI 25.7% to 42.7%, p=0.002). However, the specificity of CLE and white-light endoscopy was significantly lower than white-light endoscopy alone: 92.7% (95% CI 90.8% to 94.6%) versus 87.8% (95% CI 85.5% to 90.1%; p<0.001). For white-light endoscopy alone, the PPV was 42.7% (32.8% to 52.6%) and the NPV was 89.8% (95% CI 87.7% to 92.0%). For white-light endoscopy with probe-based CLE, the PPV was 47.1% (95% CI 39.7% to 54.5%) and the NPV was 94.6% (95% CI 92.9% to 96.2%). White-light endoscopy alone missed 79 of 120 (66%) areas with high-grade dysplasia or early carcinoma and white-light endoscopy with CLE missed 38 (32%) areas. On a per-patient basis, 31 patients were diagnosed with high-grade dysplasia or early carcinoma. White-light endoscopy alone failed to identify four of these patients (sensitivity, 87%), whereas white-light endoscopy and CLE failed to identify two patients (sensitivity, 93.5%).

Another RCT was published in 2012 by Bertani in Italy; this was a single-center study.[20] The study compared the dysplasia detection rate of biopsies obtained by standard white-light endoscopy only to the detection rate with standard endoscopy followed by probe-based CLE in patients with BE who were enrolled in a surveillance program. One hundred consecutive patients were included, and 50 were randomly assigned to each group. In both groups, targeted biopsies of suspicious lesions and random four-quadrant biopsies (one biopsy every one cm) were taken. The authors described the criteria they used for classifying CLE images as dysplastic or neoplastic. According to histopathologic analysis, the reference standard,

high-grade dysplasia, was diagnosed in three patients and low-grade dysplasia was diagnosed in 16 patients, for an overall detection rate of 19 in 100 (19%) cases. Five cases were in the standard endoscopy group (one case of high-grade dysplasia and four cases of low-grade dysplasia) and 14 were in the CLE group (two cases of high-grade dysplasia and 12 cases of low-grade dysplasia). No suspicious lesions were identified in the standard endoscopy group and thus, only random biopsies were performed. In the CLE group, no suspicious lesions were identified when patients were initially evaluated with standard endoscopy but CLE detected areas suspicious for neoplasia in 21 of 50 (42%) of patients. All the cases of dysplasia were in patients with areas suspicious for neoplasia at CLE but not standard endoscopy. The sensitivity, specificity, PPV and NPV of probe-based CLE for detecting dysplasia were 100%, 83%, 67%, and 100%, respectively. Overall, the mean number of biopsies did not differ between groups (mean of 6.6 per patient in the standard endoscopy group and 6.1 in the CLE group, p=0.77), so the increased detection rate in the CLE group cannot be explained by a larger number of biopsies.

A single-center crossover RCT was published in 2009 by Dunbar.[21] This study was able to evaluate whether CLE can reduce the biopsy rate. This study was described in the systematic review and meta-analysis described by Gupta (2014) in the previous section. Forty-six patients with BE were enrolled, and 39 (95%) completed the study protocol. Of these, 23 were undergoing BE surveillance and 16 had BE with suspected neoplasia. All patients received endoscopy-based CLE and standard endoscopy, in random order. One endoscopist performed all CLE procedures and another endoscopist performed all standard endoscopy procedures; endoscopists were blinded to the finding of the other procedure. During the standard endoscopy procedure, biopsies were taken of any discrete lesions followed by four-quadrant random biopsy (every one cm for suspected neoplasia and every two cm for BE surveillance). During the CLE procedure, only lesions suspicious of neoplasia were biopsied. Endoscopists interpreted CLE images using the Confocal Barrett's Classification system, developed in a previous research study. Histopathologic analysis was the reference standard. Among the 16 study completers with suspected high-risk dysplasia, there were significantly fewer biopsies per patient with CLE compared to standard endoscopy (mean of 9.8 biopsies vs 23.9 biopsies per patient, p=0.002). Although there were fewer biopsies, the mean number of biopsy specimens showing high-grade dysplasia or cancer was similar in the two groups: 3.1 during CLE and 3.7 during standard endoscopy, respectively. The diagnostic yield for neoplasia was 33.7% with CLE and 17.2% with standard endoscopy. None of the 23 patients undergoing BE for surveillance were found to have high-grade dysplasia or cancer. The mean number of mucosal specimens obtained for patients in this group was 12.6 with white-light endoscopy and 1.7 with CLE (p<0.001).

Nonrandomized Studies

Richardson (2019) conducted a prospective study at eight centers to compare probe-based CLE to conventional histology using the Seattle Protocol (random 4-quadrant biopsy) to identify intestinal metaplasia among 172 patients undergoing screening or surveillance endoscopy for BE.[22] Endoscopists recruited for the study were early users of CLE with less than two years of experience and no formal pathology training. All patients underwent a standardized endoscopy with white light and narrow band imaging evaluation, identification of landmarks, and recording of columnar lined esophagus visualized according to the Prague classification. Patients then received fluorescein followed by optical biopsy; images were interpreted both in real time and immediately following the procedure. After CLE images were acquired, esophageal biopsies were taken via the Seattle Protocol. Endoscopists were able to

identify intestinal metaplasia among 99 patients (57.6%) using CLE compared to 46 patients (27%) using the Seattle Protocol (p<0.0001). Dysplasia was identified in 6 patients using CLE compared to 2 patients using the Seattle Protocol (both of which were also identified via CLE). Confocal laser endomicroscopy also identified significantly more patients with intestinal metaplasia compared to the Seattle Protocol among those with visible columnar lined esophagus (75 vs. 31 patients, respectively; p<0.0001), but not among those without columnar lined esophagus (24 vs. 15 patients; p=0.067). Identification of intestinal metaplasia was not found to be significantly different when comparing CLE to expert review.

Section Summary

Several RCTs and a meta-analysis of RCTs and non-randomized, observational studies suggest that CLE has high accuracy for identifying dysplasia in patients with BE. A 2014 meta-analysis found that the pooled sensitivity, specificity, and negative predictive value in available studies is not sufficiently high to replace the standard Seattle protocol, according to criteria adopted by the American Society for Gastrointestinal Endoscopy (ASGE).

The sensitivity of CLE in the individual studies was higher than for white-light endoscopy alone, but the specificity was not consistently higher. There are limited data comparing standard protocols using random biopsies to protocols using CLE and targeted biopsies, so data are inconclusive regarding the potential for CLE to reduce the number of biopsies in patients with BE undergoing surveillance without compromising diagnostic accuracy. Moreover, studies do not appear to use a consistent approach to classifying lesions viewed using CLE as dysplastic.

PANCREATIC DISEASES

Systematic Reviews

Saghir (2022) conducted a systematic review to evaluate the diagnostic accuracy of CLE for pancreatic lesions.[23] A total of 443 patients were included in the analysis which demonstrated a pooled diagnostic accuracy of 83%. The pooled rate of sensitivity, specificity, positive predictive value, and negative predictive value were 85.29% (95% CI = 76.9-93.68), 90.49% (95% CI = 82.24-98.74), 94.15% (95% CI = 88.55-99.76), and 73.44% (95% CI = 60.16-86.72), respectively. Additional studies are needed evaluating pancreatic lesions in order to establish diagnostic criteria and to establish the clinical utility of CLE for pancreatic lesions.

Konjetia (2020) conducted a systematic review to evaluate the diagnostic performance and safety of needle-based confocal laser endomicroscopy (nCLE) in the diagnosis of pancreatic cystic lesions.[24] Seven studies were included in the review with a total sample size of 324 patients. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ration of nCLE was 85% (95% CI, 71-93), 99% (95% CI, 90-100), 78.66 (95% CI, 7.99-774.68), and 0.15 (95% CI, 0.07-0.31) respectively. The diagnostic accuracy as measured by summary receiver operating characteristic curve was 99%. The results showed that nCLE may be effective in diagnostic evaluation of PCLs, however a large amount of heterogeneity was present in the analysis which is consistent with prior reviews.

In 2020, Facciorusso published a meta-analysis of needle-based confocal laser endomicroscopy (nCLE) in pancreatic cystic lesions.[25] Ten studies with a total of 536 patients met inclusion criteria. Three studies were rated as low-quality and the rest as high quality using the Newcastle/Ottawa scale. There was no evidence of publication bias. Diagnostic outcomes from the included studies were pooled using a random-effects mode. Overall pooled diagnostic

accuracy was 88.6% (83.7 to 93.4%; I^2=41.73%). Pooled sensitivity and specificity of nCLE were calculated from nine studies to be 82.4% and 96.6%, respectively. A direct comparison between the diagnostic sensitivity of nCLE and endoscopic ultrasound-guided fine needle aspiration (FNA) was conducted. No statistically significant difference was reported (OR=1.51, 0.34 to 6.68), although the authors cautioned that there was high heterogeneity.

Also in 2020, Chin published a systematic review on the role of needle-based confocal laser endomicroscopy in the evaluation of pancreatic cystic lesions.[26] Twelve studies were included, six retrospective and six prospective. No meta-analysis was completed. The accuracy of nCLE was between 46% and 95%, although only one study reported accuracy below 71%. The reported incidence of acute pancreatitis, the most common complication related to nCLE, was 1.3% to 12%.

Nonrandomized Studies

Hao (2020) published a study to study was to evaluate the diagnostic efficacy of EUS-guided nCLE in solid pancreatic lesions (SPLs) and pancreatic cystic lesions (PCLs).[27] A total of 172 patients were enrolled and underwent EUS-nCLE. The reported mean sensitivity, specificity, negative predictive value, positive predictive value and accuracy of the nCLE in diagnosis of pancreatic ductal adenocarcinoma were 90.3%, 89.5%, 93.3%, 85.0% and 90.0%, respectively.

Nakaoka (2020) reported a study of 30 patients who underwent endoscopic retrograde cholangiopancreatography with pCLE for the evaluation of indeterminate pancreatic diseases.[28] Compared to cytology, the diagnostic accuracy (96.7% vs. 76.7%; p=0.0227) and the sensitivity (91.7% vs. 41.7%; p=0.0094) of pCLE for pancreatic ductal adenocarcinoma was significantly higher. The diagnostic accuracy (93.3% vs. 63.3%; p=0.0048) and the specificity (90.9% vs. 50%; p=0.0029) for pancreatitis were significantly higher for pCLE than for cytology. However, the diagnostic accuracies of the two methods did not significantly differ for main duct intrapapillary mucinous neoplasms.

Haghighi (2019) reported results of a study to determine the diagnostic utility of nCLE compared to endoscopic ultrasound-guided FNA (EUS-FNA) for PCLs.[29] A total of 32 patients diagnosed with PCL who had undergone nCLE and FNA over a 10-year period within a major urban teaching hospital were included. The diagnoses in the included patients were serous cystadenoma (n=13), intraductal papillary mucinous neoplasms (n=7), mucinous cystic neoplasms (n=2), well-differentiated neuroendocrine tumors (n=2), cysts (n=2), benign pancreatic lesions (n=2), adenocarcinoma (n=1), gastrointestinal stromal tumor (GIST; n=1), and lymphangioma (n=1). The diagnostic accuracy varied by diagnosis. The highest diagnostic accuracy was for intraductal papillary mucinous neoplasms (n=7, vs. 100% for nCLE compared to 42.8% for EUS-FNA, n=3,), while the diagnostic accuracy rate for serous cystadenoma was 69.2% (n=9; vs. 76.9% for EUS-FNA, n=10). Overall, the sensitivity, specificity, PPV, and NPV were 91.7%, 87.5%, 84.6%, and 93.3%, respectively, for nCLE and 80.0%, 92.3%, 88.9%, and 85.7%, respectively, for EUS-FNA.

ASSESSING THE ADEQUACY OF ENDOSCOPIC TREATMENT OF GASTROINTESTINAL LESIONS

Evidence is not clear regarding whether use of CLE improves the determination of residual disease compared with conventional techniques (i.e., white-light endoscopy). In 2014, Ypsilantis published a systematic review of the literature.[30] They included retrospective and

prospective studies that reported diagnostic accuracy of CLE for the detection of residual disease after endoscopic mucosal resection (EMR) of gastrointestinal lesions. After examining full-text articles, a total of three studies (one RCT and two prospective, non-randomized comparative studies) met the eligibility criteria. Studies included patients with BE, gastric neoplasia, and colorectal neoplasia. There was significant heterogeneity among studies. In a per-lesion meta-analysis, pooled sensitivity of CLE for detecting neoplasia was 91% (95% CI 83% to 96%), and pooled specificity was 69% (95% CI 61 to 76%). Based on the small number of studies and heterogeneity among studies, the authors concluded that evidence on the usefulness of CLE in assessing the adequacy of EMR is weak. The single RCT was published in 2012 by Wallace[31] This multicenter trial included patients with BE who were undergoing ablation. After an initial attempt at ablation, patients were randomized to follow-up with either with high-definition white light (HDWL) endoscopy or HDWL endoscopy plus CLE. The primary outcome was the proportion of optimally treated patients, defined as those with no evidence of disease at follow-up, and those with residual disease who were identified and treated. Enrollment in the study was halted after an interim analysis showed no difference between groups. Among the 119 patients who had enrolled by the time of the interim analysis, 15 (26%) of 57 in the HDWL group and 17 (27%) of 62 in the HDWL plus CLE group were optimally treated; the difference was not statistically significant. Moreover, other outcomes were similar in the two groups.

Section summary

There is insufficient evidence that CLE improves upon standard practice for assessing the adequacy of endoscopic treatment of gastrointestinal lesions. The single RCT on this topic was stopped early because an interim analysis reported that CLE did not improve upon high-definition white light endoscopy.

OTHER POTENTIAL APPLICATIONS OF CLE

Preliminary studies have been published evaluating CLE for diagnosing a variety of conditions including lung cancer,[32-34] bladder cancer,[35-40] head and neck cancer,[41-44] gastric cancer,[45-52] atrophic gastritis,[53, 54] esophageal cancer,[55, 56] breast surgery,[57] biliary strictures and stenosis,[58-62] gastric intestinal metaplasia,[63-65] malignant pleural mesothelioma,[66] basal and squamous cell carcinoma,[67] liver[68] and peritoneal nodules[69], gastrointestinal polypoid lesions,[70] gastroesophageal reflux disease (GERD),[71] inflammatory bowel disease,[72, 73] aganglionosis associated with Hirschsprung's disease,[74] and bile duct malignancies[75, 76]. There are insufficient studies to determine the accuracy of CLE for these applications and their potential role in clinical care.

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2011 the American Gastroenterological Association (AGA) published a position statement on the management of Barrett esophagus.[77] The statement includes the following recommendations regarding endoscopic surveillance of Barrett esophagus:

> The AGA suggest that endoscopic surveillance be performed in patients with Barrett esophagus (weak recommendation, moderate-quality evidence).
>
> The AGA suggest the following surveillance intervals (weak recommendation, low-quality evidence):

- No dysplasia: three to five years
- Low-grade dysplasia: 6 to 12 months
- High-grade dysplasia in the absence of eradication therapy: three months

For patients with Barrett esophagus who are undergoing surveillance, the AGA recommended:

- Endoscopic evaluation be performed using white light endoscopy (strong recommendation, moderate-quality evidence).
- Four-quadrant biopsy specimens be taken every 2 cm (strong recommendation, moderate-quality evidence).
- Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist (strong recommendation, moderate-quality evidence).
- Four-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia (strong recommendation, moderate-quality evidence).

The AGA recommend against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett esophagus at this time (weak recommendation, low-quality evidence).

AMERICAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY

In 2019, the American Society for Gastrointestinal Endoscopy (ASGE) published a guideline on screening and surveillance of Barrett's esophagus.[78] The guideline includes the following recommendation regarding surveillance of dysplasia in patients with Barrett's esophagus: "In patients with BE undergoing surveillance, we suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence)."

The ASGE published a guideline (2006; reaffirmed in 2011) on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.[79] Regarding the use of confocal endoscopy as an adjunct to white-light endoscopy, the guidelines stated that this technique is "still in development." The guideline also included the following statements on surveillance of patients with BE:

> The cost effectiveness of surveillance in patients without dysplasia is controversial. Surveillance endoscopy is appropriate for patients fit to undergo therapy, should endoscopic/histologic findings dictate. For patients with established Barrett's esophagus of any length and with no dysplasia, after 2 consecutive examinations within 1 year, an acceptable interval for additional surveillance is every 3 years.
>
> Patients with high-grade dysplasia are at significant risk for prevalent or incident cancer. Patients who are surgical candidates may elect to have definitive therapy. Patients who elect surveillance endoscopy should undergo follow-up every 3 months for at least 1 year, with multiple large capacity biopsy specimens obtained at 1 cm intervals. After 1 year of no cancer detection, the interval of surveillance may be lengthened if there are no dysplastic changes on 2 subsequent endoscopies performed at 3-month intervals. High-grade dysplasia should be confirmed by an expert GI pathologist.
>
> Surveillance in patients with low-grade dysplasia is recommended. The significance of low-grade dysplasia as a risk factor for cancer remains poorly defined; therefore, the

optimal interval and biopsy protocol has not been established. A follow-up EGD (screening esophagogastroduodenoscopy) (i.e., at 6 months) should be performed with concentrated biopsies in the area of dysplasia. If low-grade dysplasia is confirmed, then one possible management scheme would be surveillance at 12 months and yearly thereafter as long as dysplasia persists.

In 2012, the ASGE stated the following in their guideline on the role of endoscopy in BE and other premalignant conditions of the esophagus: "Adjuncts to white-light endoscopy used to improve the sensitivity for the detection of BE and dysplastic BE include chromoendoscopy, electrical enhanced imaging, magnification, and confocal endoscopy."[80]

The ASGE Technology Committee published a Technology Status Evaluation Report on CLE in 2014.[81] The report concluded that CLE is an emerging technology with the potential to improve patient care. However, before the technology can be widely accepted, further studies are needed in the following areas:

- Use of CLE outside of the academic setting, particularly the applicability of the technology in community settings.
- The learning curve of CLE image interpretation and any additional time needed to perform the procedure.
- The clinical efficacy of the technology compared to other available advanced imaging technologies.
- Approaches to CLE imaging and image interpretation.

In 2016, based on a systematic review of 102 studies conducted between 2004 and 2015, the ASGE concluded additional clinical trials on CLE are still necessary.[82]

SUMMARY

There is not enough research to know if or how well confocal laser endomicroscopy (CLE) works to improve health outcomes for people with any condition. This does not mean that it does not work, but more research is needed to know. Therefore, use of CLE with endoscopy is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)
	43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy
	43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
	88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session.
HCPCS	None	

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Regence

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Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults

Effective: March 1, 2025

Next Review: September 2025
Last Review: February 2025

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

Extracorporeal Membrane Oxygenation (ECMO) is a complex treatment which utilizes a modified cardiopulmonary bypass circuit for temporary life support as a treatment for reversible cardiac and/or respiratory failure.

MEDICAL POLICY CRITERIA

Note: This policy does not address the use of ECMO in children or neonates, which may be considered medically necessary. In addition, this policy does not address the use of short-term extracorporeal support, including ECMO, such as during surgical procedures. The Policy Guidelines section below includes information regarding weaning and/or discontinuation of ECMO.

I. Extracorporeal Membrane Oxygenation (ECMO) in adults (18 years or older) may be considered **medically necessary** as a treatment of respiratory or cardiac failure that is potentially reversible when both of the following Criteria (A. and B.) are met:

   A. At least one of the following criteria is met:

1. Hypoxic respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one or more of the following:
    a. Murray Lung Injury Score three or higher (see Policy Guidelines for Murray Lung Injury Score); or
    b. PaO2/FiO2 of less than100 mm Hg on fraction of inspired oxygen (FiO2) greater than 90%; or
    c. Inability to maintain airway plateau pressure (Pplat) less than 30 cm H2O despite a tidal volume of four to six mL/kg ideal body weight (IBW); or
    d. Oxygenation Index greater than 30: Oxygenation Index equals FiO2 times 100 times MAP divided by PaO2 mm Hg. [FiO2 times 100 equals FiO2 as percentage; MAP equals mean airway pressure in cm H2O; PaO2 equals partial pressure oxygen in arterial blood].
2. Respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one of the following:
    a. Significant hypercapnea despite high Pplat (greater than 30 cm H_2O); or
    b. A pH of less than 7.20 due to significant uncompensated hypercapnia
3. Severe air leak syndromes including, but not limited to:
    a. Significant tracheal airway injuries; or
    b. An air-leak or broncho-pleural fistula that prevents adequate ventilation with lung-protective ventilation (see Policy Guidelines) strategies.
4. Refractory cardiogenic shock as demonstrated by one of the following:
    a. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume; or
    b. Shock which persists despite volume administration, inotropes and vasoconstrictors, and intra-aortic balloon counterpulsation.
5. Hypothermia with a core temperature of less than 28 degrees centigrade.
6. As a bridge to heart, lung, or heart-lung transplantation.

B. None of the following contraindications are present:
1. Ventilation with high ventilator pressure (Pplat greater than 30 cm H2O) sustained throughout a seven-day period and/or high FiO2 (greater than 80%) sustained throughout a seven-day period; or
2. Signs of intracranial bleeding, or other major central nervous system injury without the potential to recover meaningful function; or
3. Presence of an irreversible, terminal illness; or
4. Cardiac decompensation and not meeting medical necessity criteria for heart transplant or ventricular assist device; or
5. Chronic organ failure without the potential to recover meaningful function; or
6. Prolonged CPR without adequate tissue perfusion; or

7. Patient choice to decline extraordinary life support interventions. (see Policy Guidelines)

II. The continued use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients may be considered **medically necessary** when all of the following criteria are met (A. – D.):

A. ECMO was determined to be medically necessary at initiation; and

B. No neurologic devastation determined by at least two physicians agreeing after evaluation, (including neurologic examination, head CT, and EEG), that the patient has sustained irreversible cessation of all functioning of the brain, including the brain stem and an outcome better than "persistent vegetative state" at six months is unlikely. At least one of these physicians should be a neurologist, neurosurgeon, and/or neuro-intensivist; and

C. No hypotension and/or hypoxemia recalcitrant to all maneuvers which causes inadequate aerobic metabolism demonstrated by evidence of profound tissue ischemia [creatine phosphokinase (CPK), lactate, lactate to pyruvate (L/P) ratio, near-infrared spectroscopy (NIRS)]; and

D. No end-stage cardiac or lung failure without alternative long-term plan (i.e., ineligible for assist device and/or transplant), and the patient is unable to wean from ECMO.

III. The continued use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients is considered **not medically necessary** when Criterion II. is not met.

IV. The use of Extracorporeal Membrane Oxygenation (ECMO) as a treatment of respiratory or cardiac failure in adult patients is considered **not medically necessary** if Criterion I.A. is not met OR if any of the contraindications listed in Criterion I.B. are present.

V. The use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients is considered **investigational** in all other situations, including but not limited to use for indications other than respiratory or cardiac failure.

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

POLICY GUIDELINES

RESPIRATORY FAILURE REVERSIBILITY

The reversibility of the underlying respiratory failure is best determined by the treating physicians, ideally physicians with expertise in pulmonary medicine and/or critical care. Some of the underlying causes of respiratory failure which are commonly considered reversible are as follows:

- Acute respiratory distress syndrome (ARDS)
- Acute pulmonary edema
- Acute chest trauma
- Infectious and noninfectious pneumonia
- Pulmonary hemorrhage

- Pulmonary embolism
- Asthma exacerbation
- Aspiration pneumonitis.

MAXIMAL LUNG-PROTECTIVE VENTILATION

The American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline made the following recommendations regarding lung-protective ARDS ventilation management:[1]

- Low tidal volume ventilation (4 to 8 mL/kg of predicted body weight)
- Plateau pressure (pPlat) less than 30 cm H_2O

Additional lung protective options include prone positioning[2] and neuromuscular blockade[3].

MURRAY LUNG INJURY SCORE

The Murray Lung Injury Score is a system for classifying the severity of respiratory failure. It was developed for use in ARDS, but has been applied to other indications.[4] This score includes four subscales, each of which is scored from 0 to 4. The final score is obtained by dividing the collective score by the number of subscales used. A score of 0 indicates no lung injury; a score of 1 to 2.5 indicates mild or moderate lung injury; and a score of 2.5 indicates severe lung injury, e.g. ARDS. Table 1 shows the components of the Murray scoring system.

Table 1: Murray Lung Injury Score

Subscale	Criteria	Score
Chest x-ray score	No alveolar consolidation	0
	Alveolar consolidation confined to 1 quadrant	1
	Alveolar consolidation confined to 2 quadrants	2
	Alveolar consolidation confined to 3 quadrants	3
	Alveolar consolidation in all 4 quadrants	4
Hypoxemia score	PaO_2/FiO_2 >300	0
	PaO_2/FiO_2 225-299	1
	PaO_2/FiO_2 175-224	2
	PaO_2/FiO_2 100-174	3
	PaO_2/FiO_2 ≤ 100	4
PEEP score (when ventilated)	PEEP ≤ 5 cm H_2O	0
	PEEP 6-8 cm H_2O	1
	PEEP 9-11 cm H_2O	2
	PEEP 12-14 cm H_2O	3
	PEEP ≥ 15 cm H_2O	4
Respiratory system compliance score (when available)	Compliance >80 mL/cm H_2O	0
	Compliance 60-79 mL/cm H_2O	1
	Compliance 40-59 mL/cm H_2O	2
	Compliance 20-39 mL/cm H_2O	3
	Compliance ≤ 19 mL/cm H_2O	4

CPAP – continuous positive airway pressure; FiO_2 – fraction of inspired oxygen; PaO_2 – partial pressure of oxygen in arterial blood; PEEP – peak end expiratory pressure.

In addition to the Murray Lung Injury Score, the Berlin Definition is gaining acceptance for classifying ARDS.[5]

PATIENT CHOICE TO DECLINE EXTRAORDINARY LIFE SUPPORT INTERVENTIONS

Choices to decline extraordinary life support interventions may include, but is not limited to, the presence of an advanced directive, healthcare directive, Physician Orders for Life Sustaining Treatment (POLST), or Physician Orders for Scope of Treatment (POST) to indicate the patient or the patient's health care representative or agent has selected any of the following upon which life-sustaining support would be withheld or withdrawn:

- A Do Not Resuscitate (DNR, DNAR, No Code) order; or
- Allow Natural Death; or
- No CPR or advanced cardiac life support interventions; or
- An equivalent choice.

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
- Indication for the requested service
- Documentation of symptoms, associated diagnoses, and treatments

CROSS REFERENCES

1. Treatment of Adult Sepsis, Medicine, Policy No. 172
2. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52

BACKGROUND

Extracorporeal Membrane Oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), or extracorporeal lung assist (ELA), has been proposed as an alternative treatment for cardiac and respiratory failure in adult patients and is described by the Extracorporeal Life Support Organization (ELSO) as, "the use of mechanical devices to temporarily (days to months) support heart or lung function (partially or totally) during cardiopulmonary failure, leading to organ recovery or replacement."[6] ECMO is used for prolonged time periods (days to weeks) and involves removing a portion of the patient's blood, pumping it through a membrane oxygenator, removing carbon dioxide, rewarming the blood, and returning it to the patient. ECMO is a complex treatment requiring a specialized staff and specific equipment. The ELSO specialty group maintains a registry of detailed data from a voluntary international consortium of health care centers which utilize ECMO.[6]

Historically, ECMO has been used in neonatal and pediatric populations to treat respiratory failure related to a variety of respiratory diseases. The treatment may be used in newborn infants with neonatal respiratory distress due to congenital diaphragmatic hernia, meconium aspiration, hyaline membrane disease, pulmonary hypertension and pulmonary hypoplasia, and pneumonia with sepsis. ECMO is associated with a 55% survival rate in this subgroup and has become an accepted treatment for respiratory failure in pediatric and neonatal patients, despite the lack the randomized trials.[7-9]

With improvements in ECMO circuit technology and methods of supportive care, ECMO has

been proposed as salvage therapy to prevent irreversible neurologic damage in adults with acute, reversible respiratory or cardiac failure. In critically ill adult patients, ECMO also may be considered a non-ventilatory treatment by which to avoid ventilator induced lung injury (VILI) associated with mechanical ventilation. In these situations, death would be imminent unless medical interventions can immediately reverse the underlying disease process or physiologic functions can be supported for long enough that normal reparative processes or treatment can occur (e.g., resolution of ARDS or treatment of infection) or other life-saving intervention can be delivered (e.g., provision of a lung transplant).

DISEASE-SPECIFIC INDICATIONS FOR ECMO

Venoarterial (VA) and venovenous (VV) ECMO have been investigated for a wide range of adult conditions that can lead to respiratory or cardiorespiratory failure, some of which overlap clinical categories (e.g., H1N1 influenza infection leading to ARDS and cardiovascular collapse), which makes categorization difficult. ARDS has been defined by consensus in the Berlin definition, which includes criteria for the timing of symptoms, imaging findings, exclusion of other causes, and degree of oxygenation.[5] However, in general, indications for ECMO can be categorized as follows:

- Acute respiratory failure due to potentially reversible causes. Acute respiratory failure refers to the failure of either oxygenation, removal of carbon dioxide, or both, and may be due to a wide range of causes. In these cases, ECMO is most often used as a bridge to recovery. Specific potentially reversible or treatable indications for ECMO may include ARDS, acute pneumonias, and a variety of other pulmonary disorders.

- Bridge to lung transplant. Lung transplant is used for management of chronic respiratory failure, most frequently in the setting of advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to alpha-1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. In the end stages of these diseases, patients may require additional respiratory support while awaiting an appropriate donor. In addition, patients who have undergone a transplant may require retransplantation due to graft dysfunction after the primary transplant.

- Acute-onset cardiogenic or obstructive shock is defined as shock that is due to cardiac pump failure or vascular obstruction, refractory to inotropes and/or other mechanical circulatory support. Examples of this category include postcardiotomy syndrome (ie, failure to wean from bypass), acute coronary syndrome, myocarditis, cardiomyopathy, massive pulmonary embolism, and prolonged arrhythmias.

- ECMO-assisted cardiopulmonary resuscitation (ECPR). ECMO can be used as an adjunct to CPR in patients who do not respond to initial resuscitation measures.

TECHNOLOGY DESCRIPTION

The basic components of ECMO include a pump, an oxygenator, sometimes referred to as a “membrane lung,” and some form of vascular access. Based on the vascular access type, ECMO can be described as VV or VA. VA ECMO has the potential to provide cardiac and ventilatory support.

More recently, these include ventilation support devices that provide oxygenation and removal of CO_2 without the use of a pump system or interventional lung assist devices (e.g., iLA®

Membrane Ventilator, Novalung GmbH). These technologies are not the focus of this evidence review but are described briefly because there is overlap in patient populations treated with extracorporeal carbon dioxide removal ($ECCO_2R$) and those treated with ECMO, and some studies have reported on both technologies.

In contrast to VA and VV ECMO, which use large-bore catheters and generally high flow through the ECMO circuits, other systems use pumpless systems to remove CO_2. These pumpless devices achieve $ECCO_2R$ via a thin double-lumen central venous catheter and relatively low extracorporeal blood flow. They have been investigated as a means to allow low tidal volume ventilator strategies, which may have benefit in ARDS and other conditions where lung compliance is affected. Although ECMO systems can effect CO_2 removal, dedicated $ECCO_2R$ systems are differentiated by simpler mechanics and the fact that they do not require dedicated staff.[10]

Venovenous ECMO

Technique

In venovenous extracorporeal membrane oxygenation (VV ECMO), the ECMO oxygenator is in series with the native lungs, and the ECMO circuit provides respiratory support. Venous blood is withdrawn through a large-bore intravenous line, oxygen is added and CO_2 removed, and oxygenated blood is returned to the venous circulation near the right atrium. Venous access for VV ECMO can be configured through two single lumen catheters (typically in the right internal jugular and femoral veins), or through one dual lumen catheter in the right internal jugular vein. In the femoro-jugular approach, a single large multiperforated drainage cannula is inserted in the femoral vein and advanced to the cavo-atrial junction, and the return cannula is inserted into the superior vena cava via the right internal jugular vein. Alternatively, in the bi-femoral-jugular approach, drainage cannulae are placed in both the superior vena cava and the inferior vena cava via the jugular and femoral veins, and a femoral return cannula is advanced to the right atrium. In the dual-lumen catheter approach, a single bicaval cannula is inserted via the right jugular vein and positioned to allow drainage from the inferior vena cava and superior vena cava and return via the right atrium.

Indications

VV ECMO provides only respiratory support, and therefore is used for conditions in which there is progressive loss in ability to provide adequate gas exchange due to abnormalities in the lung parenchyma, airways, or chest wall. Right ventricular (RV) dysfunction due to pulmonary hypertension that is secondary to parenchymal lung disease may sometimes be effectively treated by VV ECMO.

However, acute or chronic obstruction of the pulmonary vasculature (e.g., saddle pulmonary embolism) may require VA ECMO. There may be cases in which RV dysfunction due to pulmonary hypertension caused by severe parenchymal lung disease may be severe enough to require VA ECMO. In adults, VV ECMO is generally used only in situations in which all other reasonable avenues of respiratory support have been exhausted, including mechanical ventilation with lung protective strategies, pharmacologic therapy, and prone positioning.

Venoarterial ECMO

Technique

In venoarterial extracorporeal membrane oxygenation (VA ECMO), the ECMO oxygenator is in parallel with the native lungs and the ECMO circuit provides both cardiac and respiratory support. In VA ECMO, venous blood is withdrawn, oxygen is added, and CO_2 removed similar to VV ECMO, but blood is returned to the arterial circulation. Cannulation for VA ECMO can be done peripherally, with withdrawal of blood from a cannula in the femoral or internal jugular vein and return of blood through a cannula in the femoral or subclavian artery. Alternatively, it can be done centrally, with withdrawal of blood directly from a cannula in the right atrium and return of blood through a cannula in the aorta. VA ECMO typically requires a high blood flow extracorporeal circuit.

Indications

VA ECMO provides both cardiac and respiratory support. Thus, it is used in situations of significant cardiac dysfunction that is refractory to other therapies, when significant respiratory involvement is suspected or demonstrated, such as treatment-resistant cardiogenic shock, pulmonary embolism, or primary parenchymal lung disease severe enough to compromise right heart function. Echocardiography should be used before ECMO is considered or started to identify severe left ventricular dysfunction which might necessitate the use of VA ECMO. The use of peripheral VA ECMO in the presence of adequate cardiac function may cause severe hypoxia in the upper part of the body (brain and heart) in the setting of a severe pulmonary shunt.

MEDICAL MANAGEMENT DURING ECMO

During ECMO, patients require supportive care and treatment for their underlying medical condition, including ventilator management, fluid management, and systemic anticoagulation to prevent circuit clotting, nutritional management, and appropriate antimicrobials. Maintenance of the ECMO circuit requires frequent monitoring by medical and nursing staff and evaluation at least once per 24 hours by a perfusion expert.

ECMO may be associated with significant complications, which can be related to the vascular access required to the need for systemic anticoagulation, including hemorrhage, limb ischemia, compartment syndrome, cannula thrombosis, and limb amputation. Patients are also at risk of progression of their underlying disease process.

EVIDENCE SUMMARY

The ideal study design to evaluate the specific therapeutic effects of VA ECMO or VV ECMO for adult respiratory and cardiorespiratory conditions would be multicenter randomized controlled trials (RCTs) that compare ECMO with best standard therapy, such as mechanical ventilation. RCTs are needed to adequately control for confounding factors, evaluate adverse effects, safety, effectiveness, and individual patient differences (age, condition, and severity of illness) compared to standard therapy. The RCT is the most rigorous and reliable study design for demonstrating a causal relationship between the therapy under investigation and the health outcomes of interest. Specifically, questions regarding appropriate patient selection, standardization, and duration of ECMO treatment and complication and survival rates, would be addressed. However, there are challenges in conducting RCTs to evaluate ECMO due to several factors, such as small patient populations and the urgent and emergent setting in which EMCO is typically utilized. Given these confounding factors, data from large randomized controlled trials are not expected in the near future.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of utilizing ECMO as a treatment of respiratory or cardiac failure in adults is greater than the combined influence of all confounding factors for the given condition.[11] Given that RCTs are unlikely, evidence from non-randomized trials may be considered when treatment with ECMO results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible concurrent treatments or natural progression of the disease. Currently, there is limited evidence of this magnitude regarding patient selection, timing and therapeutic strategies in adult patients with respiratory or cardiac failure.[12, 13] Therefore large studies with adequate follow-up are needed in order to validate appropriate patient selection criteria, treatment strategies and timing of ECMO use.

ECMO IN ADULTS WITH ACUTE RESPIRATORY FAILURE

The current evidence regarding ECMO in adult patients is primarily limited to nonrandomized studies with heterogenous patient populations, treated at various healthcare institutions with differing ECMO treatment protocols. In addition, ECMO technology and treatment protocols have evolved over the past several decades with the use of lung-protective ventilation systems.[12, 13] Therefore, the following literature review focuses on systematic reviews and meta-analyses regarding the use of ECMO in adults in the past two decades.

Systematic Reviews and Technology Assessments

Turgeon (2024) published a systematic review and meta-analysis of the impact of ECMO on long-term outcomes of patients with severe ARDS.[14] The review included one RCT and 31 observational studies, seven of which compared ECMO to conventional mechanical ventilation. The reviewers rated most studies as low (45%) or fair (32%) quality. There was no significant difference in health-related quality of life, measured with the SF-36 scale, between ECMO and conventional mechanical ventilation patients (physical component score [PCS]: mean difference 3.91 (- 6.22 to 14.05), mental component score [MCS] mean difference 1.33 (- 3.93 to 6.60)). There was no difference between cognitive function, mental health, functional status, and respiratory symptoms between ECMO and conventional mechanical ventilation, but data available for comparison were limited. There were high rates of disability for ECMO survivors with 49% of patients returning to work and 23% needing assistance at home on follow-up.

Shrestha (2022) performed a systematic review and meta-analysis of trials conducted after 2000 comparing ECMO to standard mechanical ventilation in patients with ARDS.[15] 12 studies, two of which were RCTs, were included in the meta-analysis. ECMO did not significantly improve in-hospital mortality (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.40 to 1.41) or hospital length of stay (mean deviation, 3.92; 95% CI, -6.26 to 14.11). However, 30-day (OR, 0.56; 95% CI, 0.37 to 0.84) and 90-day (OR, 0.59; 95% CI, 0.41 to 0.85) mortality improved in patients treated with ECMO compared with those managed with standard mechanical ventilation.

The systematic review by Chong (2022) analyzed the use of ECMO in coronavirus disease 2019 (COVID-19) and compared the clinical characteristics between COVID-19 survivors and non-survivors.[16] 16 cohort studies with 706 COVID-19 patients who required ECMO were included in this study. The survivors of COVID-19 who required ECMO were younger than the non survivors (51 vs. 55 years old), had fewer comorbidities, less renal replacement therapy, and vasopressor requirement. The duration of mechanical ventilation before ECMO support initiation and total ECMO support duration was similar among survivors and non-survivors. Another systematic review and meta-analysis by Ling (2022) comments on the extensive use

of ECMO for COVID-19 from December 2019 to January 2022 in adults.[17] This analysis included 52 studies comprising 18,211 patients in the meta-analysis. The authors concluded that the mortality rate for patients receiving ECMO for COVID-19-related ARDS has increased as the pandemic has progressed. Mortality could be predicted based on age, time of final patient enrollment, administration of corticosteroids, and reduced duration of ECMO run.

A systematic review and meta-analysis by Ramanathan (2021) evaluated the use of ECMO in patients with COVID-19 on patient survival.[18] The meta-analysis included 22 retrospective observational studies with a total of 1,896 patients. Of the 19 studies that reported ECMO modality, VV ECMO was predominately used (98.6%). The pooled in-hospital mortality of COVID-19 ECMO patients was 37.1% (95% CI 32.3 to 42.0%). However, this analysis included patients that were still hospitalized (including 68 patients still on ECMO), so the calculated mortality is likely an underestimate of the true value. For the 18 studies that reported complications (n=1,721), there were 1,583 reported complications. Renal complications were the most common (559), followed by mechanical complications (429) and infection (171).

Combes (2020) performed an individual patient data meta-analysis of the two most recent RCTs that compared VV ECMO to standard mechanical ventilation in severe ARDS. The two RCTs included a total of 429 patients.[19] The primary outcome of the meta-analysis was 90-day mortality. Mortality rates at 90 days were 36% in the ECMO group and 48% in the standard mechanical ventilation group (relative risk [RR] 0.75, 95% CI 0.6 to 0.94, p=0.013, I^2=0%). The risk of 90-day treatment failure, defined as death for the ECMO group and death or crossover to ECMO for the mechanical ventilation group, was also lower in the ECMO group (RR 0.65, 95% CI 0.52 to 0.8, I^2=0%).

Aoyama (2019) reported results of a systematic review and meta-analysis analyzing mortality in ARDS patients following different lung protective ventilation strategies.[20] Included studies were limited to RCTs of interventions for adults with moderate to severe ARDS that used lung protective ventilation. A total of 25 RCTs were included evaluating nine interventions. Prone positioning and VV ECMO were found to have a statistically significant association with lower 28-day mortality compared with lung protective ventilation alone (prone positioning: RR 0.69, 95% credible interval 0.48 to 0.99, low quality of evidence; VV ECMO RR 0.60, 95% CI 0.38 to 0.93, moderate quality of evidence).

Vaquer (2017) performed a systematic review and meta-analysis analyzing complications and hospital mortality associated with ARDS patients who underwent VV ECMO.[21] Twelve studies were included that comprised 1,042 patients with refractory ARDS. The pooled mortality at hospital discharge was 37.7% (z = -3.73; CI 95% = 31.8 to 44.1; I2 = 74.2%; p<0.001). This review included some H1N1 populations. H1N1 as the underlying cause of ARDS was determined to be an independent moderator of mortality.

In 2015, the Washington State Health Care Authority published a health technology assessment (HTA) for ECMO in adults.[22] Evidence of clinical efficacy of ECMO compared to conventional treatment included RCTs, good-quality comparative cohort studies, and good-quality systematic reviews. The review identified two RCTs, both of good quality. Among the 41 comparative cohort studies identified, 16 were of good quality, eight of fair quality and 17 of poor quality. The bulk of the good quality evidence was for pulmonary support, including two randomized control trials[23, 24] and six observational studies. Based on the evidence, which was admitted to have significant limitations for some indications, and expert consensus, the

committee determined that ECMO is effective for patients with severe life-threatening respiratory or cardiac dysfunction that is not responding to conventional management but is potentially reversible; as a bridging therapy for patients in pulmonary and/or cardiac failure for transplantation.

Tramm (2015) published a Cochrane review on the use of ECMO for critically ill adults. The reviewers included RCTs, quasi-RCTs, and cluster RCTs that evaluated VV or VA ECMO compared with conventional respiratory and cardiac support.[25] Four RCTs were identified (Peek [2009][24], Morris [1994][26], Bein [2013][23], Zapol [1979][27]), which are described below. Combined, the trials included 389 subjects. Inclusion criteria (acute respiratory failure with specific criteria for arterial oxygen saturation and ventilator support) were generally similar across studies. Risk of bias was assessed as low for the trials by Peek, Bein, and Zapol, and high for the trial by Morris. The reviewers were unable to perform a meta-analysis due to clinical heterogeneity across studies. The Morris and Zapol trials were not considered to represent current standards of care. The reviewers summarized the outcomes from these studies (findings described individually above). They concluded: “We recommend combining results of ongoing RCTs with results of trials conducted after the year 2000 if no significant shifts in technology or treatment occur. Until these new results become available, data on use of ECMO in patients with acute respiratory failure remain inconclusive.”

Schmidt (2015) conducted a systematic review of studies reporting outcomes for extracorporeal gas exchange, including both ECMO and $ECCO_2R$, in adults with acute respiratory failure.[28] The review identified 56 studies, of which four were RCTs, seven were case-control studies, and 45 were case series. Two of the RCTs evaluated $ECCO_2R$ in ARDS patients, while the other two evaluated ECMO in ARDS. One RCT evaluating ECMO in ARDS was from the 1970s and was noted to have significant methodologic issues. The second RCT evaluating ECMO in ARDS was the CESAR trial (described above). The reviewers have reported that retrospective cohort studies of ECMO using more updated technology reported high rates (approximately 60% to 80%) of short-term survival. The RCTs reporting on $ECCO_2R$ in ARDS patients included those by Morris (1994) and Bein (2013). As noted in the Randomized Controlled Trials section below, the Morris trial was stopped early due to futility. In the second RCT of $ECCO_2R$ in ARDS (Bein), the number of ventilator-free days did not differ significantly between groups.

Zampieri (2013), reported the results of a systematic review and meta-analysis evaluating the role of VV ECMO for severe acute respiratory failure in adults.[29] The authors searched for RCTs and observational case-control studies with severity-matched patients that evaluated the use of ECMO in severe acute respiratory failure in adults. Three studies were included in the meta-analysis that comprised a total of 353 patients of whom 179 received ECMO, one RCT (CESAR trial,[30] described below) and two case control studies[31, 32] with severity-matched patients. For the primary analysis, the pooled in-hospital mortality in the ECMO-treated group was not significantly different from the control group (OR, 0.71; 95% CI, 0.34 to 1.47; p=0.358). Both nonrandomized studies included only patients treated for H1Noneinfluenza A infection, which may limit their generalizability to other patient populations.

Zangrillo (2013), reported the results of a systematic review and meta-analysis that evaluated the role of ECMO for respiratory failure due to H1N1 influenza A infection in adults.[33] The meta-analysis included eight studies, all observational cohort studies, that included 1357 patients with confirmed or suspected H1N1 infection requiring ICU admission, 266 (20%) of whom were treated with ECMO. The median age of those receiving ECMO was 36 years, with

43% men. In 94% of cases, VV ECMO was used, with VA ECMO used only in patients presenting with respiratory and systolic cardiac failure or unresponsive to VV ECMO. The median ECMO use time was 10 days. Reported outcomes were variable across the studies, but in a random-effects pooled model, the overall in-hospital mortality was 27.5% (95% CI, 18.4% to 36.7%), with a median ICU stay of 25 days and an overall median length of stay of 37 days.

Hirshberg (2013) conducted a review of evidence regarding ECMO use in critically ill adults with ARDS.[34] Studies included in the review were limited to the two most recent years' publications. A total of 12 case series and 12 review articles were considered in the assessment. Successful ECMO treatment of ARDS secondary to H1N1 was reported within the literature; however, studies were limited in the discussion of alternative modes of ventilation or other interventions. In addition, two national registry reports published conflicting conclusions regarding H1N1-related ARDS and ECMO treatment.[31, 32] The authors made key observations, concluding:

- Increase in ARDS survival over time makes historical controls and comparisons to determine the efficacy of ECMO challenging and likely unreliable.
- Scientifically credible evidence to support the use of ECMO in the routine management of patients with ARDS is lacking.
- The use of ECMO as a salvage therapy in practice biases the interpretation of case series results.

Additional systematic reviews[35, 36] were identified which also noted the heterogeneous nature of patients studied as well as a lack of well-designed randomized trials comparing ECMO to other therapies.

There are some older systematic reviews on H1N1-related respiratory distress/failure published prior to 2013 that will not be described in detail here.[37-39]

Randomized Controlled Trials

Combes (2018) reported the results of an RCT comparing the use of ECMO to conventional treatment for severe ARDS.[40] The ECMO group included 124 patients and the control group included 125. Sixty-day mortality was 35% and 46% in the ECMO and control groups, respectively, and the relative risk was 0.76 (95% CI 0.55 to 1.04, p=0.09). From the control group, 35 patients who had refractory hypoxemia crossed over to the ECMO group. Of these, 20 (57%) died. Differences in frequency of complications between groups included a greater number of bleeding events leading to transfusions, more cases of severe thrombocytopenia, and fewer cases of ischemic stroke in the ECMO group. One limitation of this study involves the risk of bias due to crossover, such as carryover, period effects, and missing data. Another limitation of this study was the possible confounding factors associated with non-standardized treatment protocols between the two groups. The ECMO group underwent percutaneous venovenous cannulation and was given heparin in varying doses to achieve a targeted activated PTT time; the control group was not exposed to these variables. In contrast, the control group was exposed to ventilatory treatment, neuromuscular blocking agents, and prone positioning that differed from the comparative group, limiting the generalizability of any findings.

The Xtravent study, reported by Bein (2013), randomized patients with ARDS to a strategy of low tidal volume ventilation combined with $ECCO_2R$ (n=40) or a conventional ventilation

strategy (n=39).[23] For the study's primary end point (28 and 60 ventilator-free days), there was no significant difference between treatment groups. However, the interventions evaluated are better characterized as pumpless extracorporeal lung assist devices (CO_2 removal only), making them less relevant to the evaluation of ECMO.

Peek (2010) conducted an RCT and economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation in adults with severe respiratory failure (CESAR trial).[30] Patients were 18 to 65 years old with severe, but reversible, respiratory failure (defined as a Murray score ≥ 3.0), or uncompensated hypercapnia with a pH <7.20. The primary study outcome was death or severe disability at six-month follow-up. Secondary outcomes included: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of intensive care unit stay, and length of hospital stay - and (for ECMO patients only) mode (VV or VA), duration of ECMO, blood flow and sweep flow. Exclusion criteria were: high pressure (>30 cm H_2O for peak inspiratory pressure) or high FIO_2 (>0.8) ventilation for more than seven days; intracranial bleeding; other contraindication to limited heparinization; or any contraindication to continuation of active treatment. A total of 180 patients (90 in each arm) were randomized from 68 centers. Data from 87 patients in the conventional management (CM) group and 68 patients from the ECMO group were available at six-month follow-up. Authors reported significantly better mortality and disability rates in the ECMO arm compared to the CM arm six months after randomization, (33/90 [36.7%] versus 46/87 [52.9%] respectively). However, these outcomes included the 22 patients who were randomized to the ECMO treatment arm, but who never received ECMO due to death or improvement with conventional treatment. A comparison of patients actually treated with ECMO to those treated with CM did not result in a significant difference between groups [33/68 (49%) versus 46/87 (52.9%) respectively] at six-month follow-up. The study is further limited by a lack of standardized mechanical ventilation management in the CM group.

Two early small RCTs were identified that compared some form of extracorporeal support with standard care. They are described here briefly. Morris (1994) reported the results of an RCT comparing a ventilator strategy of low-frequency positive-pressure ventilation (LFPPV) $ECCO_2R$ (ECCO2R; n=21) to standard care (n=19) in adults with ARDS.[26] In this trial, there was no significant difference in 30-day survival between groups (33% for LFPPV-ECCO2R patients vs 42% for conventional ventilation patients; p=0.8), although the trial was stopped early due to futility. The clinical practices in this trial are likely not representative of current practice. In a very early RCT, Zapol (1979)[27] compared mechanical ventilation with partial VA bypass (n=42) to conventional ventilation (n=48) in individuals with severe hypoxemic respiratory failure.

Nonrandomized Studies

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for cardiac or respiratory failure due to a variety of conditions. Several key nonrandomized comparative studies are reviewed below:

Shaefi (2021) published a multicenter retrospective cohort study examining ECMO receipt versus no ECMO receipt within seven days of ICU admission in mechanically ventilated patients with severe respiratory failure due to COVID-19.[41] The study used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) and performed a target trial emulation that included 130 ECMO-treated patients and 1,167 patients who did not receive ECMO. During a median follow-up of 38 days, 45 (34.6%) patients

who received ECMO and 553 (47.4%) patients who did not died (adjusted HR 0.55, 95% CI 0.41 to 0.74).

Davies (2009), published an observational series to characterize patients with influenza A (H1N1)-associated ARDS treated with ECMO.[42] A total of 61 patients with confirmed H1N1 influenza (n=53) or influenza A, not otherwise subtyped (n=8) and an additional 133 influenza patients treated with mechanical ventilation were included in the study. Compared to the 133 patients who improved with conventional care, median days of mechanical ventilation were longer in patients treated with ECMO (18 [9 to 27] vs. 8 [4 to 14] days, p=0.001), median ICU days were higher (22 [13 to 32] vs. 12 [7 to 18] days, p=0.001) and ICU mortality was higher (23% vs. 9%, p=0.01). At the point of data assessment, 48 (71%) of the ECMO patients had survived to ICU discharge, 14 (21% mortality) had died, and six remained in the ICU. Of the 22 patients still remaining in the hospital, 16 had survived to ICU discharge. By comparison, the non-ECMO cohort had 13% mortality at the time of reporting, suggesting no observable benefit with ECMO treatment.

Additional nonrandomized studies regarding the use of ECMO for a variety of conditions have been published[43-52], with a majority of studies reporting an overall survival to discharge ranging from 50% to 68%[46, 47, 53-55] in patients with severe respiratory failure. Overall, these publications suggest some survival benefit with ECMO treatment; however, 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.
- Results from studies with short-term follow-up (hospital discharge) are not adequate to determine the durability of the treatment effect.
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.

Section Summary: Acute Respiratory Failure

Although evidence to establish standardized protocols regarding patient selection and treatment strategies is lacking, there is sufficient evidence to suggest the use of ECMO in patients with severe acute respiratory or cardiac failure may provide some survival benefit when the risks associated with mechanical ventilation are very high. Questions remain about the generalizability of findings from the CESAR trial and nonrandomized study results to other patient populations, and further clinical trials in more specific patient populations are needed.

ECMO IN ADULTS AS A BRIDGE TO TRANSPLANTATION

The evidence related to the use of ECMO as a bridge to transplantation consists of three large nonrandomized comparative studies and small case series ranging from 13 to 46 patients.[48, 53, 56-66] Some retrospective studies have compared outcomes for patients treated with and without ECMO preoperatively. Overall, these studies report success rates of 81 to 87%, and one-year survival rates of 74 to 100%. Adverse events reported in these series include: renal failure requiring temporary dialysis, pulmonary infections, sepsis, tracheostomy required, and distal digital ischemia. Since ECMO is generally determined to be medically necessary as a bridge to transplant, the published studies are not described in detail. Of note, three large studies are described below.

Fukuhara (2018) performed a retrospective analysis of the use of ECMO as a bridge to heart

transplant in patients whose data were collected by the United Network of Organ Sharing (UNOS).[67] Of 25,168 recipients identified between 2003 and 2016, 104 were bridged with ECMO and 6,148 were bridged with a continuous-flow left ventricular assist device (CF-LVAD). Differences between the groups at baseline included younger age, more likely to have severely disabled functional status, shorter waitlist time, higher model for end-stage liver disease excluding international normalized ration (MELD-XI) score, and more frequent mechanical ventilation in the ECMO group as compared to the CF-LVAD group. Kaplan-Meier calculated estimated posttransplant survival was 73.1% and 93.1% in the ECMO and CF-LVAD groups, respectively at 90 days ($p<0.001$) and 67.4% and 82.4% in the ECMO and CF-LVAD groups, respectively at three years ($p<0.001$). Multivariable logistic and Cox regression analyses showed that for ECMO patients, the only contributor to both 90-day and three-year mortality was MELD-XI score. Limitations of this study include a difference in cohort size between the groups and a high rate of missing data.

Moonsamy (2020) also performed a retrospective analysis of ECMO as a bridge to heart transplant in patients in the UNOS database, but for procedures conducted between 2005 and 2017.[68] Of 24,905 recipients identified, 177 were bridged with ECMO, 203 were bridged with temporary circulatory support-ventricular assist devices (TCS-VAD), and 7,904 were bridged with a left ventricular assist device (LVAD). Unadjusted posttransplant survival at one and five years was 90 ± 0.4% and 77 ± 0.7% for durable LVAD, 84 ± 3% and 71 ± 4% for all TCS-VAD types, 79 ± 9% and 73 ± 14% for biventricular TCS-VAD, and 68 ± 3% and 61 ± 8% for ECMO. According to the propensity-matched pairwise comparisons, ECMO had significantly poorer outcomes ($p=0.019$) than all TSC-VAD, which had similar outcomes to LVAD ($p=0.380$). According to the Cox analysis, ECMO was a predictor of posttransplant mortality compared with TSC-VAD (hazard ratio [HR] 2.4, 05% CI 1.44 to 4.01, $p=0.001$).

Schechter (2016) published a survival analysis comparing types of preoperative support prior to lung transplantation, using data from UNOS.[69] Included in the analysis were 12,403 adult lung transplantations from 2005 through 2013: 11,607 (94.6%) did not receive invasive support prior to transplantation, 612 (4.9%) received invasive mechanical ventilation (iMV) only, 119 (1%) received iMV plus ECMO, and 65 (0.5%) received ECMO only. Table 2 shows the cumulative survival for patients at six months, one year, and three years, by support prior to transplantation. Compared to patients with no invasive support, patients receiving iMV with or without ECMO had an increased mortality risk. The mortality of patients receiving ECMO alone was not significantly different from patients receiving no support at three years. A limitation of the study is related to the use of registry data, in that complications due to the bridge strategy and certain details, such as equipment and technique of ECMO, are not available. In addition, underlying demographic differences are not represented in the comparisons.

Table 2. Cumulative Survival among Patients Undergoing Lung Transplantation, by Type of Support (Schechter 2016)

Support	N	6 Months	1 Year	3 Years
No support	11,607	89.4%	84.2%	67.0%
Invasive mechanical ventilation only	612	79.9%	72.0%	57.0%
Invasive mechanical ventilation plus ECMO	119	68.1%	61.0%	45.1%
ECMO only	65	75.2%	70.4%	64.5%

ECMO: extracorporeal membrane oxygenation.

Jayarajan (2014) evaluated survival rates of ECMO and mechanical ventilation (MV) treatment as a bridge to heart-lung transplantation (HLT).[70] The primary study outcome was risk-adjusted all-cause mortality. Of 542 adult patients who received HLT between 1995 and 2011, 15 (2.8%) received ECMO and 22 (4.1%) received MV as a bridge to transplantation. At 30-day survival, the ECMO group had worse survival than the control group (patients who did not receive either ECMO or MV) (20% vs. 83.5%, respectively). Similar results were reported at 5-year survival (20% vs. 47.4%, respectively; p<0.001). Both ECMO (HR 3.820, p=0.003) and MV (HR 2.011, p=0.030) were independently associated with mortality. The authors concluded that HLT recipients receiving ECMO or MV as a bridge to transplantation had increased short and long-term mortality and that additional studies were needed in order to establish optimal treatment protocols and patient selection criteria for ECMO as a bridge to HLT.

ECMO IN ADULTS WITH REFRACTORY CARDIOGENIC SHOCK

Systematic Reviews

Zavalichi (2020) performed a systematic review of studies of VA ECMO for patients with cardiogenic shock due to myocardial infarction.[71] Nine observational studies with a total of 1,998 adult patients were included. The quality scores of the included studies ranged from 5 to 9, with a mean quality score of 7 (medium-to-high quality). The survival rate at discharge ranged from 30.0% to 79.2%. Rates of acute kidney failure were reported in only three studies and ranged from 24% to 47%. Other reported complications included hypoxic ischemic encephalopathy (75% and 45.7% in the two reporting studies), gastrointestinal bleeding (3.6% in one study) and multiple organ failure (48.8% and 39.1% in the two reporting studies).

Biancari (2018) performed a systematic review and meta-analysis of patients requiring postcardiotomy VA-ECMO.[72] A total of 31 studies, 25 of which were considered good quality, were included in the analysis and with a total of 2,986 patients. The mean age of patients was 58.1 years. Hospital survival was 36.1%, which was not influenced by study quality. The mean duration of ECMO was not associated with hospital survival. The weaning rate from VA-ECMO, pooled rate of reoperation for bleeding, and major neurological event were 59.5%, 42.9%, and 11.3%, respectively. Rates of lower limb ischemia, deep sternal wound infection/mediastinitis, and renal replacement therapy were reported as 10.8%, 14.7%, and 47.1%, respectively. Patients stayed in the intensive care unit for a mean of 13.3 days. From the 11 studies that reported Kaplan-Meier estimates of one-year survival including operative deaths, the pooled one-year survival rate after postcardiotomy VA-ECMO was 30.9%. Limitations of this analysis include that many of the included studies were small and retrospective and used heterogeneous procedures.

Wang (2018) reported the results of a meta-analysis of 20 observational studies of ECMO for postcardiotomy cardiogenic shock.[73] A total of 2,877 patients were included in the analysis. The pooled rates of one-year survival and midterm survival were 34.0% and 24.0%, respectively. Leg ischemia, redo surgery, renal failure, neurologic complications, and infection were reported in 18.0%, 14.0%, 50.0%, 57.0%, 16.0%, and 31.0% of patients, respectively. Commonly reported risk factors of in-hospital mortality were age greater than 65 years, pre-ECMO or post-ECMO blood lactate, renal insufficiency, a longer duration of ECMO, and neurologic complications.

Xie (2015) reported on a meta-analysis evaluating VA ECMO for cardiogenic shock and cardiac arrest that included observational studies and clinical trials with at least 10 adult patients.[36] Twenty-two studies, all observational, with a total of 1199 patients (12 studies

[n=659 patients] with cardiogenic shock; five studies [n=277 patients] with cardiac arrest; five studies [n=263 patients] with both patient types) met inclusion criteria. Across the 16 studies (n=841 patients) that reported survival to discharge, the weighted average survival was 40.2% (95% CI 33.9% to 46.7%). Across the 14 studies that reported 30-day survival, the weighted average survival was 52.8% (95% CI 43.9% to 61.6%), with similar survival rates at three, six, and 12 months across studies that reported those outcomes. Across studies that reported on cardiogenic shock only, the weighted average survival to discharge was 42.1% (95% CI 32.2% to 52.4%, I^2=79%). Across all studies, complications were common, most frequently acute kidney injury (pooled incidence 47.4%, 95% CI 30.2% to 64.9%, I^2=92%), followed by renal dialysis (pooled incidence 35.2%, 95% CI 23% to 47.4%, I^2=95%) and reoperation for bleeding (pooled incidence 30.3%, 95% CI 1.8% to 72.2%, I^2=98%). However, the authors noted that it is uncertain that the complications were entirely due to ECMO, given the underlying illness in patients who receive ECMO.

Randomized Controlled Trials

Ostadal (2023) published results of a multicenter RCT that compared immediate implementation of VA-ECMO (n=58) to an initially conservative therapy that permitted downstream use of VA-ECMO (n=59), in patients with either rapidly deteriorating or severe cardiogenic shock.[74] The composite primary end point was death from any cause, resuscitated circulatory arrest, and implementation of another mechanical circulatory support device at 30 days. The composite primary end point was similar between the two treatment groups and occurred in 37 (63.8%) and 42 (71.2%) patients in the immediate VA-ECMO and the no early VA-ECMO groups, respectively (HR, 0.72; 95% CI, 0.46 to 1.12; p=0.21). VA-ECMO was used in 23 (39%) of the no early VA-ECMO patients. 30-day incidence of resuscitated cardiac arrest, all-cause mortality, and serious adverse events (sepsis, pneumonia, stroke, leg ischemia, and bleeding) were not significantly different between the two treatment groups. The authors concluded that immediate implementation of VA-ECMO in patients with cardiogenic shock did not improve clinical outcomes compared to an early conservative treatment that allowed downstream use of VA-ECMO in cases of worsening hemodynamic status.

Nonrandomized Studies

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for refractory cardiogenic shock. Several key nonrandomized studies that are either large or comparative are reviewed below:

Kowalewski (2021) published a retrospective case review of 7,185 adults included in the Extracorporeal Life Support Organization registry who received VA ECMO for PCCS between January 2010 and December 2018.[75] Successful weaning from ECMO was achieved in 56.4%, and survival to hospital discharge occurred in 41.7%. Complications included kidney failure (48.9%), surgical site bleeding (26.4%), cardiac arrhythmias (15.9%), sepsis (12.1%), metabolic disorders (26.9%), and neurologic complications (9.1%).

Biancari (2021) reported survival rates among 665 patients who received VA ECMO for postcardiotomy cardiogenic shock between January 2010 and March 2018 at 17 cardiac surgery centers.[76] Of the 665 patients in the study, only 240 (36.1%) survived to hospital discharge. With a mean follow-up of 1.7 years for the overall cohort and 4.6 years for the patients who survived to hospital discharge, the five-year survival rate was 27.7% for the overall cohort and 76.9% for the cohort of patients surviving to hospital discharge. The five-

year survival rate was lower in patients greater than 70 years of age (12.2% vs 34.4% in younger patients; HR, 1.84; 95% CI, 1.522 to 2.224).

Hernandez-Montfort (2020) published a report of longitudinal outcomes of patients with advanced heart failure and cardiogenic shock treated with temporary circulatory support.[77] Patients registered into the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support with continuous flow left ventricular assist devices or biventricular assist devices were analyzed. Of the 5,632 patients treated with pre-operative temporary circulatory support, ECMO was used in 1,138 cases and intra-aortic balloon pumps (IABP) were used in 3,901 cases. Patients treated with ECMO had greater need of biventricular support after durable ventricular assist devices (22% ECMO, 5% IABP, and 7% other TCS; p<0.001) and longer post-implant intensive care stays (ECMO 24 days, IABP 14 days, and other TCS 12 days; p<0.001). Propensity score matching analysis indicated ECMO was associated with a higher hazard impacting early phase survival vs. other temporary circulatory support (hazard ratio, 1.80; p<0.01) and IABP (hazard ratio, 1.65; p<0.01).

Lemor (2020) reported a retrospective comparison between ECMO and Impella placement in 6,290 patients with cardiogenic shock secondary to acute myocardial infarction.[78] Study data was derived from the National Inpatient Sample, a publicly available database of all-payer hospital inpatient stays developed by the Agency for Healthcare Research and Quality. After propensity score matching (n=450 propensity score-matched patients per treatment), in-hospital mortality was higher among patients who received ECMO (43.4% vs 26.7%, OR 2.10; 95% CI 1.12 to 3.95, p=0.021). Before propensity score matching, the incidence of acute ischemic stroke was greater in the ECMO group (OR 3.28, 95% CI 1.04 to 10.31, p=0.042), but this difference was not significant after propensity score matching (OR 5.24, 95% CI 0.60 to 45.68, p=0.134). Vascular complications were greater in ECMO-treated patients (propensity score-matched cohort OR 2.87, 95% CI 1.01 to 8.28, p=0.05).

A retrospective case series reported by El Sibai (2018) reported outcomes of patients undergoing ECMO for cardiogenic shock. Of the 922 patients included in the study, 51.0% survived to hospital discharge. Mean length of stay was 21.8 days. An association was reported between increased mortality and respiratory diseases, genitourinary diseases, undergoing an echocardiogram, and presenting during seasons other than Fall. A decrease in mortality was associated with injury and poisoning, certain vascular procedures, and increased length of stay.

Aso (2016) analyzed 5,263 patients from the Japanese Diagnosis Procedure Combination database who received VA ECMO during hospitalization.[79] Reasons for receiving VA ECMO included: cardiogenic shock (88%), pulmonary embolism (7%), hypothermia (2%), trauma (2%), and poisoning (1%). Among patients in the cardiogenic shock group, 33% died during VA ECMO, 40% died after weaning from VA ECMO, and 25% were discharged following weaning from VA ECMO. Multivariate logistic regression for in-hospital mortality showed an increased risk among patients 60 years of age and older, a BMI less than 18.5 kg, a BMI of 25 kg or more, ischemic heart disease, myocarditis, use of intra-aortic balloon pumping, use of continuous serial replacement therapy, and cardiac arrest.

Diddle (2015) reported on 147 patients (150 ECMO runs), treated with ECMO for acute myocarditis, who were identified from the Extracorporeal Life Support Organization database.[80] Patients in this group were relatively young (median age, 31 years) and were most often treated with VA ECMO (91%). Of the cohort, 101 (69%) were decannulated from

ECMO and 90 (61%) survived to discharge. In multivariable analysis, the occurrence of pre-ECMO cardiac arrest and the need for higher ECMO support at four hours were significantly associated with in-hospital mortality (OR 2.4, 95% CI 1.1 to 5.0, p=0.02 for pre-ECMO arrest; OR 2.8, 95% CI 1.1 to 7.3, p=0.03 for increased ECMO support at four hours).

Chamogeorgakis (2013) conducted a retrospective chart review of patients with cardiogenic shock at a single center, comparing outcomes of 18 patients treated with a temporary miniaturized percutaneous ventricular assist device (mpVAD) with 61 patients who underwent ECMO.[81] The patient population was mostly male adults who had had myocardial infarction documented during the same hospital admission. Mean follow-up time was 14.3 months. No benefit from use of ECMO was found on in-hospital survival (ECMO 50.0% mp-VAD 49.2%), successful weaning off mechanical support (ECMO 33.3%, mp-VAD 19.7%), or bridging to long-term support or transplant (ECMO 27.8%, mp-VAD 31.1%).

Section Summary: Refractory Cardiogenic Shock

The evidence on ECMO for adults with refractory cardiogenic shock includes meta-analyses, case series, and several observational studies. For the use of ECMO in the failure to wean from bypass population, retrospective studies and case series found some successful cases of weaning patients from ECMO in the setting of very high expected morbidity and mortality rates. However, without comparative studies, it is difficult to assess whether rates of weaning from bypass are better with ECMO than with standard care. When used for refractory cardiogenic shock, ECMO is accompanied by high mortality and complication rates. A propensity score-matched retrospective cohort study found higher rates of in-hospital mortality with ECMO compared to Impella among patients with cardiogenic shock secondary to acute myocardial infarction.

ECMO-ASSISTED CARDIOPULMONARY RESUSCITATION

Systematic Reviews

Scquizzato (2022) published a systematic review and meta-analysis of two RCTs and four propensity score-matched studies of patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation with those treated with conventional cardiopulmonary resuscitation.[82] Patients treated with extracorporeal cardiopulmonary resuscitation had higher rates of survival with favorable neurological outcome (81 of 584 patients [14%] vs. 46 of 593 patients [7.8%]; OR = 2.11; 95% CI, 1.41 to 3.15; p<0.001) and of survival at the longest follow-up available compared with conventional cardiopulmonary resuscitation (131 of 584 patients [22%] vs. 102 of 593 patients [17%]; OR = 1.40; 95% CI, 1.05-1.87; p=0.02). Survival at hospital discharge or 30 days was similar among the two treatment groups (142 of 584 patients [24%] vs. 122 of 593 patients [21%]; OR = 1.26; 95% CI, 0.95 to 1.66; p=0.10).

Twohig (2019) reported a systematic review and meta-analysis of the effectiveness of ECMO-assisted cardiopulmonary resuscitation (ECPR) versus conventional CPR in patients in cardiac arrest.[83] 17 papers were included, six papers compared ECPR to CPR, three papers evaluated parameters of patients that survived ECPR, and three papers evaluated both. 11 papers were graded as being at moderate risk of bias and the remainder were considered to be at either serious or critical risk of bias. One comparative study was prospective and six used propensity scoring. ECPR showed a survival benefit (OR 0.40, p<0.001), and a greater likelihood of being neurologically intact (OR 0.10, p<0.001) compared to conventional CPR.

Having an initial shockable rhythm was associated with survival (OR 0.38) as was the arrest to ECPR time (mean difference -10.17 min, 95% CI -19.22 to -1.13), but high heterogeneity limits confidence in this finding.

Debaty (2017) published a systematic review and meta-analysis on prognostic factors for patients receiving ECPR following out-of-hospital refractory cardiac arrest, to inform the decision of which patients benefit most from ECPR.[84] The search included literature through September 2016. Fifteen retrospective and prospective cohort studies were included (total n=841 patients). The overall rate of a favorable outcome following ECPR was 15%, though the range among the studies was wide (0% to 50%) due to heterogeneity of inclusion criteria, outcome definition, and compliance with protocol. Favorable outcomes occurred more frequently among patients with initial shockable cardiac rhythms, shorter low-flow duration, higher arterial pH, and lower serum lactate concentration on hospital admission. No significant differences were found when age, gender, and bystander CPR attempt were evaluated.

Randomized Controlled Trials

Two RCTs evaluated the use of ECPR in out-of-hospital cardiac arrest. Yannopoulos (2020) reported the results of the Advanced REperfusion STrategies for Refractory Cardiac Arrest (ARREST) trial, a small (n=30) phase 2 adaptive RCT comparing early ECPR to standard emergency department-based advanced cardiac life support (ACLS) for out-of-hospital cardiac arrest.[85] Patients were randomized to treatment groups upon arrival to the hospital. Patients without pulses who were assigned to standard ACLS were treated for at least 15 minutes after emergency department arrival or for at least 60 minutes after the 911 call; after that, declaration of death or continuation of CPR was at the discretion of the treating emergency physician. Only two patients in the standard ACLS group achieved return of spontaneous circulation in the emergency department and were admitted to the hospital. In the early ECPR group, two patients were declared dead prior to starting ECMO due to severe metabolic derangement and hypoxemia on presentation. The trial was terminated early after a planned interim analysis showed that the posterior probability of ECMO superiority exceeded the prespecified monitoring boundary. Members of the data safety and monitoring board indicated given that the primary endpoint was survival to hospital discharge, that there were ethical concerns with continuing the trial in the presence of strong evidence for efficacy. The primary outcome, survival to hospital discharge, occurred in 6 of 14 (43%) patients treated with early ECPR and 1 patient of 15 (7%) treated with standard ACLS (risk difference 36.2%, 95% CI 3.7 to 59.2, posterior probability of ECMO superiority 0.9861). One patient in the early ECPR group withdrew from the study prior to discharge and was not included in the primary endpoint analysis. Cumulative survival over six months was significantly better with early ECPR than with standard ACLS treatment (HR 0.16, 95% CI 0.06 to 0.41, log-rank test $p<0.0001$). No unanticipated serious adverse events occurred during the trial; however, the small sample size of the trial limits its ability to detect differences in safety.

Behlolavek (2022) conducted a RCT at a single-center in the Czech Republic (the Prague OHCA [out-of-hospital cardiac arrest] study) comparing an early invasive approach including ECPR to a standard ACLS approach in adults experiencing refractory out-of-hospital cardiac arrest (n=264).[86] The participants were adults aged 18 to 65 years receiving ongoing resuscitation for a witnessed out-of-hospital cardiac arrest of presumed cardiac etiology. The trial was terminated early at the recommendations of the data safety and monitoring board because the standardized test statistics for results of the primary end point (survival with minimal or no neurologic impairment at 180 day) intersected a prespecified stopping rule for

futility. The authors concluded that an invasive strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation. The authors reanalyzed the data of the Prague OHCA trial dividing all participants into three cohorts: those who achieved prehospital spontaneous circulation (n=83), those who did not achieve prehospital spontaneous circulation and received conventional CPR (n=81), and those who did not achieve prehospital spontaneous circulation and received ECPR (n=92).[87] 180-day survival was longest in patients who achieved spontaneous circulation (61.5%) and lower in those who did not achieve spontaneous circulation (1.2% in patients with CPR and 23.9% in patients with ECPR). ECPR was associated with a lower risk of 180-day death (HR, 0.21; 95% CI, 0.14 to 0.31; p<.001).

Nonrandomized Studies

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for cardiopulmonary resuscitation. Several key nonrandomized studies that are large or comparative are reviewed below:

Park (2014) developed a predictive score for survival to discharge using a series of 152 consecutive patients who received ECPR for in-hospital cardiac arrest.[88] In this series, in-hospital death occurred in 104 (68.4%) patients. Factors significantly associated with improved survival were an age of 66 years or less, the presence of an arrest rhythm of pulseless electrical activity or ventricular fibrillation or pulseless ventricular tachycardia, shorter CPR to ECMO time, higher initial mean arterial pressure, and higher Sequential Organ Failure Assessment scores. A score developed from these factors and evaluated in a test set generated from the initial sample using a bootstrap method was associated with a sensitivity and specificity of 89.6% and 75.0%, respectively, for predicting survival to discharge. This score may help select patients for ECMO, but further validation is needed.

Maekawa (2013) reported results from a prospective observational cohort of adult patients who underwent ECPR after prolonged conventional CPR after out-of-hospital cardiac arrest.[89] The study included 162 patients, 53 in the ECPR group and 109 in the conventional CPR group. After propensity score matching, 24 patients in each group were analyzed. The survival rate was higher in the matched ECPR group (29.2%) than in the matched conventional CPR group (8.3%, p=0.018).

Shin (2011) compared ECPR with conventional CPR in adult patients who had undergone CPR for more than 10 minutes after witnessed in-hospital cardiac arrest.[90] 406 patients were included, 85 who underwent ECPR and 321 who underwent conventional CPR. The cause of arrest was considered cardiac in most cases (n=340 [83.7%]) and noncardiac (secondary to respiratory failure or hypovolemia) in the remainder (n=66 [16.3%]). The decision to initiate ECPR was made by the CPR team leader. Typically, the ECMO device was available in the catheterization laboratory, coronary care unit, and operating room, and an ECMO cart was transported to the CPR site within 5 to 10 minutes during the day and within 10 to 20 minutes at night. After propensity score matching, 120 patient pairs were included; in the matched group, ECPR was associated with significantly higher rates of survival to discharge with minimal neurologic impairment (OR for mortality or significant neurologic deficit, 0.17, 95% CI 0.04 to 0.68, p=0.012) and survival at six months with minimal neurologic impairment (HR 0.48, 95% CI 0.29 to 0.77, p=0.003).

In contrast, in a single institution cohort of 122 patients with in-hospital cardiac arrest of cardiac origin with prolonged (greater than 10 minutes) conventional CPR, Lin demonstrated no survival difference between patients who had return of spontaneous breathing after ECMO and those who had return of spontaneous circulation after conventional CPR.[91] After propensity score matching, 59 patients experienced return of spontaneous breathing after ECPR and 63 patients experienced sustained return of spontaneous circulation after conventional CPR. Acute coronary syndrome was the most common etiology of cardiac arrest, occurring in 73% of the ECPR patients and 50.9% of the conventional CPR patients. In the 27 ECPR response group, eight (29.6%) patients survived to discharge, while in the conventional CPR response group, five (18.5%) patients survived to discharge. In a multivariable model, ECPR was not associated with reduced mortality (adjusted HR 0.618, 95% CI 0.325 to 1.176 p=0.413).

In an earlier prospective study, Chen (2008) compared ECPR with conventional CPR in adult patients who had undergone prolonged (>10 minutes) conventional CPR after in-hospital cardiac arrest of cardiac origin.[92] 172 patients were included, 59 in the ECPR group and 113 in the conventional CPR group. The decision to call the extracorporeal life-support team was made by the physician in charge. The average duration from the call to team arrival was five to seven minutes during the day and 15 to 30 minutes overnight. Survival to discharge occurred in 17 (28.8%) patients in the ECPR group and in 14 (12.3%) patients in the conventional CPR group. In a multivariable logistic regression model to predict survival at discharge, use of ECPR was associated with reduce risk of death before discharge (adjusted HR 0.50, 95% CI 0.33 to 0.74, p=0.001).

Other noncomparative case series have described the use of ECPR for refractory cardiac arrest.[91, 93-103] Overall, these studies suggest that ECPR is feasible, particularly for in-hospital cardiac arrests, although mortality rates are high.

Section Summary: Cardiopulmonary Resuscitation

Evidence for the use of ECPR in cardiac arrest consists of a single RCT and meta-analyses of nonrandomized comparative studies, most of which demonstrated a survival benefit with ECPR. The ARREST trial enrolled 30 patients and found a significant difference in survival to discharge favoring early ECPR in the cardiac catheterization laboratory over standard ACLS management in the ED. However, only one patient in the standard ACLS group survived to discharge, so further studies are required to examine comparative effects on long-term survival and functional outcomes. In the other RCT, a strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation; however, the authors stated that "the trial was possibly underpowered to detect a clinically relevant difference." Nearly all of the nonrandomized comparative studies were retrospective and at risk of bias, limiting conclusions. Selection for ECMO in these studies was at the discretion of treating physicians, and although propensity matching was used in some studies, selection bias in the small studies may remain. Multiple unanswered questions remain about the role of ECPR in refractory cardiac arrest, including appropriate patient populations, duration of conventional CPR, and assessment of futility. Studies have begun to address the question of appropriate patient population, with results indicating that patients with an initial shockable cardiac rhythm, shorter low-flow duration, higher arterial pH, and lower serum lactate concentrations on hospital admission experienced favorable outcomes. Further study is needed to evaluate efficacy and define the population that may benefit from this treatment.

ECMO IN ADULTS WITH OTHER CONDITIONS

Systematic Reviews

Lazzeri (2013) evaluated the use of ECMO to improve outcomes after refractory cardiac arrest (CA).[104] Authors concluded that analyses of the available observational studies were characterized by heterogeneity and controversial results. In addition authors noted, "the impact of ECMO implantation in CA patients can be considered a clinical challenge, since it is strictly linked to the 'clinical selection of patients'", as well as the technical skills and experience of the team. The study concluded that improved outcomes from the use of ECMO, in patients with refractory CA, could not be established but that, "…optimal utilization requires a dedicated local health-care organization and expertise in the field (both for the technical implementation of the device and for the intensive care management of these patients). A careful selection of patients guarantees optimal utilization of resources and a better outcome."

In 2009, Cardarelli conducted a meta-analysis regarding the use of ECMO in adult patients in cardiac arrest or immediately after cardiopulmonary resuscitation (CPR).[39] Data was collected from observational studies published between: 1990-2007, and included 11 case series and nine case reports. A total of 135 patients were included in the analysis with a median age of 56 years (18 to 83). Overall survival to discharge in patients receiving ECMO was 40% (54 of 135 patients). Survival was notably improved in younger patients (17 to 41 years) and in patients where ECMO was used for short periods of time (0.875 to 2.3 days, odds ratio 0.2). Authors noted that major complications such as neurologic sequelae were not well described in the pooled studies.

Nonrandomized Studies

Myers (2020) reported results of a retrospective analysis of adult patients treated with ECMO who had septic shock at the time of cannulation.[105] A total of 32 patients met the inclusion criteria during the seven-year study period. Median ejection fraction was 51% and median time on ECMO was 5.8 days. 13 patients (41%) survived to discharge and median survival was 14.5 days. No statistically significant subgroup differences were reported.

Ro (2018) reported the outcomes of venoarterial ECMO in 71 adult patients with septic shock.[106] Of the 11 patients (15.5% of the total) that were successfully weaned from ECMO, five survived to discharge. This was compared to the rate of successful weaning in 253 cardiogenic shock patients receiving ECMO, which was 45.5% ($p<0.001$). Lactate levels, both pre- and six-hours-post-procedure, were significantly higher in the nonsurvivors ($p=0.002$).

Huesch (2018) published a retrospective chart review of outcomes, length of stay, and discharge destination of adult patients treated with ECMO between 2007 and 2015.[107] From a review of Pennsylvania state-regulated hospitals, 2,948 consecutive patients admitted for respiratory, cardiac, cardiac arrest, or uncategorized based on administrative data were treated with ECMO. The average observed death rate was 51.7%. Of patients who survived, 14.6% went home to self-care and 15.2% went to home health care. Readmission was reported for 43.8% within one month and 60.6% within one year.

Sauneuf (2017) evaluated patients admitted to the ICU for pheochromocytoma crisis. A total of 34 patients were included, 14 of whom received ECMO.[108] 90-day mortality was not significantly different between patients who were or were not treated with ECMO, despite the ECMO group having higher severity scores at admission.

Ramanathan (2017) analyzed data from the Extracorporeal Life Support Organization Registry database of patients treated with ECMO for community-acquired pneumonia and in 2019 of patients treated with ECMO for adenoviral pneumonia.[109, 110] Their data came from a greater than 10-year period, over which timethe number of patients treated with ECMO increased. Of the community-acquired pneumonia patients (a total of 1,055 patients), 66% survived. Duration of mechanical ventilation prior to extracorporeal membrane oxygenation, lower arterial pressure, fungal pneumonia, and advancing age were all factors indicated as predictors of mortality via a multiple regression analysis. Of the adenoviral pneumonia patients (a total of 542 patients), overall mortality was 58% overall (307/529 patients), and when divided by age, 86.4% for neonates (108 of 125), 49% for children (158 of 327), and 49% for adults (41 of 83).

Dangers (2017) reported the outcomes from 105 patients implanted with VA ECMO for acute decompensated heart failure at one ICU.[111] One-year survival was 42%. Independent predictors of one-year mortality were determined with multivariable analyses to be pre-extracorporeal membrane oxygenation Sequential Organ Failure Assessment score of more than 11, idiopathic cardiomyopathy, cardiac disease duration greater than two-years pre-ECMO, pre-ECMO blood lactate greater than 4 mmol/L.

Other nonrandomized studies reported outcomes following ECMO for trauma[112], as a bridge to long-term left ventricular assist device or durable mechanical circulatory support [113, 114], as post-cardiovascular surgery support[115], ischemic heart disease[116], COVID-19[117], and others[118].

ADVERSE EFFECTS OF ECMO IN ADULTS

Systematic Reviews

Hssain (2024) published a systematic review and meta-analysis of the incidence, risk factors, and outcomes of nosocomial infection in adult patients supported by ECMO.[119] 30 retrospective studies of 4,733 participants were included. 1,249 ECMO-related nosocomial infections per 1,000 ECMO days were reported. The pooled incidence of nosocomial infections across 18 studies involving 3,424 patients was 26% (95% CI 14 to 38%). Ventilator-associated pneumonia and bloodstream infections were the most common nosocomial infections. Infected patients had lower ECMO survival and overall survival rates compared to non-infected patients, with risk ratio values of 0.84 (95% CI 0.74 to 0.96, p=0.01) and 0.80 (95% CI 0.71 to 0.90, p<0.001), respectively.

Reid (2024) published a systematic review of obesity-related complications and mortality in adults with respiratory failure on ECMO.[120] 18 studies of 517 patients were included. Common complications included acute renal failure (175 of 377, 46.4%), venous thrombosis (175 of 293, 59.7%), and bleeding (28 of 293, 9.6%). Decreased mortality was associated with a body mass index greater than or equal to 30 (92, 37.1% of BMI <30 vs. 30, 11% of BMI ≥30, p ≤ 0.0001).

Abruzzo (2022) performed a systematic review of venous thromboembolic events in adults receiving ECMO support in patients with cardiac and respiratory dysfunction.[121] This review included studies that were published over the past 15 years, primary or original research publications, full text articles, and relevance to the research topic. This study reported that ECMO-supported patients not only experienced high rates of venous thrombosis (VT) and venous thromboembolism (VTE), ECMO was also a positive predictor for VTE. The study found that anticoagulation is critical for prevention and treatment of thromboses in patients on ECMO but can also increase complications including bleeding risk. Severe bleeding is a very

common complication that is seen in patients supported by ECMO and can require multiple blood transfusions. Due to the lack of knowledge and literature centered on this topic area, currently there are no official guidelines for prompt diagnosis by screening or to optimize prevention and treatment of VTE in this specific population.

Thongprayoon (2019) performed a systematic review and meta-analysis on the incidence and mortality risk of acute kidney injury in patients receiving ECMO.[122] A total of 41 studies met the inclusion criteria, including 10,282 patients receiving ECMO. Studies were only included if they reported acute kidney injury using standard definitions including RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcomes) classifications, severe acute kidney injury requiring renal replacement therapy (RRT), and mortality risk of AKI among adult patients (age ≥ 18 years old) on ECMO. The pooled estimated incidence of acute kidney failure and severe acute kidney failure requiring RRT while on ECMO were 62.8% (95%CI: 52.1% to 72.4%) and 44.9% (95%CI: 40.8% to 49.0%), respectively. In patients receiving RRT for acute kidney injury, the pooled OR was 3.73 (95% CI, 2.21 to 4.99).

A systematic review by Fletcher-Sandersjöö (2018) analyzed the incidence, outcome, and predictors of ECMO-associated intracranial hemorrhage in adult patients. 25 articles met inclusion criteria. In the included studies, the incidence of intracranial hemorrhage was between 1.8 and 21%. For patients who developed intracerebral hemorrhage, relative risk of mortality was 1.27 to 4.43 compared to those that did not.

Zangrillo (2013) conducted a systematic review and meta-analysis regarding outcomes and complications related to ECMO.[123] Studies reporting complications and mortality in 100 or more patients were included in the analysis. The primary outcome was mortality at the longest follow-up date, while secondary outcomes were fatal and non-fatal complications. A total of 12 studies were included (1763 patients) with ECMO treatment utilized for acute respiratory failure, cardiogenic shock, or both. The most common ECMO-associated complications were as follows:

- renal failure requiring continuous venovenous hemofiltration (52%)
- bacterial pneumonia (33%)
- any bleeding (33%)
- oxygenator dysfunction requiring replacement (29%)
- sepsis (26%)
- hemolysis (18%)
- liver dysfunction (16%)
- leg ischemia (10%)
- venous thrombosis (10%)
- central nervous system complications (8%)
- gastrointestinal bleeding (7%)
- aspiration pneumonia (5%)
- disseminated intravascular coagulation (5%).

The overall mortality at 30-day follow-up was 54%, with 45% of fatal events occurring during ECMO and 13% occurring after ECMO.

Cheng (2013) conducted a systematic review and meta-analysis evaluating complications related to ECMO treatment of cardiogenic shock or cardiac arrest in adult patients.[124] Studies

reporting complication rates and including at least 10 patients were included for a total of 20 studies (1,866 patients). The pooled estimated complication rates with 95% confidence were as follows:

Complication	Pooled Estimated Complication Rate (%)	95% Confidence Interval
Acute kidney injury	55.6	35.5% to 74.0%
Renal replacement therapy	46.0	36.7% to 55.5%
Rethoracotomy for bleeding or tamponade in postcardiotomy patients	41.9	24.3% to 61.8%
Major or significant bleeding	40.8	26.8% to 56.6%
Significant infection	30.4	19.5% to 44.0%
Lower extremity ischemia	16.9	12.5% to 22.6%
Neurologic complications	13.3	9.9% to 17.7%
Fasciotomy or compartment syndrome	10.3	7.3% to 14.5%
Stroke	5.9	4.2% to 8.3%
Lower extremity amputation	4.7	2.3% to 9.3%

In addition, 17 studies reported survival to discharge with a pooled survival rate of 534 of 1,529 patients, ranging from 20.8% to 65.4%. The authors concluded that, “although ECMO can improve survival of patients with advanced heart disease, there is significant associated morbidity with performance of this intervention.” Similar complication rates were reported in a 2014 review by Xie.[36]

Given the significant complications associated with ECMO, additional studies are needed which compare ECMO to other standard treatments, such as mechanical ventilation (MV), in order to better define appropriate patient selection criteria and treatment strategies in these high-risk patients.

Nonrandomized Studies

Numerous nonrandomized studies were identified which demonstrated that ECMO was associated with other serious complications[7, 125], including, but not limited to: brachial plexus injury[126], thoracic complications (including bleeding and pneumothorax)[127-129], infection[130-133] (e.g., systemic, surgical site, respiratory tract, urinary tract), limb ischemia[134], neurological injury[135, 136], abdominal compartment syndrome[137], groin lymphocele[138], chronic kidney failure[139], and major vascular complications[136, 140]. Furthermore, a recent analysis of ELSO database indicated that ECMO-related infections were higher in adults compared to children and neonates (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days, respectively).[141]

PRACTICE GUIDELINE SUMMARY

AMERICAN THORACIC SOCIETY-LED INTERNATIONAL TASK FORCE

An International Task Force consisting of clinicians from academic centers active in COVID-19 patient care developed consensus suggestions on management of COVID-19 using the electronic decision-making portion of the Convergence of Opinion on Recommendations and Evidence (CORE) process.[142] The task force suggestions are based upon scarce direct evidence, indirect evidence, and clinical experience. Regarding ECMO, the Task Force made the following recommendation:

For patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS), we suggest that extracorporeal membrane oxygenation (ECMO) be considered if prone ventilation fails.

AMERICAN THORACIC SOCIETY

In 2023, the American Thoracic Society published updated guidance on the management of adult patients with acute respiratory distress syndrome (ARDS).[143] Regarding ECMO, the guideline suggests "using venovenous extracorporeal membrane oxygenation (VV-ECMO) in selected patients with severe ARDS (conditional recommendation, low certainty of evidence)".

EXTRACORPOREAL LIFE SUPPORT ORGANIZATION

The ELSO guidelines for the use of ECMO for adult respiratory failure has been replaced by the ELSO Guideline for Adult Respiratory Failure Managed with Venovenous ECMO (VV ECMO) in June 2021.[144]

Adult Respiratory Failure

ELSO indicated VV ECMO could be considered in patients who met one or more of the following criteria:

1. Hypoxemic respiratory failure (PaO_2/FiO_2 < 80 mm Hg)*, after optimal medical management, including, in the absence of contraindications, a trial of prone positioning.
2. Hypercapnic respiratory failure (pH < 7.25), despite optimal conventional mechanical ventilation (respiratory rate 35 bpm and plateau pressure [Pplat] ≤ 30 cm H_2O).
3. Ventilatory support as a bridge to lung transplantation or primary graft dysfunction following lung transplant.

Specific clinical conditions:

- Acute respiratory distress syndrome (e.g., viral/bacterial pneumonia and aspiration)
- Acute eosinophilic pneumonia
- Diffuse alveolar hemorrhage or pulmonary hemorrhage
- Severe asthma
- Thoracic trauma (e.g., traumatic lung injury and severe pulmonary contusion)
- Severe inhalational injury
- Large bronchopleural fistula
- Peri-lung transplant (e.g., primary lung graft dysfunction and bridge to transplant)

Relative contraindications for venovenous extracorporeal membrane oxygenation

- Central nervous system hemorrhage
- Significant central nervous system injury
- Irreversible and incapacitating central nervous system pathology
- Systemic bleeding
- Contraindications to anticoagulation
- Immunosuppression
- Older age (increasing risk of death with increasing age, but no threshold is established)
- Mechanical ventilation for more than seven days with Pplat > 30 cm H_2O and FiO_2 > 90%

Adult Cardiac Failure

ELSO, along with other organizations published guidelines regarding the use of ECMO for adults postcardiotomy, which included the following statements/recommendations:[145]

- There is no consensus regarding when to initiate ECLS in this setting. The decision to start ECLS is based on the risks and benefits of high-dose inotropes and low cardiac output compared to ECLS with its associated complications and challenges.
- It is recommended that postcardiotomy support be initiated prior to end-organ injury or onset of anaerobic metabolism (lactate level <4 mmol/L) in patients with likelihood of myocardial recovery and in the absence of uncontrollable bleeding not amenable to surgical repair (class I, level B).
- When the likelihood of native myocardial recovery is low, postcardiotomy ECLS is recommended in patients who are eligible for long-term mechanical circulatory support or a heart transplant (class I, level C).
- The early use of ECLS after cardiac surgery in a patient with an intra-aortic balloon pump and optimal medical therapy and failure to wean from bypass or marginal hemodynamics is recommended (class I, level B).

The guidelines also listed contraindications for ECMO in this setting:

- The only absolute contraindication is uncontrollable bleeding.
- Significant comorbidities, advanced age, elevated lactate level, and renal injury are risk factors associated with death and should be considered prior to ECLS initiation (class IIa, level B).
- Other relative contraindications:
    - Known cerebrovascular disease
    - Aortic valve insufficiency
    - or anticoagulation, advanced age, obesity

Coronavirus Disease 2019 (COVID-19)

ELSO published guidelines in 2021 regarding the use of ECMO for COVID-19, which stated that:[146]

During the pandemic, indications for ECMO should remain unchanged. Conventional therapies for ARDS should be applied according to the standard algorithm, leading to use of ECMO after other measures, including prone positioning, have been attempted unless contraindicated. There is no evidence to support delaying ECMO when it is indicated. ECMO is recommended if the following are met:

- PaO_2/FiO_2 ≥150 mm Hg and pH <7.2 with $PaCO_2$ ≥60 mmHg for >6 hours
- PaO_2/FiO_2 <150 mm Hg plus 1 of the following despite recommended measures (eg, prone positioning, neuromuscular blockade, high PEEP strategy):
- PaO_2/FiO_2 <80 mm Hg for >6 hours
- PaO_2/FiO_2 <50 mm Hg for >3 hours
- pH <7.25 with Paco2 ≥60 mmHg for >6 hours with respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep Pplat <32 cm H_2O

ECMO centers should establish descriptions for levels of diminishing ECMO capacity; when capacity diminishes, selection criteria should become more stringent based on likelihood of survival. Exclusion criteria include:

- End-stage chronic organ failure without anticipated recovery and not a candidate for durable device or transplant
- Severe acute multiple organ failure with anticipated death despite ECMO support
- Severe acute neurologic injury with poor prognosis for recovery
- Additional potential contraindications:
  - Long invasive mechanical ventilation duration >10 days
  - Patient/surrogate declines blood products
  - Inability to receive systemic anticoagulation
  - Ongoing CPR
  - Significant underlying comorbidities
  - Advanced age
  - Immunocompromise

INTERNATIONAL EXTRACORPOREAL MEMBRANE OXYGENATION NETWORK

In 2014, the International ECMO Network, with endorsement by ELSO, published a position paper detailing institutional, staffing, and reporting requirements for facilities providing ECMO.[147]

AMERICAN HEART ASSOCIATION

In 2020, the American Heart Association (AHA) issued updated guidelines on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care, which included a new systematic review of the evidence for ECPR and recommendations about the use of ECPR for adults with in- or out-of-hospital cardiac arrest.[148] The systematic review identified no RCTs evaluating ECPR for cardiac arrest and variability in the inclusion and exclusion criteria of the studies was noted, which potentially affects generalizability. The guidelines make the following recommendations related to ECPR:

> "There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support" (Class IIb, level of evidence C—limited data)."

SUMMARY

The research for extracorporeal membrane oxygenation (ECMO) for adult respiratory or cardiac failure has limitations. Despite these limitations, the research shows that ECMO for adult respiratory or cardiac failure improves health outcomes, including survival rates, compared to conventional therapy. Therefore, ECMO may be considered medically necessary as a treatment of respiratory or cardiac failure in adults when policy criteria are met.

The continuation of extracorporeal membrane oxygenation (ECMO) in adults is not clinically indicated when continued use criteria are not met. Therefore, ECMO continued use is

considered not medically necessary when criteria are not met.

The use of extracorporeal membrane oxygenation (ECMO) in adults is not clinically indicated for cardiac or pulmonary failure when policy criteria are not met, or when contraindications are present. Therefore, ECMO is considered not medically necessary in these circumstances.

Due to a lack of research and clinical practice guidelines, the use of ECMO is considered investigational in all other situations.

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CODES

Codes	Number	Description
CPT	33946	Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-venous
	33947	;initiation, veno-arterial
	33948	;daily management, each day, veno-venous
	33949	;daily management, each day, veno-arterial
	33952	;insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)
	33954	;insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
	33956	;insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older
	33958	;reposition peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)
	33962	;reposition peripheral (arterial and/or venous) cannula(e), open, 6 years and older (includes fluoroscopic guidance, when performed)
	33964	;reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed)
	33966	;removal of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older
	33984	;removal of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
	33986	;removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older
	33987	Arterial exposure with creation of graft conduit (eg, chimney graft) to facilitate arterial perfusion for ECMO/ECLS (List separately in addition to code for primary procedure)
	33988	Insertion of left heart vent by thoracici incision (eg, sternotomy, thoracotomy) for ECMO/ECLS

	33989	Removal of left heart vent by thoracic incision (eg, sternotomy, thoracotomy) for ECMO/ECLS
ICD-9 PCS	39.65	Extracorporeal membrane oxygenation [ECMO]
ICD-10 PCS	5A15223	Extracorporeal Membrane Oxygenation, continuous
HCPCS	None	

Date of Origin: *July 2014*

Regence

Medical Policy Manual Medicine, Policy No. 153

Gender Affirming Interventions for Gender Dysphoria

Effective: December 11, 2024

Next Review: September 2025
Last Review: January 2025

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 interventions for gender dysphoria, a marked incongruence between one's experienced/expressed gender and assigned gender.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- The Washington Gender Affirming Treatment Act (SSB 5313; https://legiscan.com/WA/bill/SB5313/2021) addresses coverage for gender affirming treatment for relevant member contracts.
- The Oregon Reproductive Health Rights Act (HB 2002; https://olis.oregonlegislature.gov/liz/2023R1/Downloads/MeasureDocument/HB2002 addresses coverage for gender affirming treatment for relevant member contracts.
- This policy does not address the following interventions:

- Psychotherapy, which may be considered medically necessary for gender dysphoria; and
- Medications such as hormonal therapy (see Cross References).

I. Gender affirming interventions for gender dysphoria may be considered **medically necessary** when either of the following criteria is met:

A. For *member contracts subject to Washington's Gender Affirming Treatment Act* (SSB 5313) or *Oregon Reproductive Health Rights (HB 2002)*, all of the following criteria are met (1. –6.):

1. Documentation that a licensed health care professional or licensed mental health professional with experience in the assessment and treatment of gender dysphoria (see Policy Guidelines) has established the medical necessity of the requested intervention for gender-affirming care (including documentation of the suitability of the patient for the intervention and agreement with the treatment plan); and
2. A documented diagnosis (see Policy Guidelines) of gender dysphoria by a licensed mental health professional (see Policy Guidelines); and
3. Six continuous months of hormone therapy as appropriate to the patient's gender goals unless hormones are not clinically indicated for the individual (Notes: hormonal therapy is not required prior to breast/chest surgery); and
4. At least 6 months of living in a role that is congruent with the patient's identity; and
5. The request is for treatment(s) as prescribed (see Policy Guidelines) by the treating provider because of, related to, or consistent with a person's gender expression or identity and is prescribed in accordance with accepted standards of care; and
6. Either of the following is met:
   a. Age at least 18 years; or
   b. Request is not for genital surgery and documentation is provided that earlier intervention is medically necessary and that the individual demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment. Provider must be a mental health provider who specializes in adolescent transgender care.

B. For *all other member contracts*, both of the following criteria are met (1. – 2.):

1. All of following general criteria are met (a. – f.):
   a. Age at least 18 years (Note: age requirement will not be applied to breast/chest surgery with documentation that earlier intervention is medically necessary and that the individual demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment. Documentation must be from a mental health provider who specializes in adolescent transgender care.); and
   b. Documentation that a licensed health care professional or licensed mental health professional with experience in the assessment and treatment of

gender dysphoria (see Policy Guidelines) has established the medical necessity of the requested intervention for gender-affirming care (including documentation of the suitability of the patient for the intervention and agreement with the treatment plan); and

c. A documented diagnosis (see Policy Guidelines) of gender dysphoria by a licensed mental health professional (see Policy Guidelines); and

d. Six continuous months of hormone therapy as appropriate to the patient's gender goals unless hormones are not clinically indicated for the individual (Note: hormonal therapy is not required prior to breast/chest surgery); and

e. At least 6 months of living in a role that is congruent with the patient's identity; and

f. The requested procedure is specific to the primary and/or secondary sex characteristics of some alternative gender different from one's assigned gender and would not be pursued for other reasons, e.g., to improve appearance or to correct medical or surgical problems unrelated feminization, masculinization, or non-binary transition.

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

   a. The request is for any of the following procedures:

      i. Clitoroplasty

      ii. Hysterectomy (Note: Hysterectomy is considered medically necessary without routine review and is not required to meet Criterion I.B.1.)

      iii. Labiaplasty

      iv. Breast/chest surgery (i.e., breast augmentation, breast reduction, mastectomy, mastopexy, nipple/areola reconstruction/repositioning, nipple tattoo)

      v. Metoidioplasty

      vi. Orchiectomy

      vii. Penectomy

      viii. Penile prostheses implantation

      ix. Phallic reconstruction/Phalloplasty

      x. Salpingo-oophorectomy

      xi. Scrotoplasty

      xii. Testicular prostheses implantation

      xiii. Urethroplasty

      xiv. Vaginectomy

      xv. Vaginoplasty

   b. Clinical documentation is submitted expressly documenting that the intervention would improve otherwise documented significant gender dysphoria and the request is for one or more of the following procedures:

i. Hair removal

ii. Hair transplantation

iii. Facial gender confirmation surgery when the purpose of the surgery is to be publicly identified as gender congruent and not to improve appearance for any of the following procedures (see Required Documentation):

a.) Hairline advancement/brow lift

b.) Forehead contouring/frontal sinus setback

c.) Implants (cheek/malar, frontal, mandible, or chin) when used in facial masculinization

d.) Canthoplasty

e.) Rhinoplasty/Rhinoseptoplasty

f.) Lip lift/lip fat grafting

g.) Mandible (jaw) bone reshaping/Mandibular angle and body contouring

h.) Genioplasty

i.) Tracheal shave

j.) Face lift (rhytidectomy) or liposuction (only as needed in conjunction with one of the above procedures).

iv. Voice modification surgery

v. Endometrial ablation when **all** of the following criteria are met:

a.) Hysteroscopy, sonohysterography (SIS), or pelvic ultrasound has been performed and report is provided; and

b.) Endometrial sampling or dilation and curettage (D&C) has been performed or is planned according to any of the following:

i.) Endometrial sampling or D&C has been performed and report is provided. The histopathology report is provided showing absence of endometrial hyperplasia or uterine cancer; or

ii.) Endometrial sampling or D&C has been performed and report is provided. The histopathology report is provided, but inadequate tissue was obtained for diagnosis; or

iii.) Cervical stenosis precludes endometrial sampling, and D&C is planned concomitantly with ablation procedure.

II. Gender affirming surgical interventions for gender dysphoria are considered **not medically necessary** for gender dysphoria when either of the following is met:

A. For member contracts subject to *Washington's Gender Affirming Treatment Act* (SSB 5313) or *Oregon Reproductive Health Rights (HB 2002)*, when Criterion I.A. is not met; or

B. For member contracts ***not*** subject to Washington's Gender Affirming Treatment Act (SSB 5313) or *Oregon Reproductive Health Rights (HB 2002)*, when any of the following is met:

1. Interventions listed in Criterion I.B.2 that do not meet the medical necessity criteria listed in Criterion I.B.1.; or
2. Interventions not listed in Criterion I.B.2. including, but not limited to abdominoplasty, blepharoplasty, calf implants, nose implants, collagen injections, neck tightening, panniculectomy, pectoral implants, suction-assisted lipoplasty of the waist, and revision to a previous gender affirming surgery because of dissatisfaction with the appearance; or
3. Procedures intended solely to reduce the appearance of aging that will not result in significant improvement of the condition being treated; or
4. Reversal of gender affirming interventions.

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

POLICY GUIDELINES

Some procedures that do not require a prescription (e.g., hair removal or nipple tattooing) may be considered prescribed based on the referral for the procedure from a licensed mental health professional.

LICENSED MENTAL HEALTH PROFESSIONAL (MHP)

- State licensed to practice independently (without supervision) as master's degree level mental health clinicians, doctoral level mental health clinicians, psychiatric nurse practitioners, psychiatric physician assistants, or Board-Eligible or Board-Certified psychiatrists.
- Statutorily regulated mental health professionals with lower levels of qualification under the clinical supervision of a qualified MHP who takes ultimate clinical responsibility for the quality and accuracy of the completed assessment.

LICENSED HEALTH CARE PROFESSIONALS (HCP)

- State licensed to practice independently (without supervision) as master's degree level or equivalent (doctoral level clinicians, nurse practitioners, physician assistants, or Board-Eligible or Board-Certified psychiatrists)
- Experienced in the assessment and treatment of gender dysphoria and providing gender-affirming care.

DOCUMENTED DIAGNOSIS

Documentation from a licensed mental health professional must include confirmation that they have directly assessed the member and verified that the member has a current diagnosis of gender dysphoria

FACIAL PROCEDURES

Below are some different terms for the procedures listed in the Policy Criteria:

- Tracheal shave may be known as thyroid chondroplasty, chondrolaryngoplasty, or thyroid cartilage reduction, Adam's apple contouring
- Chin reconstruction may include genioplasty, chin contouring
- Mandible (jaw) bone reshaping may include mandibular angle and body contouring

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 the review and decision outcome:

- History and Physical/Chart Notes
    - Documentation of therapy requested if applicable
    - Documentation of patient capacity to make decisions/consent to treatment
- For medical treatment or mastectomy:
    - Documentation that a licensed mental health professional has diagnosed gender dysphoria
    - Documentation of length of time living as desired gender
    - Documentation of length of time therapy occurred including licensure of therapist
    - For patients under the age of 18, documented provider determination of medical necessity of earlier intervention
- For all surgical treatments:
    - Documentation that at least one licensed mental health professional has diagnosed gender dysphoria
    - Documentation that a licensed health care professional or mental health professional with experience assessing and treating gender dysphoria has recommended the surgical treatment. Documentation to demonstrate experience assessing and treating gender dysphoria may include the following: WPATH certification or a statement of experience (e.g., a letter, or note in the clinical chart)
- For all surgical treatments, excluding breast/chest surgery:
    - Documentation of hormonal therapy including length of time administered
    - Documented treatment plan including if planned procedures are reversals
- For procedures in Criteria I.B.2.b.:
    - Documentation that the intervention would improve otherwise documented significant gender dysphoria
- In addition to the above, for facial gender confirmation surgery:
    - The surgical plan must include a description of how the requested procedures will address the client's noncongruent features, feminize or masculinize the face, and treat the individual's gender dysphoria. All codes requested must be

addressed in the documented surgical plan to determine medical necessity of requested procedures.

- In addition to the above, for endometrial ablation:
    - Endometrial histopathological report or documentation cervical stenosis precludes endometrial sampling and D&C is planned to be completed concomitantly with ablation procedure.
    - Hysteroscopy, sonohysterography (SIS), or pelvic ultrasound report

CROSS REFERENCES

1. Endometrial Ablation, Surgery, Policy No. 01
2. Cosmetic and Reconstructive Surgery, Surgery, Policy No. 12
3. Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants, Surgery, Policy No. 40
4. Reduction Mammaplasty, Surgery, Policy No. 60
5. Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells, Surgery, Policy No. 182
6. Hysterectomy, Surgery, Policy No. 218
7. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

This policy supports applicable professional association statements,[1-5] and is also intended to support the Affordable Care Act (ACA) Section 1557 final implementing regulations published on May 18, 2016, and applicable state requirements[6].

MEDICAL AND SURGICAL INTERVENTIONS FOR GENDER DYSPHORIA

A clinical diagnosis of gender dysphoria is required prior to intervention for the disorder. Gender affirming interventions typically include hormone therapy and in some cases surgical procedures. Psychotherapy followed by hormone therapy is often the first medical treatment sought, although not all transgender individuals on hormone therapy choose to undergo gender affirming surgery.[2]

Gender Dysphoria

Gender dysphoria is defined by the Diagnostic and Statistical Manual of Mental Disorders DSM-5 Diagnostic Criteria as follows:[7]

Gender Dysphoria in Children 302.6

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion 1):
    1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender, different from one's assigned gender).
    2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to wearing of typical feminine clothing.
    3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for toys, games, or activities stereotypically used or engaged in by the other gender.
5. A strong preference for playmates of the other gender.
6. In boys (assigned gender), a strong rejection of typically masculine toys, games and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games and activities.
7. A strong dislike of one's sexual anatomy.
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.0 [E34.50] androgen insensitivity syndrome).
Coding note: Code the disorder of sex development as well as gender dysphoria.

Gender Dysphoria in Adolescents and Adults 302.85

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and /or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.0 [E34.50] androgen insensitivity syndrome).
Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Post transition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen- namely regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in the natal male; mastectomy or phalloplasty in the natal female).

Hormone Therapy

Hormone therapy is undertaken in order to feminize or masculinize individuals' bodies to conform to their desired gender identities. For transgender individuals, hormone replacement therapy (HRT) causes the development of many of the secondary sexual characteristics of their gender identity. Prescribed hormones differ depending upon the natal gender of the individual. For individuals seeking to feminize, hormone treatment may include estradiol, finasteride, and spironolactone. For individuals seeking to masculinize, hormone treatment may include androgenic hormones such as testosterone.

Surgical Interventions

Surgical intervention for gender dysphoria differs depending upon the gender assigned at birth. For individuals who are assigned male at birth (AMAB), surgery may involve orchiectomy, vaginoplasty, and gender-affirming breast surgery. Complications rates related to vaginoplasty may include the formation of granulation tissue, wound dehiscence, fistulas from the bladder or bowel into the vagina, and stenosis of the neovaginal canal or urethra.[5, 8]

For individuals who are assigned female at birth (AFAB), surgery may involve gender-affirming chest surgery, hysterectomy/oophorectomy, metoidioplasty, and phalloplasty. The creation of a neophallus for these patients is a multistage reconstructive procedure. Currently, techniques for penile reconstruction procedures vary and complications may include frequent urinary tract stenoses and fistulas, diverticulae, and mucocele due to vaginal remnant.[5, 9] Mastectomy may involve a complete resection of all breast tissue; however, the nipple/areola sparing technique is typically performed to preserve the nipple/areola. For those who are taking androgen hormones, menstruation usually ceases with the medication intervention alone. In those who experience continued uterine bleeding other hormonal regimes may be attempted, or endometrial ablation.[10]

There are various additional surgical procedures which may be sought in order to complete the physical gender transformation and align an individual to their gender identity. To date, studies assessing these procedures have limitations, including small sample sizes and heterogeneous assessments and World Professional Association for Transgender Health (WPATH) recommends further study.

EVIDENCE SUMMARY

Evidence regarding interventions for gender dysphoria in transgender individuals primarily consists of systematic reviews consisting of small cohort studies. Randomized clinical trials (RCTs) comparing gender dysphoria interventions with no intervention are ideal. However, there are challenges in conducting RCTs for these interventions due to several factors, such as small patient populations, and ethical concerns regarding the high morbidity and mortality rates associated with no intervention. Therefore, large RCTs are not anticipated. This policy

relies on the following systematic reviews and non-randomized studies, as well as professional association recommendations to support applicable federal and state requirements.

SYSTEMATIC REVIEWS

Aristizabal (2024) published a systematic review (SR) summarizing studies, including upper and lower body contouring procedures in transgender patients.[11] A total of 15 studies, including trans male chest wall contouring, trans female breast augmentation, and lower body contouring, with 1811 patients were included. The double incision (DI) techniques consistently resected more tissue and had better BODY Q scores. Bleeding was increased in periareolar, semicircular, and obese patients with DI techniques. Nipple depigmentation and sensation loss were more common with double-incision-free nipple graft techniques (DIFNG). Lower body contouring patients had average implant sizes bigger than 200 mL and reported two gluteal implant displacements, one exposure, and one rupture. Eight percent of patients who underwent large-volume fat grafting reported dissatisfaction due to fat reabsorption. Variations of the DIFNG technique continue to be the most common approach; however, nipple depigmentation and loss of sensation are also more common with this technique. There is no evidence that hormonal therapy may play a role regarding increased bleeding with periareolar techniques. For lower-body trans female contouring, implants could help with the longevity of contouring results in patients needing large-volume fat grafting. There is an increasing evaluation of gender-affirming body contouring patient-reported outcomes; however, there is still a need for a validated way to report satisfaction scores in lower body contouring.

Kumar (2022) published a systematic review (SR) evaluating the health-related outcomes of oophorectomy in transmasculine and gender diverse (TMGD) population treated with chronic testosterone therapy in order to guide clinicians and patients in the decision to retain or remove their ovaries.[12] A total of 39 studies were included. Three studies discussed fertility outcomes, 11 assessed histopathological changes to the ovaries, six discussed ovarian oncological outcomes, eight addressed endocrine considerations, three discussed cardiovascular health outcomes, and eight discussed bone density. No studies were found that examined surgical outcomes or neurocognitive changes. There is limited evidence to suggest that fertility preservation is successful after total hysterectomy with bilateral salpingectomy with ovarian retention. Current evidence does not support regular reduction in testosterone dosing following oophorectomy. Estradiol levels are likely higher in individuals that choose ovarian retention, but this has not been clearly demonstrated. Although bone mineral density decreases following oophorectomy, data demonstrating an increased fracture risk are lacking. No studies have described the specific impact on neurocognitive function, or changes in operative complications. Further research evaluating long-term health outcomes of oophorectomy for TMGD individuals treated with chronic testosterone therapy is warranted to provide comprehensive, evidence-based healthcare to this patient population.

Coon (2022) published a SR of facial gender affirming surgery following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] A total of 21 articles were identified addressing facial gender surgery. The majority were case series published by the same few authors and included relatively limited numbers of participants. In the 16 studies that included patient-centered outcomes, most reported high rates of satisfaction and improved quality of life. Seven studies reported complications (mostly minor), five studies reported whether patients sought revision surgery (4% underwent revision), and seven studies assess patients' perceptions of their postsurgical face and change in self-perceived femininity (80% reported feeling more feminine as a result of surgery).

Javier (2022) published a systematic review of surgical satisfaction and quality of life outcomes long-term (at least one year) following gender-affirming surgery.[14] A total of 79 studies met inclusion criteria. All were rated as low quality. Strength of evidence (SoE) was graded on a number of factors, including sample size and use of a control group. No studies evaluating facial masculinization surgery or vocal cord surgery in transgender men met inclusion criteria. Overall, included studies primarily reported positive surgical satisfaction and quality of life outcomes at the one year or longer follow-up. The authors reported that direct evidence with medium study limitations suggests that most transgender individuals report satisfaction with their chest, genital facial, vocal cord, and Adam's apple removal surgeries (SoE high) and that the vast majority of transgender individuals do not regret undergoing chest/genital surgery (SoE medium). The authors also reported that low SoE from studies with high limitations suggests that transgender men who underwent chest surgery reported moderately high levels of psychological and social functioning comparable to transgender men who did not undergo chest surgery and transgender women overall reported improvements in their psychosocial wellbeing from pre- to post-surgery. Evidence rated as high and medium SoE, respectively, suggest positive outcomes for sexual wellbeing following chest and genital surgery and for self-esteem levels following genital surgery. Evidence rated as medium SoE was reported as suggesting positive happiness levels following gender and facial surgery, lower feelings of incongruence with gender identity and positive and/or improved health-related quality of life outcomes following facial surgery and voice surgery. Low SoE was reported for evidence suggesting that most transgender women who undergo chest surgery reported that their gender dysphoria was resolved and transgender men who undergo genital surgery have a "well-balanced" emotional stability.

Wernick (2019) published a systematic review of the psychological benefits of gender affirming surgery.[15] A total of 33 studies met inclusion criteria. The key concepts searched were quality of life, gender-confirmation surgical procedures, and transgender persons. Sixteen of the identified studies addressed compared pre- and post-surgical data, while 17 studies compared between-group differences. No meta-analysis was completed. Most studies demonstrated a trend of better mental health in transgender individuals who underwent surgeries, but not all reported improvements were statistically significant. The systematic review concluded that gender affirming surgery may lead to psychological benefits for individuals with gender dysphoria and that more research is needed to understand the factors that contribute to the outcomes following these surgeries.

Berli (2017) published a review of the available literature regarding facial gender confirmation surgery (FGCS).[16] The literature search went through December, 2016. The evidence was evaluated using the Oxford Centre for Evidence-Based Medicine suggestions for levels of evidence. Based on their findings, Berli and colleagues recommended that the next World Professional Association for Transgender Health (WPATH) Standards of Care version should include specific FGCS procedures. The authors also recommended replacing the historical term, facial feminization surgery (FFS) with more inclusive terminology – facial gender confirmation surgery. The body of evidence regarding FGCS is limited to case reports and case series. The authors found most data did not include quality-of-life outcome measures, and when reported, standardized instruments were not utilized. FGCS procedures were categorized by the authors as structural (e.g., forehead reconstruction, rhinoplasty), and secondary nonstructural procedures (e.g., blepharoplasty, upper lip shortening techniques). The review was limited by the paucity of data on FGCS as a treatment for gender dysphoria. In addition, methodological limitations of the review included but were not limited to, lack of

transparent study selection and a transparent, comprehensive assessment of study quality and risk of bias. These limitations prohibit conclusions about overall health outcomes.

Nonrandomized Studies

Primary evidence is limited to cohort studies with a variety of methodological limitations, including but not limited to small sample size, short-term follow-up, lack of comparison group, and varied treatment methods. Many of these studies and their limitations are discussed in the systematic reviews above. Despite these limitations, significant improvements in quality of life, psychological comorbidities, and sexual functioning were consistently reported in patients who received gender-confirming medical treatments.[17] Below are summaries of representative publications not addressed in the above systematic reviews.

Park (2022) reported long-term outcomes following gender affirming surgery.[18] Based on chart review, 97 individuals with comprehensive preoperative assessment for gender dysphoria at a tertiary care center from 1970 to 1989 were identified for follow-up. Of these, 15 agreed to participate in a phone interview and survey. The mean age was 65.5 (range 58 to 76). Nine respondents were transmasculine and six were transfeminine. Body congruence with self-image was rated at 89.5 out of 100 for all respondents, and 91.3 and 87.5 for transmasculine and transfeminine respondents, respectively. Pre- versus 40 years postoperative reports of suicidal ideation were eight versus one, mental health treatment was ten versus six, and depression was eight versus seven.

Almazan and Keuroghlian (2021) analyzed data from the 2015 US Transgender Survey to assess the relationship between gender affirming surgeries and mental health outcomes.[19] Survey respondents who reported having undergone gender affirming surgeries were compared with respondents who reported desiring gender affirming surgery but not having undergone any. A total of 27,715 individuals responded to the survey, of whom 12.8% reported having undergone one or more types of gender affirming surgery and 59.2% reported a desire to undergo gender affirming surgery but reported no prior gender affirming surgeries. Undergoing one or more type of gender affirming surgery was associated with reduced severe psychological distress (past month), smoking (past year), and suicidal ideation (past year), adjusted for sociodemographic factors and other gender affirming care ($p<0.001$ for all). Binge alcohol use (past month) and suicide attempts were not significantly different between groups.

Summary

The evidence is limited by a lack of well-designed studies comparing the safety and effectiveness gender affirming surgery to no treatment or to hormone therapy alone. There are challenges in conducting these large studies, and therefore such studies are not expected in the near future. Although additional research is needed, the research addressing genital and chest surgeries has consistently suggested significant improvement in symptoms and overall quality of life. With regard to other surgeries, such as body contouring, more research is needed to understand their effect on health outcomes.

PRACTICE GUIDELINE SUMMARY

WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH

The World Professional Association for Transgender Health (WPATH) is a multidisciplinary professional society representing the specialties of medicine, psychology, social sciences and

law that has published clinical guidelines regarding health services for patients with gender disorders. In 2022, WPATH approved the update of their evidence and consensus-based guideline, the *Standards of Care (SOC) for the Health of Transgender and Gender Diverse People, 8th Version*.[5] WPATH guidelines describe gender affirming surgery as "a constellation of procedures designed to align a person's body with their gender identity."

Physical Interventions for Adolescents

The WPATH guidelines include section on care and treatment of transgender adolescents. This section includes information on gender development during adolescence as well as challenges of adolescent transgender care. Regarding consideration of ages for gender-affirming medical and surgical treatment for adolescents, WPATH guidelines state that "[a]ge has a strong, albeit imperfect, correlation with cognitive and psychosocial development and may be a useful objective marker for determining the potential timing of interventions." They go on to state that "[h]igher (i.e., more advanced) ages may be required for treatments with greater irreversibility, complexity, or both. This approach allows for continued cognitive/emotional maturation that may be required for the adolescent to fully consider and consent to increasingly complex treatments." In addition, they highlight that "[g]ender-diverse youth should fully understand the reversible, partially reversible, and irreversible aspects of a treatment, as well as the limits of what is known about certain treatments."

Assessment Process

WPATH guidelines indicate that surgical interventions can be initiated by a referral from a qualified mental health professional. Regarding referrals for adults, they state:

- Health care professionals assessing transgender and gender diverse adults seeking gender-affirming treatment should liaise with professionals from different disciplines within the field of trans health for consultation and referral, if required (Graded as suggested criteria)
- If written documentation or a letter is required to recommend gender affirming medical and surgical treatment (GAMST), only one letter of assessment from a health care professional who has competencies in the assessment of transgender and gender diverse people is needed.

Regarding referrals for adolescents, they state:

- A comprehensive biopsychosocial assessment including relevant mental health and medical professionals;
- Involvement of parent(s)/guardian(s) in the assessment process, unless their involvement is determined to be harmful to the adolescent or not feasible;
- If written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST), only one letter of assessment from a member of the multidisciplinary team is needed. This letter needs to reflect the assessment and opinion from the team that involves both medical and mental health professionals (MHPs).

Criteria for Surgery

<u>Adults</u>

a. Gender incongruence is marked and sustained;

b. Meets diagnostic criteria for gender incongruence prior to gender-affirming surgical intervention in regions where a diagnosis is necessary to access health care;
c. Demonstrates capacity to consent for the specific gender-affirming surgical intervention;
d. Understands the effect of gender-affirming surgical intervention on reproduction and they have explored reproductive options;
e. Other possible causes of apparent gender incongruence have been identified and excluded;
f. Mental health and physical conditions that could negatively impact the outcome of gender-affirming surgical intervention have been assessed, with risks and benefits have been discussed;
g. Stable on their gender affirming hormonal treatment regime (which may include at least 6 months of hormone treatment or a longer period if required to achieve the desired surgical result, unless hormone therapy is either not desired or is medically contraindicated).

Adolescents

a. Meets the diagnostic criteria of gender incongruence in situations where a diagnosis is necessary to access health care;
b. Demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment;
c. Mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed; sufficiently so that gender-affirming medical treatment can be provided optimally.
d. Informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility;
e. At least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

Facial Gender Affirming Surgery

The WPATH guidelines state that “[w]hile gender-affirming facial surgery for [assigned female at birth] individuals is an emerging field, current limited data points toward equal benefits in select patients. Future studies are recommended.”

THE ENDOCRINE SOCIETY

In 2017, the Endocrine Society in conjunction with American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health published updated guidelines for the treatment of gender-dysphoric/gender-incongruent persons.[10] The guideline employed transparent methods for evidence review and for rating the quality of evidence. Guidelines were referenced as *recommendations* or *suggestions*, by the numbers 1 and 2, respectively. Evidence was ranked as very low-quality |⊕○○○; low quality |⊕⊕○○; moderate quality |⊕⊕⊕○; and high quality |⊕⊕⊕⊕. The consortium made the following statements:

1.0 Evaluation of Youth and Adults

1.1 We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/ gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/ gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕○○)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕○)

2.0 Treatment of Adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕○○)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕○○)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕○○)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕○○).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/ gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments

administered before age 13.5 to 14 years. As with the care of adolescents 16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕○○○)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕○○)

3.0 Hormonal Therapy for Transgender Adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕○)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕○)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕○○)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

4.0 Adverse Outcome Prevention and Long-term Care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕○○)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕○○)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕○○)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕○○)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕○○)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕○○○)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for Sex Reassignment and Gender Confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕○○)

5.2. We advise that clinicians approve genital gender affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
5.4. We recommend that clinicians refer hormone treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕○○○)
5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕○○).
5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 **|**⊕○○○)

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGY

In 2021, the American College of Obstetricians and Gynecology (ACOG) published an updated committee opinion regarding care for health care for transgender and gender diverse individuals.[20] These guidelines are not based on evidence. ACOG makes the following statements:

“Obstetrician–gynecologists should be prepared to assist or refer transgender individuals for routine treatment and screening as well as hormonal and surgical therapies. Hormonal and surgical therapies for transgender patients may be requested, but should be managed in consultation with health care providers with expertise in specialized care and treatment of transgender patients.”

Regarding adolescents, ACOG highlights age-specific concerns with a focus on medical management, stating “Consensus guidelines support initiating medical therapy after an adolescent has an established diagnosis of transgender identity and has reached Tanner stage II development.”

In addition, ACOG guidelines made specific recommendations regarding surgery and screening for both female-to-male and male-to-female patients:

Female-to-Male Transgender Individuals

Surgery

Transmasculine individuals may choose chest reconstruction, hysterectomy with or without salpingo-oophorectomy, or metoidioplasty, phalloplasty, or both.

Screening

For transmasculine individuals, screening includes breast cancer screening for patients who have breast tissue and cervical cancer screening for those who have a cervix.

…on the basis of limited data, recommendations for screening for endometrial cancer for transmasculine individuals are no different than for cisgender women. Additionally, evaluation of transmasculine individuals with abnormal uterine bleeding are the same as those for cisgender women

Male-to-Female Transgender Individuals

Surgery

Potential procedures for transfeminine individuals include breast augmentation, orchiectomy, vaginoplasty, and facial feminization surgeries.

Screening

A neovagina does not require routine cytologic screening. Prostate cancer screening for transfeminine individuals should follow the recommendations for cisgender men.

It is likely that transfeminine individuals have a lower risk of breast cancer than cisgender women… General consensus is that screening should begin after 50 years of age and a minimum of 5 years of feminizing hormone use, with a health care professional-patient discussion about the potential harms of over screening.

SUMMARY

For member contracts subject to Washington's Gender Affirming Treatment Act (SSB 5313) or Oregon Reproductive Health Rights (HB 2002)

For member contracts subject to the Washington Gender Affirming Treatment Act (SSB 5313) or Oregon Reproductive Health Rights (HB 2002), criteria for gender affirming interventions are based on the research, guidelines developed using the available evidence and expert clinical consensus, and on the Act. Therefore, for member contracts subject to the Washington Gender Affirming Treatment Act (SSB 5313) or Oregon Reproductive Health Rights (HB 2002), gender affirming interventions for gender dysphoria may be considered medically necessary when specified policy criteria are met.

For member contracts subject to the Washington Gender Affirming Treatment Act (SSB 5313) or Oregon Reproductive Health Rights (HB 2002), criteria for gender affirming interventions are based on the Act and on guidelines developed using the available evidence and expert clinical consensus. Therefore, for these members, when these criteria are not met, gender affirming interventions for gender dysphoria are considered not medically necessary.

For member contracts *not* subject to Washington's Gender Affirming Treatment Act (SSB 5313) or Oregon Reproductive Health Rights (HB 2002)

The research lacks well-designed studies comparing the safety and effectiveness of no intervention for gender dysphoria with interventions such as gender affirming surgery. However, there are challenges in conducting large studies to evaluate existing treatments, and such studies are not expected in the near future. Although additional research is needed, the research has consistently suggested significant improvement in symptoms and overall quality of life in those who have received certain interventions for gender dysphoria.

The World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) for the Health of Transgender and Gender Diverse People recommend that specific criteria are met prior to surgical interventions for gender dysphoria. These guidelines are based on evidence and expert clinical consensus and the included criteria were developed to promote optimal patient care. Therefore, gender affirming interventions for gender dysphoria may be considered medically necessary when specified policy criteria are met.

The World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) for the Health of Transgender and Gender Diverse People recommend that specific criteria are met prior to surgical interventions for gender dysphoria. These guidelines are based on evidence and expert clinical consensus and the included criteria were developed to promote optimal patient care. Therefore, when criteria are not met, gender affirming interventions for gender dysphoria are considered not medically necessary.

There are no evidence-based clinical practice guidelines that recommend gender affirming surgical interventions not listed in Criterion I.B.2. or revision to a previous gender affirming surgery because of dissatisfaction with the appearance improve health outcomes. Therefore, gender affirming surgical interventions not listed in Criterion I.B.2. and revision to a previous gender affirming surgery because of dissatisfaction with the appearance are considered not medically necessary.

The World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) for the Health of Transgender and Gender Diverse People describe reversible and irreversible interventions, and the ideal order and timing of these approaches. Surgery as an intervention is considered irreversible. Therefore, reversal of gender affirming surgery for gender dysphoria is considered not medically necessary.

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CODES

NOTES:

- Follicular unit extraction (FEU) of individual hairs is correctly coded with code 15775 or 15776 and is determined by the number of "punch grafts" performed. Be advised that standard CMS Medically Unlikely Edits (MUEs or Maximum Units of Service) will apply.
- Code 17999 should be reported for laser hair removal. This code may also be used for abdominoplasty or calf/pectoral implants.
- Codes 31552, 31554, 31580, 31584, 31587, and 31591 are not appropriate to use to represent voice modification. Unlisted code 31599 should be reported instead.
- Code 31899 should be reported for reduction thyroid chondroplasty (e.g. tracheal shave; reduction of the thyroid cartilage or Adam's Apple).
- Code 40799 should be reported for lip reduction.
- Code 55899 should be reported for phallic reconstruction/phalloplasty.
- Codes 55970 and 55980 are non-specific. The specific procedure code(s) must be requested in place of these non-specific codes.

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
	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 cc
	11970	Replacement of tissue expander with permanent implant
	11971	Removal of tissue expander(s) without insertion of implant
	14020	Adjacent tissue transfer or rearrangement, scalp, arms and/or legs; defect 10 sq cm or less
	14021	Adjacent tissue transfer or rearrangement, scalp, arms and/or legs; defect 10.1 sq cm to 30.0 sq cm
	14061	Adjacent tissue transfer or rearrangement, eyelids, nose, ears and/or lips; defect 10.1 sq cm to 30.0 sq cm
	14301	Adjacent tissue transfer or rearrangement, any area; defect 30.1 sq cm to 60.0 sq cm
	14302	Adjacent tissue transfer or rearrangement, any area; each additional 30.0 sq cm, or part thereof (List separately in addition to code for primary procedure) Just 1 primary procedure 14301
	15730	Midface flap (ie, zygomaticofacial flap) with preservation of vascular pedicle(s)
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15770	Graft; derma-fat-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
15820	Blepharoplasty, lower eyelid
15821	;with extensive herniated fat pad
15822	Blepharoplasty, upper eyelid
15823	;with excessive skin weighting down lid
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
15830	Excision, excessive skin and subcutaneous tissue (includes lipectomy); abdomen, infraumbilical panniculectomy
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
15838	Excision, excessive skin and subcutaneous tissue (includes lipectomy); submental fat pad
15839	Excision, excessive skin and subcutaneous tissue (includes lipectomy); other area
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)
15876	Suction assisted lipectomy; head and neck
15877	Suction assisted lipectomy; trunk
15878	Suction assisted lipectomy; upper extremity
15879	Suction assisted lipectomy; lower extremity
17380	Electrolysis epilation, each 30 minutes
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
19303	Mastectomy, simple, complete
19316	Mastopexy
19318	Breast reduction
19325	Breast augmentation with implant
19350	Nipple/areola reconstruction
19499	Unlisted procedure, breast
21025	Excision of bone (eg, for osteomyelitis or bone abscess); mandible
21120	Genioplasty; augmentation (autograft, allograft, prosthetic material)
21121	Genioplasty; sliding osteotomy, single piece
21122	Genioplasty; sliding osteotomies, 2 or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)
21123	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)
21125	Augmentation, mandibular body or angle; prosthetic material
21127	Augmentation, mandibular body or angle; with bone graft, onlay or interpositional (includes obtaining autograft)
21137	Reduction forehead; contouring only

21139	Reduction forehead; contouring and setback of anterior frontal sinus wall
21141	Reconstruction midface, LeFort I; single piece, segment movement in any direction (eg, for Long Face Syndrome), without bone graft
21142	Reconstruction midface, LeFort I; 2 pieces, segment movement in any direction, without bone graft
21143	Reconstruction midface, LeFort I; 3 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; 2 pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (eg, ungrafted unilateral alveolar cleft)
21147	Reconstruction midface, LeFort I; 3 or more pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (eg, ungrafted bilateral alveolar cleft or multiple osteotomies)
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 (includes obtaining 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
21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
21209	Osteoplasty, facial bones; reduction
21235	Graft; ear cartilage, autogenous, to nose or ear (includes obtaining graft)
21270	Malar augmentation, prosthetic material
21299	Unlisted craniofacial and maxillofacial procedure
30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip
30410	;complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip
30420	;including major septal repair
30430	Rhinoplasty, secondary; minor revision (small amount of nasal tip work)
30435	;intermediate revision (bony work with osteotomies)
30450	;major revision (nasal tip work and osteotomies)
30465	Repair of nasal vestibular stenosis (eg, spreader grafting, lateral nasal wall reconstruction)
31599	Unlisted procedure, larynx
31750	Tracheoplasty; cervical
31899	Unlisted procedure, trachea, bronchi
40799	Unlisted procedure, lips
53400	Urethroplasty; first stage, for fistula, diverticulum, or stricture (eg, Johannsen type)
53405	Urethroplasty; second stage (formation of urethra), including urinary diversion
53410	Urethroplasty, 1-stage reconstruction of male anterior urethra
53415	Urethroplasty, transpubic or perineal, 1-stage, for reconstruction or repair of prostatic or membranous urethra
53420	Urethroplasty, 2-stage reconstruction or repair of prostatic or membranous urethra; first stage

	53425	Urethroplasty, 2-stage reconstruction or repair of prostatic or membranous urethra; second stage
	53430	Urethroplasty, reconstruction of female urethra
	54125	Amputation of penis; complete (Penectomy)
	54400	Insertion of penile prosthesis; non-inflatable (semi-rigid)
	54401	Insertion of penile prosthesis; inflatable (self-contained)
	54405	Insertion of multi-component, inflatable penile prosthesis, including placement of pump, cylinders, and reservoir
	54520	Orchiectomy, simple (including subcapsular), with or without testicular prosthesis, scrotal or inguinal approach
	54660	Insertion of testicular prosthesis
	54690	Laparoscopy, surgical; orchiectomy
	55175	Scrotoplasty; simple
	55180	Scrotoplasty; complicated
	55899	Phallic reconstruction/Phalloplasty (Unlisted procedure, male genital system)
	55970	intersex surgery; male to female
	55980	intersex surgery; female to male
	56625	Vulvectomy simple; complete
	56800	Plastic repair of introitus
	56805	Clitoroplasty for intersex state
	57106	Vaginectomy, partial removal of vaginal wall
	57110	Vaginectomy, complete removal of vaginal wall;
	57291	Construction of artificial vagina; without graft
	57292	Construction of artificial vagina; with graft
	57295	Revision (including removal) of prosthetic vaginal graft; vaginal approach
	57296	Revision (including removal) of prosthetic vaginal graft; open abdominal approach
	57335	Vaginoplasty for intersex state
	57426	Revision (including removal) of prosthetic vaginal graft, laparoscopic approach
	58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
	58180	Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)
	58260	Vaginal hysterectomy, for uterus 250 g or less
	58262	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s)
	58270	Vaginal hysterectomy, for uterus 250 g or less; with repair of enterocele
	58275	Vaginal hysterectomy, with total or partial vaginectomy;
	58290	Vaginal hysterectomy, for uterus greater than 250 g
	58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
	58353	Endometrial ablation, thermal, without hysteroscopic guidance
	58356	Endometrial cryoablation with ultrasonic guidance, including endometrial curettage, when performed
	58541	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less
	58542	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)
	58543	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g
	58544	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
	58550	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less

58552	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less;
58553	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g
	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250
58563	Hysteroscopy, surgical; with endometrial ablation (eg. Endometrial resection, electrosurgical ablation, thermoablation)
	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less
58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)
	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g
58573	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate
67900	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)
	Repair of blepharoptosis; frontalis muscle technique with suture or other
67902	Repair of blepharoptosis; frontalis muscle technique with autologous fascial sling (includes obtaining fascia)
	Repair of blepharoptosis; (tarso) levator resection or advancement, internal
67904	Repair of blepharoptosis; (tarso) levator resection or advancement, external approach
	Repair of blepharoptosis; superior rectus technique with fascial sling (includes
67908	Repair of blepharoptosis; conjunctivo-tarso-Muller's muscle-levator resection (eg, Fasanella-Servat type)
	Reduction of overcorrection of ptosis
67950	Canthoplasty (reconstruction of canthus)
	Prosthesis, breast (implantable)
C1813	Prosthesis, penile, inflatable
C2622	Prosthesis, penile, noninflatable
L8039	Breast prosthesis, not otherwise specified
L8600	Implantable breast prosthesis, silicone or equal

Date of Origin: *September 2014*

Regence

Medical Policy Manual Medicine, Policy No. 170

Bioengineered Skin and Soft Tissue Substitutes and Amniotic Products

Effective: April 1, 2025

Next Review: February 2026
Last Review: March 2025

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

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue, synthetic materials, or a composite of these materials. Amniotic products may be derived from amnion, chorion, amniotic fluid, and umbilical cord. There are many potential applications for these products, including breast reconstruction, chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, severe burns, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions.

MEDICAL POLICY CRITERIA

Notes:

- Product-specific HCPCS codes are listed below in brackets, where applicable. Skin substitutes without a specific code may use Q4100/A4100.
- This policy does not apply to dural substitutes used during surgical procedures involving the central nervous system (brain and spinal cord) or to unprocessed cadaver skin allografts used as wound dressing.

I. Breast reconstructive surgery using any of the following allogeneic acellular dermal matrix products may be considered **medically necessary**:

A. AlloDerm® [Q4116]
B. AlloMend®
C. Cortiva® (AlloMax™)
D. DermACELL® [Q4122]
E. DermaMatrix™
F. FlexHD® [Q4128]
G. FlexHD® Pliable™
H. GraftJacket® [Q4107]

II. Treatment of non-healing diabetic lower-extremity ulcers that have not adequately responded following a 1-month period of conventional ulcer therapy, using any of the following tissue-engineered or amniotic skin substitutes, may be considered **medically necessary**:

A. Affinity® [Q4159]
B. AlloPatch® [Q4128]
C. AmnioBand® Membrane [Q4151]
D. AmnioExcel® [Q4137]
E. Apligraf® [Q4101]
F. Biovance® [Q4154]
G. Dermagraft® [Q4106]
H. EpiCord® [Q4187]
I. EpiFix® [Q4186]
J. Grafix® [Q4132, Q4133]
K. Integra® Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™) [Q4105]
L. Integra® Flowable Wound Matrix [Q4114]
M. mVASC®
N. TheraSkin® [Q4121]

III. Treatment of chronic, noninfected, lower-extremity skin ulcers due to venous insufficiency that have not adequately responded following a 1-month period of conventional ulcer therapy, using any of the following tissue-engineered skin substitutes, may be considered **medically necessary**:

A. Apligraf® [Q4101]
B. Oasis®™ Wound Matrix [Q4102]

IV. Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be considered **medically necessary**:

A. OrCel® (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration [FDA]).

V. Treatment of second- and third-degree burns using any of the following tissue-engineered skin substitutes may be considered **medically necessary**:

A. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)

B. Integra® Dermal Regeneration Template [Q4105]

VI. Human amniotic membrane grafts not listed as investigational (see Policy Guidelines) may be considered **medically necessary** as a component of ophthalmologic surgery or repair, including but not limited to Prokera®, AmbioDisk™, AmnioGraft®, or AmnioPlast™.

VII. Treatment of lower-extremity ulcers due to diabetes or venous insufficiency is considered **not medically necessary** when there has not been at least 1 month of conventional ulcer therapy.

VIII. The use of bioengineered skin and soft tissue substitutes for hernia repair or parastomal reinforcement is considered **not medically necessary**.

IX. The use of amniotic membrane grafts or bioengineered skin and soft tissue substitutes for tendon repair is considered **investigational**.

X. For the specific amniotic membrane grafts and bioengineered skin and soft tissue substitutes listed above (Criteria I.-VI.), all other uses are considered **investigational**.

XI. All other amniotic products and bioengineered skin or soft tissue substitutes not listed above are considered **investigational** (see Policy Guidelines).

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

POLICY GUIDELINES

Amniotic fluid is considered an amniotic product.

INVESTIGATIONAL PRODUCTS

The following amniotic products, placental products, and skin and soft tissue substitutes are considered investigational. There are many products available, and this list is not all-inclusive.

- Abiomend Membrane/ Hydromembrane [Q4356]
- Abiomend Xplus Membrane/ Hydromembrane [Q4355]
- AC5® Advanced Wound System [A2020]
- ACApatch™ [Q4325]
- ACell® UBM Hydrated/Lyophilized Wound Dressing
- Acesso [Q4311]
- Acesso AC [Q4312]
- Acesso DL [Q4293]
- Acesso TL [Q4300]
- Activate™ Matrix [Q4301]
- Allacor P™ [A2035]
- AlloGen® [Q4212]
- AlloPly™ [Q4323]
- AlloSkin™ [Q4115]

- AlloSkin™ AC [Q4141]
- AlloSkin™ RT [Q4123]
- AlloWrap® [Q4150]
- Altiply™ [Q4235]
- AmchoPlast [Q4316]
- AmchoPlast FD™ [Q4360]
- American Amnion™ [Q4307]
- American Amnion AC™ [Q4306]
- American Amnion AC Tri-Layer™ [Q4305]
- AmnioAmp-MP™ [Q4250]
- Amnioarmor™ [Q4188]
- AmnioBand®, particulate [Q4168]
- AmnioBind™ [Q4225]
- Amnio Burgeon Membrane/Hydromembrane [Q4363]
- Amnio Burgeon Dual-Layer Membrane [Q4365]
- Amnio Burgeon Xplus Membrane/Hydromembrane [Q4364]
- AmnioCore™ [Q4227]
- AmniCore™ Pro [Q4298]
- AmniCore™ Pro+ [Q4299]
- AmniCore™ SL [Q4367]
- AmnioCyte™ Plus [Q4242]
- AmnioMatrix® [Q4139]
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- Amnio Quad-Core [Q4292]
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- Amniorepair® [Q4235]
- Amniotext™ [Q4245]
- Amniotext™ patch [Q4247]
- AmnioTX™ [Q4324]
- Amnio Wound [Q4181]
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- Axolotl Graft™ [Q4331]
- Axolotl DualGraft™ [Q4332]
- Barrera™ sl or dl [Q4281]
- BellaCell HD [Q4220]
- Biobrane®/Biobrane-L
- Bio-ConneKt® Wound Matrix [Q4161]
- BioDFence® [Q4140]
- BioDFence® Dryflex [Q4138]
- Biovance® tri-layer or 3L [Q4283]
- Biowound™, Plus, Xplus [Q4217]
- Caregraft™ [Q4322]
- Carepatch™ [Q4236]
- Cellesta™/Cellesta™ Duo [Q4184]
- Cellesta™ Cord [Q4214]
- Cellesta™ flowable amnion [Q4185]
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- Cocoon membrane [Q4264]
- Cogenex® amniotic membrane [Q4229]
- Cogenex® flowable amnion [Q4230]
- CollaCare®
- CollaCare® Dental
- Collagen Wound Dressing (Oasis Research)
- CollaGUARD®
- CollaMend™
- CollaWound™
- Coll-e-Derm™ [Q4193]
- Collexa®
- Colliea®
- Complete™ AA [Q4303]
- Complete™ ACA [Q4302]
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- Complete™ SL [Q4270]
- Conexa™
- CoreCyte™ [Q4240]
- Coreleader Colla-Pad
- CorMatrix®

- Corplex™ [Q4232]
- Corplex P™ [A2035]
- CoreText™ or ProText™ [Q4246]
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- Dermabind CH™ [Q4288]
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- Fluid Flow™, Fluid GF™ [Q4206]
- Foundation DRS Solo [A2034]
- GammaGraft [Q4111]
- Genesis Amniotic Membrane [Q4198]
- Grafix Plus [Q4304]
- Graftjacket® Xpress, injectable [Q4113]
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- hMatrix® [Q4134]
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- InnovaMatrix® [A2001]
- InnovaMatrix® FS [A2013]
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- Integra™ Matrix Wound Dressing [Q4108]
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- Lamellas [Q4292]
- Lamellas XT [Q4291]
- Mantle™ DL [Q4349]
- MariGen™/Kerecis™ Omega3™
- MatriDerm® [A2027]
- Matrion™ [Q4201]
- Matrix HD™ [Q4345]
- Mediskin® [Q4135]
- Membrane Graft™/Membrane Wrap™ [Q4205]
- Membrane Wrap-Hydro™ [Q4290]
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- Miro3D Wound Matrix [A2025]
- Miroderm® biologic wound matrix [Q4175]
- MiroDry™ wound matrix [A2031]
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- MLG Complete™ [Q4256]
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- Myriad Matrix™ [A2032]
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- NuCel
- NuDYN® DL or DL Mesh [Q4285]
- NuDYN® SL or SLW [Q4286]
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- Omeza® Collagen Matrix [A2014]
- Orion [Q4276]
- Overlay™ SL [Q4352]
- PalinGen®/PalinGen® Xplus [Q4173]
- PalinGen® Dual-Layer Membrane [Q4354]
- PalinGen®/ProMatrX™, injectable [Q4174]
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- PelloGraft [Q4320]
- Pelvicol®/PelviSoft®
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- PermeaDerm b [A2016]
- PermeaDerm c [A2018]
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- PolyCyte™ [Q4241]
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- Puros® Dermis
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- Relese™ [Q4257]
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- Repriza [Q4143]
- Resolve Matrix™ [A2024]
- Restorigin™ [Q4191, Q4192]
- Restrata® [A2007]
- Restrata® MiniMatrix [A2026]
- Revita® [Q4180]
- Revitalon™ [Q4157]
- Revoshield+® [Q4289]
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- Strattice™ (xenograft) [Q4130]
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- Symphony [A2009]
- Talymed® [Q4127]
- TenoGlide™
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- TissueMend
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- TruSkin™ [Q4167]
- Vendaje™ [Q4252]
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- Veritas® Collagen Matrix [C9354]
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- Vim® [Q4251]
- Vitograft [Q4317]
- WoundEx® Bioskin [Q4163]
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- Woundfix™, Plus, Xplus [Q4217]
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- XWRAP Plus® [Q4357]
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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
- Indication for the requested service
- Documentation of symptoms, associated diagnoses and treatments
- Conservative treatment provided, if any
- Name of product to be used and indication

CROSS REFERENCES

None

BACKGROUND

BIOENGINEERED SKIN AND SOFT TISSUE SUBSTITUTES

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (e.g., dermis with cellular material removed, synthetic products) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (e.g., dermis, pericardium, intestinal mucosa), additives (e.g., antibiotics, surfactants), hydration (wet, freeze-dried), and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal

cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

There are many potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (e.g., breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

AMNIOTIC PRODUCTS

Human Amniotic Membrane

Human amniotic membrane (HAM) consists of two conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac or placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. Many products available using amnion, chorion, amniotic fluid, and umbilical cord are being studied for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions. The products are formulated either as patches, which can be applied as wound covers, or as suspensions or particulates, or connective tissue extractions, which can be injected or applied topically.

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.[1] There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.[2]

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being

evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures. Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

Amniotic Fluid

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea.[1] The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid-derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

REGULATORY STATUS

There are many artificial skin and soft-tissue products that are commercially available or in development. Information on specific products is available in a 2020 Technical Brief on skin substitutes for treating chronic wounds that was commissioned by the Agency for Healthcare Research and Quality.[3]

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research. ADM and amniotic products are classified as banked human tissue and therefore, not requiring FDA approval for homologous use. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[4]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

a. Is for autologous use;
b. Is for allogeneic use in a first-degree or second-degree blood relative; or
c. Is for reproductive use."

The guidance provides the following specific examples of homologous and non-homologous use for amniotic membrane:

a. "Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.
b. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.
c. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane."

The FDA noted the intention to exercise enforcement discretion for the next 36 months after publication of the guidance.

In 2003, Prokera® was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The FDA determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera® device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.”[5] The development of Prokera®, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

AmnioClip (FORTECH GmbH) is a ring designed to hold the amniotic membrane in the eye without sutures or glue fixation. A mounting device is used to secure the amniotic membrane within the AmnioClip. The AmnioClip currently has CE approval in Europe.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves health outcomes for patients. Broadly defined, health outcomes are the length of life, quality of life, and ability to function – including benefits and harms. 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.

The following is a summary of key literature to date.

BREAST RECONSTRUCTION

A meta-analysis by Lee and Mun (2016) included 23 studies (total n=6,199 cases) on implant-based breast reconstruction that were published between February 2011 and December

2014.[6] The analysis included an RCT and three prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference 79.63, 95% confidence interval [CI], 41.99 to 117.26, p<0.001) and percentage of intraoperative filling (mean difference 13.30, 95% CI 9.95 to 16.65, p<0.001), and reduced the frequency of injections to complete expansion (mean difference -1.56, 95% CI -2.77 to -0.35, p=0.01).

Table 1. Meta-Analysis of Breast Reconstruction Outcomes with and without ADM

Outcome Measure	Relative Risk	95% Confidence Interval	p
Infection	1.42	1.02 to 1.99	0.04
Seroma	1.41	1.12 to 1.78	0.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	0.006
Unplanned return to the operating room	1.09	0.63 to 1.90	NS
Implant loss	1.00	0.68 to 1.48	NS
Total complications	1.08	0.87 to 1.34	NS
Capsular contracture	0.26	0.15 to 0.47	<0.001
Implant malposition	0.21	0.07 to 0.59	0.003

Adapted from Lee and Mun (2016).[6]
ADM: acellular dermal matrix; NS: not significant.

A study by Davila (2013) used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1,717) to submuscular tissue expander breast reconstruction (n=7,442) after mastectomy.[7] Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%, p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

ALLODERM®

Randomized Controlled Trials

McCarthy (2012) reported on a multicenter, blinded RCT of AlloDerm® in two-stage expander/implant reconstruction.[8] Seventy patients were randomized to AlloDerm® ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary endpoint of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm® vs. 42.8 controls on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm® vs. 4.6 controls) or in the secondary outcome of rate of tissue expansion (91 days AlloDerm® vs. 108 days controls) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

Comparisons Between Products

AlloDerm® Versus AlloMax™

Hinchcliff (2017) conducted an RCT that compared AlloDerm® with AlloMax™ (n=15 each) for implant-based breast reconstruction.[9] Complications were assessed 7, 14, and 30 days

postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax™ biopsies was higher than in the AlloDerm® biopsies. Complications were reported in 26.1% of AlloMax™ cases and 8.0% of AlloDerm® cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm® Versus DermaMatrix™

Mendenhall (2017) published an RCT that compared AlloDerm® with DermaMatrix™ in 111 patients (173 breasts).[10] There were no significant differences in overall rates of complications (AlloDerm® 15.4%, DermaMatrix™ 18.3%, p=0.8) or implant loss (AlloDerm® 2.2%, DermaMatrix™ 3.7%, p=0.5) between the two ADMs at three months. There were no statistically significant differences in the overall complication rates (6% vs. 13%, p=0.3), severity of complications, or patient satisfaction between the AlloDerm and DermaMatrix groups at two years after definitive reconstruction.[11]

Strattice™

Dikmans (2017) reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted one-stage expansion with two-stage implant-based breast reconstruction (see Table 2).[12] One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogenic ADM or to the comparison between one-stage and two-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dikmans (2017)[12]	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

ADM: acellular dermal matrix; IBBR: implant-based breast reconstruction; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Outcomes

Study	Surgical Complications	Severe Adverse Events	Reoperation	Removal of Implant ADM, or Both
Dikmans (2017)[12]				
1-stage with ADM, n (%)	27 (46)	26 (29)	22 (37)	24 (26)
2-stage with ADM, n (%)	11 (18)	5 (5)	9 (15)	4 (5)
OR (95% CI)	3.81 (2.67 to 5.43), p<0.001		3.38 (2.10 to 5.45), p<0.001	8.80 (8.24 to 9.40), p<0.001

ADM: acellular dermal matrix; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial.

TENDON REPAIR

GraftJacket®

Barber (2012) reported an industry-sponsored multicenter RCT of augmentation with GraftJacket® human ADM for arthroscopic repair of large (>3 cm) rotator cuff tears involving two tendons.[13] Twenty-two patients were randomized to GraftJacket® augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range 12-38 months), the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the GraftJacket® group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the GraftJacket® group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score did not differ significantly between groups. Gadolinium-enhanced MRI scans showed intact cuffs in 85% of repairs in the GraftJacket® group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in three (14%) patients in the GraftJacket® group and nine (45%) patients in the control group.

Rashid (2020) reported disruption of the native extracellular matrix with either GraftJacket® or Permacol™ (porcine acellular dermis) as a patch overlay for rotator cuff repair in a small controlled study with 13 patients.[14] The disruption was greater in the Permacol™ group and there was an immune response in one of three patients following use of the xenograft.

SURGICAL REPAIR OF HERNIAS OR PARASTOMAL REINFORCEMENT

A systematic review by Bellows (2013) evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.[15] The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis®, Tutomesh®, Veritas®, AlloDerm®, FlexHD®, AlloMax™, CollaMend™, Permacol™, Strattice™, FortaGen®, ACell, DermaMatrix™, XenMatrix™, and SurgiMend®. Sixty publications with 1,212 repairs were identified and included in the review, although meta-analysis could not be performed. There were four level III studies (two AlloDerm®, two Permacol™); the remainder was level IV or V. The largest number of publications were on AlloDerm® (n=27) and Permacol™ (n=18). No publications on incisional hernia repair were identified for AlloMax™, FortaGen®, DermaMatrix™, or ACell. The overall incidence of a surgical site occurrence (e.g., postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogenic dermis, 48.3% for human dermis, and 6.3% for xenogenic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm® as an Overlay

Espinosa-de-los-Monteros (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm® performed in 37 patients and compared them with 39 randomly selected cases.[16] They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons Between Products

<u>AlloDerm® Versus Surgisis® Gold</u>

Gupta (2006) compared the efficacy and complications associated with use of AlloDerm® and Surgisis® bioactive mesh in 74 patients who underwent ventral hernia repair.[17] The first 41 procedures were performed using Surgisis® Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm®. Patients were seen 7 to 10 days after discharge from the hospital and at six weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm® mesh resulted in eight (24%) hernia recurrences. Fifteen (45%) of the AlloDerm® patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

AlloDerm® Versus FlexHD®

A study by Bochicchio (2013) compared AlloDerm® with FlexHD® for complicated hernia surgery.[18] From 2005 to 2007, AlloDerm® was used to repair large (>200 cm^2), symptomatic, complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD® was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The two groups were comparable at baseline. At one-year follow-up, all AlloDerm® patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD® group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD® Versus Strattice™

Roth (2017) reported on a prospective study assessing clinical and quality-of-life outcomes following complex hernia repair with a human (FlexHD®) or porcine (Strattice™) ADM.[19] The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD®. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice™ Versus Synthetic Mesh

Bellows (2014) reported early results of an industry-sponsored multicenter RCT that compared Strattice™ (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.[20] The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through two years of follow-up. The primary outcome was resumption of activities of daily living at one year. Secondary outcomes included complications, recurrences, or chronic pain (i.e., pain that did not disappear by three months postsurgery). At three-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk 0.98, 95% CI 0.52 to 1.86). Pain was reduced from one to three days postoperative in the group treated with Strattice™, but at three-month follow-up pain scores did not differ significantly between groups.

A double-blind RCT by Brunbjerg (2020) compared Strattice™ to synthetic mesh (Prolene®) to prevent hernia or bulging in 29 patients admitted to a single center in Denmark for pedicled

transverse rectus abdominis musculocutaneous flap surgery.[21] At two-years post-surgery, bulging frequency was higher in the Strattice™ group (35.7%) than in the synthetic mesh group (6.7%), but the difference was not statistically significant (p = 0.11). Two Strattice™ patients developed a hernia, while none of the mesh patients did. No differences were found for abdominal muscle strength between baseline and two-year measurements.

Strattice™ Versus No Reinforcement

Also in 2014, the Parastomal Reinforcement With Strattice™ (PRISM) Study Group reported a multicenter, double-blinded, randomized trial of Strattice™ for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.[22] Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice™ as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the two groups (13.2% of controls, 12.2% of study group).

Adverse Events

Permacol™ (porcine acellular dermal matrix) was reported in a case series of 13 patients to result in recurrent intestinal fistulation and intestinal failure when used for abdominal reconstructive surgery.[23]

DIABETIC LOWER-EXTREMITY ULCERS

Systematic Reviews

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.[24] Seventeen trials (total n=1,655 participants) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (relative risk 1.55, 95% CI 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (relative risk 0.43, 95% CI 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf®, EpiFix®, and Hyalograft-3D™. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft®, GraftJacket®, Kaloderm®, and OrCel®.

A systematic review by Lakmal (2021) included eight RCTs, two prospective studies and two retrospective studies that evaluated the use of amniotic membrane allografts for the treatment of diabetic foot ulcers.[25] Generally, the studies reported that better wound closure rates were seen with the amniotic membrane products than with standard care, but a meta-analysis was not possible due to study heterogeneity.

Amniotic Membranes

At least seven RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane grafts compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 4). The number of patients in these studies ranged from 25 to 155. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord® vs. alginate dressing) to 60% (EpiFix®) in the intention-to-treat (ITT) analysis (see Table 5). In a 2018 trial, the cryopreserved placental membrane

Grafix® was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft®).[26]

Table 4. Summary of Key RCT Characteristics

Study	Participants	Intervention	Comparator
Serena (2020)[27]	76 patients with chronic (>4 weeks) non-healing diabetic foot ulcers unresponsive to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon	n=38, Affinity	n=38, SOC
Ananian (2018)[26]	75 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers between 1 cm^2 and 15 cm^2	n=38, Grafix® weekly for up to 8 weeks	n=37, Dermagraft® (fibroblast-derived) weekly for up to 8 weeks
Tettelbach (2019)[28]	155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord® plus SOC	n=54 SOC with alginate dressing
DiDomenico (2018)[29]	80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand® Membrane plus SOC	SOC
Snyder (2016)[30]	29 patients with non-healing diabetic foot ulcers	AmnioExcel® plus SOC	SOC
Zelen (2015, 2016)[31, 32]	60 patients with less than 20% wound healing in a 2-week run-in period	EpiFix®	Apligraf® or SOC with collagen-alginate dressing
Tettelbach (2019)[33]	110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix®	SOC with alginate dressing
Lavery (2014)[34]	97 patients with chronic diabetic foot ulcers	Grafix® Weekly	SOC

RCT: randomized controlled trial; SOC: standard of care including debridement, nonadherent dressing, moisture dressing, a compression dressing and offloading.

Table 5. Summary of Key RCT Results

Study	Wounds Healed	Time to Complete Healing	Adverse Events
Serena (2020)[27]	16 Weeks (ITT)	Median	
N	76	76	
Affinity	58%	11 weeks	
SOC	29%	not attained by 16 weeks	
HR (95% CI), p-value	1.75 (1.16 to 2.70), p=0.01		
Ananian (2018)[26]	8 Weeks (PP) n (%)		Patients with Index Ulcer Related Adverse Events n (%)
N	62		75
Grafix®	15 (48.4%)		1 (5.9%)
Dermagraft®	12 (38.7%)		4 (16.7%)
Diff (95% CI), Lower bound for non-inferiority	9.68% (−10.7 to 28.9), -15%		
Tettelbach (2018)[28]	12 Weeks (ITT) n (%)		Patients with Adverse Events (% of total)
N	155		155

Study	Wounds Healed	Time to Complete Healing	Adverse Events
EpiCord®	71 (70%)		42 (42%)
SOC	26 (48%)		33 (61%)
p-value	0.009		
DiDomenico (2018)[29]	12 weeks (ITT) n (%)	Mean Days (95% CI)	
N	80	80	
Amnioband®	34 (85)	37.0 (29.5 to 44.4)	
SOC	13 (33)	67.3 (59.0 to 79.6)	
HR (95% CI)		4.25 (0.44 to 0.79), p<0.001	
Snyder (2016)[30]	6 Weeks (PP) Mean (95% CI)		
N	21		
AmnioExcel®	45.5% (32.9% to 58.0%)		
SOC	0%		
p-value	0.014		
Zelen (2015, 2016)[31, 32]	Wounds Healed at 12 Weeks		
N	100		
EpiFix®	NR		
Apligraf®	NR		
SOC	NR		
HR (95% CI)	5.66; (3.03 to 10.57), p<0.001 vs. SOC		
Tettelbach (2019)[33]	Wounds Healed at 12 Weeks (ITT)		
N	110		
EpiFix®	70%		
SOC	50%		
p-value	0.034		
Lavery (2014)[34]	Wounds Healed at 12 Weeks		Patients with Adverse Events
N	97	97	97
Grafix®	62.0%	42.0	44.0%
SOC	21.3%	69.5	66.0%
p-value	<0.001	0.019	0.031

CI: confidence interval; DIFF: difference; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care.

Many of these studies had methodologic limitations, including a lack of blinding and loss of patients to follow-up.

Smiell (2015) reported on an industry-sponsored, multicenter registry study of Biovance® d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds.[35] Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of eight weeks and a mean of 2.4 amniotic membrane applications.

Frykberg (2017) reported treatment of complex chronic wounds (exposed tendon or bone) with Grafix®.[36] With the cryopreserved placental membrane applied weekly for up to 16 weeks, 59% of wounds closed with a mean time to closure of nine weeks.

Apligraf®

Veves (2001) reported on a randomized prospective trial on the effectiveness of Apligraf® (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.[37] The trial involved 24 centers in the United States; 208 patients were randomized to ulcer treatment with Apligraf® (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Apligraf® was applied at the beginning of the study and weekly thereafter for a maximum of four weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf®-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.004). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf®, which was significantly lower than the 90 days observed in the control group (p=0.003). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf® group. Trialists concluded that application of Apligraf® for a maximum of four weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial was reviewed in a 2001 TEC Assessment, which concluded that Apligraf®, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.[38]

Dermagraft®

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft® (human-derived fibroblasts cultured on mesh) or control.[39] Over the 12-week study, patients received up to eight applications of Dermagraft®. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft® group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft® closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft®. Ulcer infections developed in 10.4% of the Dermagraft® patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft®-treated group (19% vs. 32.5%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft® (5.5% vs. 12.6%, p=0.031).[40] Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch®

AlloPatch® Pliable human reticular acellular dermis was compared with SOC in an industry-sponsored multicenter trial by Zelen (2017, 2018).[41, 42] The initial trial with 20 patients per group was extended to determine the percent healing at six weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At six weeks, 68% (27/40) of wounds treated using AlloPatch® had healed compared with 15% (6/40) in the SOC-alone group (p<0.001). At 12 weeks, 80% (32/40) of patients in the AlloPatch® group had healed compared to 30% (12/40) in the control group. Mean time to heal within 12 weeks was 38 days (95% CI 29 to 47 days) for the HR-ADM group and 72 days (95% CI 66 to 78 days) for the SOC group (p<0.001).

Integra® Omnigraft Dermal Regeneration Template or Integra® Flowable Wound Matrix

Integra® Dermal Regeneration Template is a biosynthetic skin substitute that is FDA-approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra® Dermal Regeneration Template (marketed as Omnigraft™) for chronic nonhealing diabetic foot ulcers under an FDA-regulated investigational device exemption.[43] A total of 307 patients with at least one chronic diabetic foot ulcer were randomized to treatment with the Integra® Template or a control condition (sodium chloride gel 0.9%). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra® Template (51% vs. 32%, p=0.001) and a shorter median time to closure (43 days vs. 78 days, p=0.001). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing (*r*=0.97). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Trial strengths included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

Integra® Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers.[44] The ulcers had developed over 39 weeks. Complete healing at six weeks was achieved in significantly more patients in the Integra® Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra® Flowable Wound Matrix (see Table 6).

Table 6. Probability of Wound Healing with IFWM Versus SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello (2017)[44]			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)
p	0.010	0.001	0.028

CI: confidence interval; IFWM: Integra® Flowable Wound Matrix; RR: relative risk; SOC: standard of care.

GraftJacket® Regenerative Tissue Matrix

Brigido (2004) reported a small (n=40) randomized pilot study comparing GraftJacket® with conventional treatment for chronic nonhealing diabetic foot ulcers.[45] Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. GraftJacket® patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket® group. Preliminary one-month results showed that, after a single treatment, ulcers treated with GraftJacket® healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%), and depth (89% vs. 25%), respectively. With follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Reyzelman (2009) reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket® with SOC in 86 patients with diabetic foot ulcers.[46] Eight patients, six in the study group and two in the control group, did not complete

the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket® group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks for the GraftJacket® group versus 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for GraftJacket® (range 1-12 weeks) and 7.0 weeks for control (range 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) than for the control group (53.9%). The authors commented that a single application of GraftJacket®, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant.

Reyzelman and Bazarov (2015)[47] reported the results of an industry-sponsored meta-analysis of GraftJacket® for diabetic foot ulcers, which included the two studies described above and a third RCT by Brigido (2006)[48] (total n=154 patients). The time to heal was estimated for the Brigido (2004) study,[45] based on the average wound reduction per week. The estimated difference in time to heal was larger for Brigido's (2004) study (-4.30 weeks) than for the other two studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman (2009). The odds ratio in the smaller study by Brigido (2006) was considerably larger, with a lack of precision in the estimate (odds ratio, 15.0, 95% CI 2.26 to 99.64), and the combined odds (3.75, 95% CI 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods.

DermACELL® Versus GraftJacket® Regenerative Tissue Matrix or Standard of Care

DermACELL® and GraftJacket® are both composed of human ADM. Walters (2016) reported on a multicenter randomized comparison of DermACELL®, GraftJacket®, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.[49] The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL®. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL®, 47.8% for GraftJacket®, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL® versus SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL® (8.6 weeks), GraftJacket® (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published by Cazzell (2017).[50] This analysis compared DermACELL® with SOC and did not include the GraftJacket® arm. The authors reported that either one or two applications DermACELL® led to a greater proportion of wounds healed compared with SOC in per-protocol analysis, but there was no significant difference between DermACELL® (one or two applications) and SOC when analyzed by ITT. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as ITT analysis, results were analyzed only for the group who received a single application of DermACELL®. This would not typically be considered ITT.

mVASC®

Gould (2022) reported results of the HIFLO (Healing in Diabetic Foot Ulcers with Microvascular Tissue) Trial.[51] This was a multicenter RCT comparing weekly application of the processed microvascular tissue (PMVT) allograft, mVASC®, in addition to a standardized diabetic foot ulcer protocol versus standard wound care with a collagen alginate dressing control in 100 adults with Wagner Grade 1 and 2 diabetic foot ulcers of at least four weeks and less than 52 weeks duration. Wound and local peripheral neuropathy assessment were performed weekly. The primary outcome of the study was complete wound closure at 12 weeks. The investigator and a blinded physician made the initial determination of wound closure, followed by adjudication and confirmation by an independent, blinded panel of plastic surgeons. All participants who attended at least one treatment visit were included in the analysis. There was missing data for 15 participants at week 12 (three in mVASC® vs. 12 in control) and 14 of these were missing due to adverse events related to the wound. These were included in the primary analysis and counted as wound healing failures. The mean age of participants was 60 years, 90% of participants were White and 10% were Black, and 66% of participants were men. At randomization, the mean size of the wound area was 3.3 cm^2 and the mean duration of the wound was 15 weeks. The proportion of participants with complete wound closure at week 12 was 74% (37/50) for mVASC versus 38% (19/50) for control ($p<0.001$). Of the wounds that healed, the mean time to healing was also statistically significantly faster for the mVASC® group (54 days, 95% CI 46 to 61 vs. 64 days, 95% CI 57 to 72, $p=0.009$). The 10-point Semmes-Weinstein monofilament test of peripheral neuropathy also favored mVASC® (118% vs. 11%, $p=0.028$). No adverse events or serious adverse events related to the study treatment or the procedure were reported. There were 11 adverse events reported, three for mVASC® and eight for controls, that were related to the wound.

Theraskin®

Armstrong (2022) reported results of an RCT including 100 adults with non-healing Wagner 1 diabetic foot ulcers comparing Theraskin (n=50) to SOC (n=50).[52]https://www.bcbsaoca.com/sites_data/mpp_pub_final/_blank The index ulcer had to have been present for greater than four weeks and less than one year with a minimum size of 1.0 cm^2 and a maximum size of 25 cm^2. Standard of care included glucose monitoring, weekly debridement as appropriate, and an offloading device. The dressing in the SOC group was calcium alginate. The primary outcome was the proportion of full-thickness wounds healed at 12 weeks. Wound healing was assessed initially by the investigator and confirmed by blinded adjudication panel. Wounds were closed when there was 100% re-epithelization and no drainage. The mean age of participants was 60 years; 53% of participants were male, 70% were White, and 15% were Black. The mean wound area at baseline was 4.1 cm^2. Participants who did not have healing of at least 50% by 6 weeks were allowed to seek alternative rescue wound care (TheraSkin® n=1, SOC n=11). In addition, three participants in the TheraSkin® group and eight in the SOC group had worsening of the wound or an adverse event before week 12. All enrolled participants were included in analysis and missing data were imputed using last observation carried forward. The percent of participants with complete wound healing at week 12 was 76% (38/50) in the intervention group compared with 36% (18/50) in the SOC group ($p<0.01$). The mean percent area reduction at 12 weeks was 77.8% in the TheraSkin® group compared with 49.6% in the SOC group ($p<0.01$). There were no statistically significant differences between groups in QOL or pain score measures.

Theraskin® Versus Dermagraft®

Sanders (2014) reported on a small (n=23) industry-funded randomized comparison of Theraskin® (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft® for diabetic foot ulcers.[53] Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the two groups (p=0.51). Grafts were applied according to manufacturers' instructions over the first 12 weeks of the study until healing, with an average of 4.4 Theraskin® grafts (every two weeks) compared with 8.9 Dermagraft® applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with Theraskin® and 33.3% of ulcers treated with Dermagraft® (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the Theraskin®-treated ulcers compared with 66.7% of the Dermagraft® group (p=0.428).

Theraskin® Versus Apligraf®

DiDomenico (2011) compared Theraskin® with Apligraf® for the treatment of diabetic foot ulcers in a small (n=29) RCT.[54] The risk of bias in this study is uncertain because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf® group and 66.7% in the Theraskin® group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf® group and 66.7% closed in the Theraskin® group. The percentage healed in the Apligraf® group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups (1.53 for Apligraf®, 1.38 for Theraskin®). The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

Cytal® (MatriStem) Versus Dermagraft®

Frykberg (2016) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal® (a porcine urinary bladder-derived extracellular matrix) versus Dermagraft® in 56 patients with diabetic foot ulcers.[55] The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to eight weeks of treatment using blinded evaluation of photographs. ITT analysis found complete wound closure in five (18.5%) wounds treated with Cytal® compared with two (6.9%) wounds treated with Dermagraft® (not statistically significant). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal® group and from 184.46 to 195.73 in the Dermagraft® group (p=0.074). It should be noted that this scale is a subjective measure and patients were not blinded to treatment.

PriMatrix®

Lantis (2021) reported on a multicenter RCT comparing PriMatrix® plus standard of care to PriMatrix® alone in 226 patients with diabetic foot ulcers.[56] Study subjects underwent a two-week run-in period of SOC treatment and were excluded if they had a wound reduction of 30% or more. Patients randomized to the SOC group received weekly treatment at the study site identical to the SOC treatment applied during the screening period. In addition, control group patients performed daily dressing changes, which consisted of wound cleaning, application of saline gel and secondary dressings. The primary endpoint was the percentage of subjects with complete wound closure, defined as 100% re-epithelialization without drainage during the 12-week treatment phase. Significantly more patients in the PriMatrix® group experienced complete wound closure at 12 weeks (45.6% vs. 27.9%, p=0.008). It is unclear if this difference

(17.7%) is clinically significant; the study was powered to detect a 20% difference between groups. The time to complete healing did not differ between groups for the wounds that healed. Major study limitations include lack of blinding, limited generalizability, and insufficient duration of follow-up to assess wound recurrence.

Oasis® Wound Matrix Versus Regranex Gel

Niezgoda (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS® Wound Matrix (a porcine acellular wound care product) to Regranex Gel.[57] This industry-sponsored, multicenter RCT was conducted at nine outpatient wound care clinics and involved 73 patients with at least one diabetic foot ulcer. Patients were randomized to receive either Oasis® Wound Matrix (n=37) or Regranex Gel (n=36) and secondary dressing. Wounds were cleaned and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks, 18 (49%) Oasis®-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis® treatment met the noninferiority margin but did not demonstrate that healing in the Oasis® group was statistically superior (p=0.055). Post hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also increased healing of plantar ulcers in the Oasis® group (52% vs. 14%). These post hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to compare the effect of Oasis® treatment to current SOC.

Autologous Grafting on HYAFF Scaffolds

Uccioli (2011) reported a multicenter RCT of cultured expanded fibroblasts and keratinocytes grown on an HYAFF scaffold (benzyl ester of hyaluronic acid) compared with paraffin gauze for difficult diabetic foot ulcers.[58] A total of 180 patients were randomized. At 12 weeks, complete ulcer healing was similar for the two groups (24% treated vs. 21% controls). At 20 weeks, complete ulcer healing was achieved in a similar proportion of the treatment group (50%) and the control group (43%, log-rank test = 0.344). Subgroup analysis, adjusted for baseline factors and possibly post-hoc, found a statistically significant benefit of treatment on dorsal ulcers but not plantar ulcers.

Omega3 Wound

Lullove (2021, 2022) reported interim results and Lantis (2023) reported the final results of a RCT of the Kerecis™ Omega3 Wound plus standard wound care compared to standard care alone in 49 patients with diabetic lower extremity skin ulcers.[59-61]. The primary outcome was healing at 12 weeks. Complete ulcer healing was based on the site investigator's assessment, as evidenced by complete (100%) re-epithelialization without drainage and need of dressing. An independent panel of wound care experts who were blinded to the patient allocation process and the principal investigator's assessment reviewed all study-related decisions made by the site investigators and confirmed healing status. Secondary outcomes were time to heal and wound area reduction by percentage at 12 weeks. Patients underwent a two-week run-in period prior to randomization. If the ulcer reduced in area by 20% or more after 14 days of standard care, the patient was excluded as a screening failure. If the wound area was reduced by less than 20%, the patient was randomized and enrolled in the study. At 12 weeks, the complete healing rate was significantly higher in the intervention arm (57% vs. 31%), but time to healing did not differ between groups for wounds that healed completely. Among the subset of wounds that did not heal completely by 12 weeks (n=65), there was a larger percent wound

reduction in the intervention group (86% vs. 64%, p=0.03). Of the 45 participants whose wound healed during the 12 weeks of the trial, 42 were available for follow-up 6 to 12 months after healing. Three (11%) ulcer recurrences were reported in the intervention arm compared to one (7%) in the control arm.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

EpiFix®

Two RCTs evaluated the use of EpiFix® for venous leg ulcers. Serena (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix® d-HAM plus compression therapy with compression therapy alone for venous leg ulcers.[62] The primary outcome in this trial was the proportion of patients with 40% wound closure at four weeks, which was achieved by about twice as many patients in the combined EpiFix® group compared with the control group. However, a similar percentage of patients in the combined EpiFix® group and the control group achieved complete wound closure during the four-week study. There was no significant difference in healing for wounds given one versus two applications of amniotic membrane (62% vs. 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at four weeks (n=®20) had a closure rate of 80% by 24 weeks; however, this analysis did not account for additional treatments after the four-week randomized trial period.

A second industry-sponsored multicenter open-label RCT, reported by Bianchi (2018, 2019), evaluated the time to complete ulcer healing following weekly treatment with EpiFix® d-HAM plus compression therapy or compression wound therapy alone.[63, 64] Patients treated with EpiFix® had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio 2.26, 95% CI 1.25 to 4.10, p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. In per-protocol analysis, healing within 12 weeks was reported for 60% of patients in the EpiFix® group and 35% of patients in the control group (p<0.013). Intent-to-treat analysis found complete healing in 50% of patients in the EpiFix® group compared to 31% of patients in the control group (p=0.0473). There were several limitations of this trial. In the per-protocol analysis, 19 (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix® group vs. 11% from the control group). There was also a difference between the groups in how treatment failures at eight weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at eight weeks were considered study failures and treated with advanced wound therapies. The ITT analysis used last-observation-carried-forward for these patients and sensitivity analysis was not performed to determine how alternative methods of handling the missing data would affect results. Kaplan-Meier analysis suggested a modest improvement in the time to heal when measured by ITT analysis, but may be subject to the same methodological limitations.

Biovance

As described above, Smiell (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers.[35] Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of eight

weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with SOC is unknown.

AmnioBand

Serena (2022) reported an industry-sponsored, multicenter, open-label RCT comparing once- or twice-weekly applications of AmnioBand® Membrane plus compression bandaging with compression bandaging alone in patients with chronic venous leg ulcers.[65] This HAM is a dehydrated aseptically processed product without terminal irradiation for sterilization. It is purported to retain the structural properties of the extracellular matrix that enhances wound healing. There were no significant differences in the proportion of wounds with percentage area reduction 40 percent at four weeks between all three study groups. A significantly greater proportion of patients assigned to weekly or twice-weekly HAM achieved the primary endpoint of blinded assessor-confirmed complete wound healing after 12 weeks of study treatment (75%) than those assigned to compression bandaging alone (30%, p=0.001). Receiving HAM was independently associated with odds of complete healing at 12 weeks after adjusting for baseline wound area (odds ratio 8.7, 95% CI 2.2 to 33.6). Median reduction in wound area from baseline was also significantly greater in patients assigned to HAM therapy (100%; interquartile range, 5.3%) than those assigned to compression bandaging alone (75%, interquartile range 68.7%, p=0.012). Adverse events were reported in 55%, 60%, and 75% of the once-weekly HAM, twice-weekly HAM, and standard-of-care groups, respectively. The most commonly reported adverse events were wound-related infections (36.7%) and new ulcer (31.6%). No adverse events were attributed to study treatment.

Apligraf®

Falanga (1998) reported on a multicenter randomized trial of Apligraf® living cell therapy.[66] A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or to compression therapy and treatment with Apligraf®. Apligraf® was applied up to a maximum of five (mean, 3.3) times per patient during the initial three weeks. The primary endpoints were the percentage of patients with complete healing by six months after initiation of treatment and the time required for complete healing. At six-month follow-up, the percentage of patients healed was higher with Apligraf® (63% vs. 49%), and the median time to complete wound closure was shorter (61 days vs. 181 days). Treatment with Apligraf® was superior to compression therapy in healing larger (>1000 mm^2) and deeper ulcers and ulcers of more than six months in duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf® (Graftskin), in conjunction with good local wound care, met TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.[38]

Oasis® Wound Matrix

Mostow (2005) reported on an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment using Oasis® Wound Matrix (xenogenic collagen scaffold from porcine small intestinal mucosa) with SOC in 120 patients who had chronic ulcers due to venous insufficiency that had not adequately responded to conventional therapy.[67] Healing was assessed weekly for up to 12 weeks, with follow-up performed after six months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis® group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis® group were 3 times more likely to heal than those in the

group receiving SOC. Patients in the SOC group whose wounds did not heal by week 12 were allowed to cross over to Oasis® treatment. None of the healed patients treated with Oasis® wound matrix who was seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described two comparative studies of the Oasis® matrix for mixed arteriovenous ulcers. In a quasi-randomized study, Romanelli (2007) compared the efficacy of two extracellular matrix-based products, Oasis® and Hyaloskin® (extracellular matrix with hyaluronic acid).[68] Fifty-four patients with mixed arteriovenous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed twice weekly, and dressings changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis®-treated ulcers compared with 46.2% of Hyaloskin®-treated ulcers. Oasis® treatment significantly increased the time to dressing change (mean, 6.4 days vs. 2.4 days), reduced pain on a 10-point scale (3.7 vs. 6.2), and improved patient comfort (2.5 vs. 6.7).

Romanelli (2010) compared Oasis® with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.[69] The trial was described as randomized, but the method of randomization was not described. After the eight-week study period, patients were followed monthly for six months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis®-treated ulcers at eight weeks compared with 65% of the SOC group. On average, Oasis®-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis® also increased the time to dressing change (5.2 days vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

Dermagraft®

Dermagraft® living cell therapy has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft® for venous ulcers is an off-label indication. Harding (2013) reported an open-label multicenter RCT that compared Dermagraft® plus compression therapy (n=186) with compression therapy alone (n=180).[70] The trial had numerous inclusion and exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had the capacity to heal. ITT analysis revealed no significant difference between the two groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft® vs. 31% control). Prespecified subgroup analysis revealed a significant improvement in the percentage of wounds healed for ulcers of 12 months or less in duration (52% vs. 37%) and for ulcers of 10 cm or less in diameter (47% vs. 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

PriMatrix®

Karr (2011) published a retrospective comparison of PriMatrix® (xenogenic ADM) and Apligraf® in 28 venous stasis ulcers.[71] The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of four weeks in duration, at least 1 cm^2 in diameter, and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The time to complete healing for PriMatrix® was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf®. Although promising, additional study with a larger number of subjects is needed to assess the effect of PriMatrix® treatment in compared with current SOC.

DermACELL®

Cazzell (2019) published an RCT on DermACELL® ADM for venous leg ulcers in 18 patients.[72] This was part of a larger study of the acellular dermal matrix for chronic wounds of the lower extremity in 202 patients; the component on diabetic lower extremity ulcers was previously reported by Cazzell (2017) and is described above.[50] When including patients who required more than one application of the ADM, the percent of wounds closed at 24 weeks was 29.4% with DermACELL® and 33.3% with SOC, suggesting no benefit DermACELL® for the treatment of venous ulcers in this small substudy.

Theraskin® Versus Standard of Care

In the propensity matched study by Gurtner (2020) described above, Theraskin® did not improve the healing rate of venous ulcers (66.1%) compared to SOC (70.1%).[73]

DEEP DERMAL BURNS

Epicel®

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel®.[74] The cultured epithelial autografts were applied to a mean of 37% of total body surface area (TBSA). Epicel® achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean 25%). Survival was 90% in these severely burned patients.

Integra® Dermal Regeneration Template

A 2013 study compared Integra® with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using three, 10 x 5 cm test sites on each of 10 burn patients.[75] The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the three methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski (2007) reported on a randomized trial that compared Integra® with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns).[76] Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra® group and controls in burn size (70% vs. 74% TBSA), mortality (40% vs. 30%), and hospital length of stay (41 vs. 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra® group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during two years, and cumulative operating room time required for these procedures. The authors concluded that Integra® can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Heimbach (2003) reported on a multicenter (13 U.S. burn care facilities) post-approval study involving 222 burn injury patients (36.5% TBSA, range 1%-95%) who were treated with Integra® Dermal Regeneration Template.[77] Within two to three weeks, the dermal layer

regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra® was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra® was 87.7%; the median take rate was 95%.

Hicks (2019) conducted a systematic review of Integra® dermal regeneration template for the treatment of acute full thickness burns and burn reconstruction.[78] A total of 72 studies with 1,084 patients (four RCTs, four comparative studies, five cohort studies, two case control studies, 24 case series, and 33 case reports) were included in the review. The majority of patients (74%) were treated with Integra® for acute burns, and the remainder (26%) for burn reconstruction. The take of the skin substitute was 86% (range 0-100%) for acute burn injuries and 95% (range 0-100%) for reconstruction. The take of the split-thickness skin graft over the template was 90% for acute burn injuries and 93% for reconstruction. There was high variability in reporting of outcomes, but studies generally supported satisfactory cosmetic results in patients who have insufficient autograft and improvement in range of motion in patients who were treated with Integra® for burn reconstruction. There was an overall complication rate of 13%, primarily due to infection, graft loss, hematoma formation, and contracture.

An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra® dermal regeneration template for burns.[79]

ReCell® Autologous Cell Harvesting Device

Two RCTs have evaluated ReCell® for deep dermal burns.[80, 81] In both studies, two similar areas with a burn injury in the same individual were randomized to the control or treatment intervention (i.e., all participants received both treatments). The studies differed in their populations, interventions, and outcome measures. Holmes (2018)[80] was a head-to-head comparison of ReCell® alone versus skin grafting alone, and Holmes (2019)[81] compared ReCell® in combination with skin grafting. In the earlier study, participants all had deep partial thickness burns, while in the 2019 study the population included individuals with mixed-depth, full thickness burns. In the 2018 study, the primary effectiveness endpoints were the incidence of wound closure at four weeks and the incidence of complete donor site healing at one week. In the 2019 trial, the co-primary effectiveness endpoints were non-inferiority of the incidence of ReCell®-treated site closure by week eight when compared to the control, and the superiority of the 37% relative reduction in donor skin for the ReCell® treatment when compared with the control. Although the ReCell® treatment was comparable to standard care on outcomes such as complete wound closure; confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

OrCel® was approved under a humanitarian device exemption (HDE) for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. HDE status has been withdrawn for Dermagraft® for this indication.

Fivenson (2003) reported the off-label use of Apligraf® in five patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.[82]

HUMAN AMNIOTIC MEMBRANE FOR OPHTHALMOLOGIC CONDITIONS

Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

Liu (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.[83] All but one of the studies was conducted outside of the U.S. There was one RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% (95% CI 0.94 to 0.99, p=0.089) of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53%, 95% CI 0.42 to 0.65, p<0.001).

Khokhar (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens.[84] At the three-month follow-up, 11 (73%) of 15 patients in the HAM group showed complete epithelialization compared with 10 (67%) of 15 patients in the conventional group. This difference was not significantly significant.

Suri (2013) published a series of 35 eyes of 33 patients who were treated with the self-retained Prokera® HAM for a variety of ocular surface disorders.[85] Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in two of nine (22%) patients with this indication. This study also reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. The mean duration of treatment prior to Prokera® insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome.

Dos Santos Paris (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.[86] Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the two treatments. Symptoms had been present for approximately two years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

John (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera® c-HAM or maximal conventional treatment.[87] The c-HAM was applied for an average of 3.4 days (range 3-5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both one-month and three-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at one month and 1.0 at three months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at three months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The DRy Eye Amniotic Membrane (DREAM) study, reported by McDonald (2018), was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical

therapy who were treated with Prokera® self-retained c-HAM.[88] A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera® for a mean of 5.4 days (range 2-11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at one week, 1.45 at one month and 1.47 at three months (p=0.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

MISCELLANEOUS

Punch Biopsy Wounds

Baldursson (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis™ Omega3 Wound (derived from fish skin) with Oasis® SIS ECM (porcine small intestinal submucosa extracellular matrix).[89] The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis™ Omega3 (p=0.041). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group.

A similar RCT by Kirsner (2020) included 85 patients and compared the Kerecis™ Omega3 to a dehydrated human amnion/chorion membrane product.[90] This study also reported faster healing in the Kerecis™ Omega3 group (hazard ratio 2.37, 95% CI 1.75 to 3.21, p=0.0014). Interpretation of these studies is limited because they did not include an accepted control condition for this indication.

Split-Thickness Donor Sites

There is limited evidence to support the efficacy of OrCel® compared with SOC for the treatment of split-thickness donor sites in burn patients. Still (2003) (examined the safety and efficacy of bilayered OrCel® to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.[91] Each patient had two designated donor sites that were randomized to a single treatment of OrCel® or standard dressing (Biobrane-L). The healing time for OrCel® sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel® sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

Pressure Ulcers

Brown-Etris (2019) reported an RCT of 130 patients with stage 3 or stage 4 pressure ulcers who were treated with Oasis® Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.[92] At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant (p=0.111). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% p=0.037), but complete wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include six-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison.

In the propensity matched study by Gurtner (2020) described above, Theraskin® improved the healing rate of pressure ulcers by 20% (66.7% vs 46.8%).[73]

Plantar Fasciitis

A 2016 network meta-analysis of 22 RCTs (total n=1,216 patients) compared injection therapies for plantar fasciitis.[93] In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term, however, this finding was based only on a single RCT. Outcomes at two to six months (seven RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

An RCT by Cazzell (2018) enrolled 145 patients and reported three-month follow-up.[94] In this trial, amniotic membrane injection led to greater improvements in the Visual Analog Scale (VAS) for pain and the Foot Functional Index between baseline and three months compared to controls. VAS at three months had decreased to 17.1 in the AmnioFix® group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference. The major limitation of the study is the short-term follow-up.

Osteoarthritis

In 2016, a feasibility study (n=6) was reported of ReNu™ cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis.[95] A single intra-articular injection of the suspension was used, with follow-up at one and two weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted.

Repair Following Mohs Micrographic Surgery

Lu (2022) published a systematic review of skin substitutes for management of Mohs micrographic surgery wounds.[96] Of the 40 studies that met inclusion criteria, there were 23 case series, 14 case reports, two cohort studies, and one RCT. The most frequently used substitutes were porcine collagen (57.5%), bovine collagen (11.3%), Integra (7.7%), hyaluronic acid-derived products (6.2%), amnion/chorion-derived products (5.8%), and allogeneic epidermal-dermal composite grafts (5.8%). Follow-up in these studies ranged from one week to 21 months. The authors noted a lack of high-quality evidence and a need for blinded RCTs comparing the performance of skin substitutes with traditional methods.

Toman (2022) conducted an observational study that compared repair using a dehydrated human amnion/chorion membrane product (EpiFix®) with surgical repair using autologous tissue in patients who underwent same-day repair following Mohs microsurgery for removal of skin cancer on the face, head, or neck.[97] Propensity-score matching using retrospective data from medical records was used to identify 143 matched pairs. The primary endpoint was the incidence of postoperative morbidity, including the rate of infection, bleeding/hematoma, dehiscence, surgical reintervention, or development of a nonhealing wound. Postoperative cosmetic outcomes were assessed at nine months or later and included documentation of suboptimal scarring, scar revision, treatment, and patient satisfaction. A greater proportion of

patients who received EpiFix® repair experienced zero complications (97.9% vs. 71.3%, p<0.0001, relative risk 13.67, 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=0.004) and were less likely to experience poor scar cosmesis (p<0.0001). Confidence in these findings is limited, however, by the study's retrospective design and potential for bias due to missing data. Additionally, the study's relevance is limited due to a lack of diversity in the study population and no comparison to non-surgical treatment options.

Other Indications

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (e.g., pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions.[98] Products that have been FDA-approved or -cleared for one indication (e.g., lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (e.g., for burns).[99] No controlled trials were identified for these indications.

PRACTICE GUIDELINE SUMMARY

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[100] The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, “healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.” References from two randomized controlled trials on dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

Society for Vascular Surgery

In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation:[101] "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."

SUMMARY

BREAST RECONSTRUCTION

There is enough evidence to show that some allogeneic acellular dermal matrix (ADM) products can improve health outcomes for individuals who are undergoing medically necessary breast reconstruction. A systematic review found no difference in overall complication rates with ADM allograft compared with standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM, however, capsular

contracture and malposition of implants may be reduced. Therefore, the use of AlloDerm®, AlloMend®, Cortiva® (AlloMax™), DermACELL®, DermaMatrix™, FlexHD®, FlexHD® Pliable™, or GraftJacket® may be considered medically necessary for breast reconstruction.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients undergoing breast reconstruction. Therefore, the use of products other than AlloDerm®, AlloMend®, Cortiva® (AlloMax™), DermACELL®, DermaMatrix™, FlexHD®, FlexHD® Pliable™, or GraftJacket® is considered investigational for this indication.

DIABETIC LOWER-EXTREMITY ULCERS

There is enough research to show that certain skin substitutes can improve health outcomes for certain patients who have diabetic lower-extremity ulcers that have not responded to conventional treatment. Randomized controlled trials have demonstrated that these products may improve ulcer healing compared with the standard of care. In addition, clinical practice guidelines for diabetic wound care recommend the use of skin substitutes in some cases. Therefore, the use of Affinity®, AlloPatch®, AmnioBand® Membrane, AmnioExcel®, Apligraf®, Biovance®, Dermagraft®, EpiCord®, EpiFix®, Grafix®, Integra® Omnigraft™, Integra® Flowable Wound Matrix, mVASC®, or TheraSkin® may be considered medically necessary for the treatment of non-healing diabetic lower-extremity ulcers that have not responded to a 1-month period of conventional ulcer therapy. Treatment of diabetic lower-extremity ulcers with skin substitutes prior to 1-month of conventional ulcer therapy is considered not medically necessary.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with nonhealing diabetic lower-extremity ulcers. Therefore, the use of products other than Affinity®, AlloPatch®, AmnioBand® Membrane, AmnioExcel®, Apligraf®, Biovance®, Dermagraft®, EpiCord®, EpiFix®, Grafix®, Integra® Omnigraft™, Integra® Flowable Wound Matrix, mVASC®, or TheraSkin® is considered investigational for this indication.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

There is enough evidence to show that the use of Apligraf® or Oasis® Wound Matrix can improve health outcomes for individuals who have nonhealing lower-extremity ulcers due to venous insufficiency. Randomized controlled trials have demonstrated that these products can improve the healing of these wounds compared with the standard of care. Therefore, Apligraf® or Oasis® Wound Matrix may be considered medically necessary for the treatment of ulcers that have not responded to 1-month period of conventional ulcer therapy. Treatment of lower-extremity ulcers due to venous insufficiency with skin substitutes prior to 1-month of conventional ulcer therapy is considered not medically necessary.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with lower-extremity ulcers due to venous insufficiency. Therefore, the use of products other than Apligraf® or Oasis® Wound Matrix is considered investigational for this indication.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

OrCel® was approved by the FDA under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and

heal wounds created by the surgery, including those at donor sites. Therefore, OrCel® may be considered medically necessary for this indication.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with dystrophic epidermolysis bullosa, and only OrCel® has received a humanitarian drug exemption for this condition. Therefore, the use of products other than OrCel® is considered investigational for dystrophic epidermolysis bullosa.

DEEP DERMAL BURNS

There is enough evidence to show that Epicel® and Integra® Dermal Regeneration Template may improve health outcomes for individuals who have deep dermal burns. Epicel® has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for Integra® Dermal Regeneration Template for the treatment of burns. Therefore, Epicel® or Integra® Dermal Regeneration Template may be considered medically necessary for the treatment of second- or third-degree burns.

There is not enough evidence to show that products other than Epicel® or Integra® Dermal Regeneration Template can improve health outcomes for patients with second- or third-degree burns. Therefore, the use of other amniotic products or bioengineered skin substitutes is considered investigational for this indication.

OPHTHALMIC INDICATIONS

There is limited evidence to show that human amniotic membrane products can improve health outcomes for patients with ophthalmologic indications, however these disorders are rare, and randomized controlled trials are unlikely. The use of certain amniotic products has become standard of care for the treatment of corneal injuries or as a component of corneal or conjunctival surgical repair, and therefore human amniotic membranes for ocular use, including but not limited to Prokera®, AmbioDisk™, or AmnioGraft® may be considered medically necessary for these indications.

SURGICAL REPAIR OF HERNIAS OR PARASTOMAL REINFORCEMENT

There is enough evidence to show that bioengineered skin substitutes do not improve health outcomes for individuals who are undergoing surgical repair of hernias or parastomal reinforcement. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. Therefore, the use of bioengineered skin substitutes is considered not medically necessary for these indications.

TENDON REPAIR

There is not enough research to show that skin substitutes or amniotic products can improve health outcomes for individuals who are undergoing tendon repair. A single trial found improved outcomes with the GraftJacket® allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate

the consistency of the effect. Therefore, the use of skin substitutes or amniotic products for tendon repair is considered investigational.

OTHER INDICATIONS

There is not enough research to show that skin substitutes or amniotic products can improve health outcomes for patients with disorders other than those listed in the medical necessity criteria. Off-label uses of bioengineered skin substitutes have included inflammatory ulcers, scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions, however there is a lack of controlled trials for these uses. Therefore, the use of skin substitutes or amniotic products for other indications is considered investigational.

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CODES

NOTE: While codes for skin substitute application (15271-15278, 15777) do not have pre-authorization requirements, they may be denied when used for the application of a product that does not meet medical necessity criteria.

Codes	Number	Description
CPT	15011	Harvest of skin for autograft; first
	15012	; each additional 25 sq cm
	15013	Preparation of skin autograft, requiring enzymatic processing; first 25 sq cm or less
	15014	; each additional 25 sq cm
	15015	Application of skin autograft; first 480 sq cm or less

Codes	Number	Description
	15016	; each additional 480 sq cm
	15018	; each additional 480 sq cm
		Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15272	; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
		Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15274	; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
		Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15276	; total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
		Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15278	; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
		Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk) (List separately in addition to code for primary
HCPCS	A2001	Innovamatrix ac, per square centimeter
	A2004	Xcellistem, 1 mg
	A2006	Novosorb synpath dermal matrix, per square centimeter
	A2008	Theragenesis, per square centimeter
	A2010	Apis, per square centimeter
		Supra sdrm, per square centimeter
	A2012	Suprathel, per square centimeter
		Innovamatrix fs, per square centimeter
	A2014	Omeza collagen matrix, per 100 mg
		Phoenix wound matrix, per square centimeter
	A2016	Permeaderm b, per square centimeter
	A2017	Permeaderm glove, each
	A2018	Permeaderm c, per square centimeter
	A2019	Kerecis omega3 marigen shield, per square centimeter
	A2020	Ac5 advanced wound system (ac5)
	A2021	Neomatrix, per square centimeter
	A2022	Innovaburn or innovamatrix xl, per square centimeter
	A2023	Innovamatrix pd, 1 mg
	A2024	Resolve matrix or xenopatch, per square centimeter
	A2025	Miro3d, per cubic centimeter

Codes	Number	Description
	A2026	Restrata minimatrix, 5 mg
	A2027	Matriderm, per square centimeter
	A2028	Micromatrix flex, per mg
	A2029	Mirotract wound matrix sheet, per cubic centimeter
	A2030	Miro3d fibers, per milligram
	A2031	Mirodry wound matrix, per square centimeter
	A2032	Myriad matrix, per square centimeter
	A2033	Myriad morcells, 4 milligrams
	A2034	Foundation drs solo, per square centimeter
	A2035	Corplex p or theracor p or allacor p, per milligram
	A4100	Skin substitute, fda cleared as a device, not otherwise specified
	A6460	Synthetic resorbable wound dressing, sterile, pad size 16 sq in or less, without adhesive border, each dressing
	A6461	Synthetic resorbable wound dressing, sterile, pad size more than 16 sq in but less than or equal to 48 sq in, without adhesive border, each dressing
	C1832	Autograft suspension, including cell processing and application, and all system components
	C8002	Preparation of skin cell suspension autograft, automated, including all enzymatic processing and device components (do not report with manual suspension preparation)
	C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
	C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per sq cm
	C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
	C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
	C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter
	C9364	Porcine implant, Permacol, per square centimeter
	Q4100	Skin substitute, not otherwise specified
	Q4101	Apligraf, per square centimeter
	Q4102	Oasis Wound Matrix, per square centimeter
	Q4103	Oasis Burn Matrix, per square centimeter
	Q4104	Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter
	Q4105	Integra Dermal Regeneration Template (DRT) or Integra Omnigraft dermal regeneration matrix, per square centimeter
	Q4106	Dermagraft, per square centimeter
	Q4107	Graftjacket, per square centimeter
	Q4108	Integra Matrix, per square centimeter
	Q4110	PriMatrix, per square centimeter
	Q4111	GammaGraft, per square centimeter
	Q4112	Cymetra, injectable, 1 cc
	Q4113	Graftjacket Xpress, injectable, 1 cc
	Q4114	Integra Flowable Wound Matrix, injectable, 1 cc
	Q4115	AlloSkin, per square centimeter
	Q4116	AlloDerm, per square centimeter
	Q4117	Hyalomatrix, per square centimeter
	Q4118	MatriStem micromatrix, 1 mg
	Q4121	TheraSkin, per square centimeter
	Q4122	Dermacell, dermacell awm or dermacell awm porous, per square centimeter (revised description 10/01/19)

Codes	Number	Description
	Q4123	AlloSkin RT, per square centimeter
	Q4124	Oasis Ultra Tri-Layer Wound Matrix, per square centimeter
	Q4125	Arthroflex, per square centimeter
	Q4126	Memoderm, Dermaspan, Transgraft or Integuply, per square centimeter
	Q4127	Talymed, per square centimeter
	Q4128	Flexhd, or allopatchhd, per square centimeter
	Q4130	Strattice TM, per square centimeter
	Q4132	"Grafix CORE and GrafixPL CORE, per square centimeter
	Q4133	Grafix prime, grafixpl prime, stravix and stravixpl, per square centimeter
	Q4134	hMatrix, per square centimeter
	Q4135	Mediskin, per square centimeter
	Q4136	EZ-derm, per square centimeter
	Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
	Q4138	BioDFence dryflex, per square centimeter
	Q4139	AmnioMatrix or biodmatrix, injectable, 1 cc
	Q4140	Biodfence, per square centimeter
	Q4141	Alloskin AC, per square centimeter
	Q4142	Xcm biologic tissue matrix, per square centimeter
	Q4143	Repriza, per square centimeter
	Q4145	Epifix, injectable, 1 mg
	Q4146	TenSIX, per square centimeter
	Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
	Q4148	NEOX CORD 1K, NEOX CORD RT, or CLARIX CORD 1K, per square centimeter
	Q4149	Excellagen, 0.1 cc
	Q4150	AlloWrap DS or dry, per square centimeter
	Q4151	AmnioBand or Guardian, per square centimeter
	Q4152	DermaPure per square centimeter
	Q4153	Dermavest and Plurivest, per square centimeter
	Q4154	Biovance, per square centimeter
	Q4155	Neoxflo or Clarixflo, 1 mg
	Q4156	NEOX 100 or CLARIX 100, per square centimeter
	Q4157	Revitalon, per square centimeter
	Q4158	Kerecis Omega3, per square centimeter
	Q4159	Affinity, per square centimeter
	Q4160	NuShield, per square centimeter
	Q4161	Bio-ConneKt Wound Matrix, per square centimeter
	Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
	Q4163	WoundEx, BioSkin, per square centimeter
	Q4164	Helicoll, per square centimeter
	Q4165	Keramatrix, per square centimeter
	Q4166	Cytal, per square centimeter
	Q4167	Truskin, per square centimeter
	Q4168	Amnioband, 1 mg
	Q4169	Artacent wound, per square centimeter
	Q4170	Cygnus, per square centimeter
	Q4171	Interfyl, 1 mg
	Q4172	Puraply or puraply am, per square centimeter

Codes	Number	Description
	Q4173	Palingen or palingen xplus, per square centimeter
	Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
	Q4175	Miroderm, per square centimeter
	Q4176	Neopatch, per square centimeter
	Q4177	Floweramnioflo, 0.1 cc
	Q4178	Floweramniopatch, per square centimeter
	Q4179	Flowerderm, per square centimeter
	Q4180	Revita, per square centimeter
	Q4181	Amnio wound, per square centimeter
	Q4182	Transcyte, per square centimeter
	Q4183	Surgigraft, per square centimeter
	Q4184	Cellesta or cellesta duo, per square centimeter
	Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
	Q4186	Epifix, per square centimeter
	Q4187	Epicord, per square centimeter
	Q4188	Amnioarmor, per square centimeter
	Q4189	Artacent ac, 1 mg
	Q4190	Artacent ac, per square centimeter
	Q4191	Restorigin, per square centimeter
	Q4192	Restorigin, 1 cc
	Q4193	Coll-e-derm, per square centimete
	Q4194	Novachor, per square centimeter
	Q4195	Puraply, per square centimeter
	Q4196	Puraply am, per square centimeter
	Q4197	Puraply xt, per square centimeter
	Q4198	Genesis amniotic membrane, per square centimeter
	Q4199	Cygnus matrix, per square centimeter
	Q4200	Skin te, per square centimeter
	Q4201	Matrion, per square centimeter
	Q4202	Keroxx (2.5g/cc), 1cc
	Q4203	Derma-gide, per square centimeter
	Q4204	Xwrap, per square centimeter
	Q4205	Membrane graft or membrane wrap, per square centimeter
	Q4206	Fluid flow or fluid GF, 1 cc
	Q4208	Novafix, per square cenitmeter
	Q4209	Surgraft, per square centimeter
	~~Q4210~~	~~Axolotl graft or axolotl dualgraft, per square centimeter~~ (Deleted 07/01/2024)
	Q4211	Amnion bio or Axobiomembrane, per square centimeter
	Q4212	Allogen, per cc
	Q4213	Ascent, 0.5 mg
	Q4214	Cellesta cord, per square centimeter
	Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
	Q4216	Artacent cord, per square centimeter
	Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
	Q4218	Surgicord, per square centimeter
	Q4219	Surgigraft-dual, per square centimeter
	Q4220	BellaCell HD or Surederm, per square centimeter
	Q4221	Amniowrap2, per square centimeter
	Q4222	Progenamatrix, per square centimeter
	Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
	Q4225	Amniobind or dermabindtl, per square centimeter

Codes	Number	Description
	Q4226	MyOwn skin, includes harvesting and preparation procedures, per square centimeter
	Q4227	Amniocore, per square centimeter
	Q4229	Cogenex amniotic membrane, per square centimeter
	Q4230	Cogenex flowable amnion, per 0.5 cc
	~~Q4231~~	~~Corplex P, per cc~~ (Deleted 04/01/2025)
	Q4232	Corplex, per square centimeter
	Q4233	Surfactor or Nudyn, per 0.5 cc
	Q4234	Xcellerate, per square centimeter
	Q4235	Amniorepair or altiply, per square centimeter
	Q4236	Carepatch, per square centimeter
	Q4237	Cryo-cord, per square centimeter
	Q4238	Derm-maxx, per square centimeter
	Q4239	Amnio-maxx or Amnio-maxx lite, per square centimeter
	Q4240	Corecyte, for topical use only, per 0.5 cc
	Q4241	Polycyte, for topical use only, per 0.5 cc
	Q4242	Amniocyte plus, per 0.5 cc
	Q4245	Amniotext, per cc
	Q4246	Coretext or Protext, per cc
	Q4247	Amniotext patch, per square centimeter
	Q4248	Dermacyte Amniotic Membrane Allograft, per square centimeter
	Q4249	AMNIPLY, for topical use only, per sq cm
	Q4250	AmnioAmp-MP, per sq cm
	Q4251	Vim, per square centimeter
	Q4252	Vendaje, per square centimeter
	Q4253	Zenith amniotic membrane, per square centimeter
	Q4254	Novafix DL, per sq cm
	Q4255	REGUaRD, for topical use only, per sq cm
	Q4256	Mlg-complete, per square centimeter
	Q4257	Relese, per square centimeter
	Q4258	Enverse, per square centimeter
	Q4259	Celera dual layer or celera dual membrane, per square centimeter
	Q4260	Signature apatch, per square centimeter
	Q4261	Tag, per square centimeter
	Q4262	Dual layer impax membrane, per square centimeter
	Q4263	Surgraft tl, per square centimeter
	Q4264	Cocoon membrane, per square centimeter
	Q4265	Neostim tl, per square centimeter
	Q4266	Neostim membrane, per square centimeter
	Q4267	Neostim dl, per square centimeter
	Q4268	Surgraft ft, per square centimeter
	Q4269	Surgraft xt, per square centimeter
	Q4270	Complete sl, per square centimeter
	Q4271	Complete ft, per square centimeter
	Q4272	Esano a, per square centimeter
	Q4273	Esano aaa, per square centimeter
	Q4274	Esano ac, per square centimeter
	Q4275	Esano aca, per square centimeter
	Q4276	Orion, per square centimeter
	~~Q4277~~	~~Woundplus membrane or e-graft, per square centimeter~~ (Deleted 07/01/2024)
	Q4278	Epieffect, per square centimeter
	Q4279	Vendaje ac, per square centimeter
	Q4280	Xcell amnio matrix, per square centimeter

Codes	Number	Description
	Q4281	Barrera sl or barrera dl, per square centimeter
	Q4282	Cygnus dual, per square centimeter
	Q4283	Biovance tri-layer or biovance 3l, per square centimeter
	Q4284	Dermabind sl, per square centimeter
	Q4285	Nudyn dl or nudyn dl mesh, per square centimeter
	Q4286	Nudyn sl or nudyn slw, per square centimeter
	Q4287	Dermabind dl, per square centimeter
	Q4288	Dermabind ch, per square centimeter
	Q4289	Revoshield + amniotic barrier, per square centimeter
	Q4290	Membrane wrap-hydro, per square centimeter
	Q4291	Lamellas xt, per square centimeter
	Q4292	Lamellas, per square centimeter
	Q4293	Acesso dl, per square centimeter
	Q4294	Amnio quad-core, per square centimeter
	Q4295	Amnio tri-core amniotic, per square centimeter
	Q4296	Rebound matrix, per square centimeter
	Q4297	Emerge matrix, per square centimeter
	Q4298	Amnicore pro, per square centimeter
	Q4299	Amnicore pro+, per square centimeter
	Q4300	Acesso tl, per square centimeter
	Q4301	Activate matrix, per square centimeter
	Q4302	Complete aca, per square centimeter
	Q4303	Complete aa, per square centimeter
	Q4304	Grafix plus, per square centimeter
	Q4305	American amnion ac tri-layer, per square centimeter
	Q4306	American amnion ac, per square centimeter
	Q4307	American amnion, per square centimeter
	Q4308	Sanopellis, per square centimeter
	Q4309	Via matrix, per square centimeter
	Q4310	Procenta, per 100 mg
	Q4311	Acesso, per square centimeter
	Q4312	Acesso ac, per square centimeter
	Q4313	Dermabind fm, per square centimeter
	Q4314	Reeva ft, per square cenitmeter
	Q4315	Regenelink amniotic membrane allograft, per square centimeter
	Q4316	Amchoplast, per square centimeter
	Q4317	Vitograft, per square centimeter
	Q4318	E-graft, per square centimeter
	Q4319	Sanograft, per square centimeter
	Q4320	Pellograft, per square centimeter
	Q4321	Renograft, per square centimeter
	Q4322	Caregraft, per square centimeter
	Q4323	Alloply, per square centimeter
	Q4324	Amniotx, per square centimeter
	Q4325	Acapatch, per square centimeter
	Q4326	Woundplus, per square centimeter
	Q4327	Duoamnion, per square centimeter
	Q4328	Most, per square centimeter
	Q4329	Singlay, per square centimeter
	Q4330	Total, per square centimeter
	Q4331	Axolotl graft, per square centimeter
	Q4332	Axolotl dualgraft, per square centimeter
	Q4333	Ardeograft, per square centimeter

Codes	Number	Description
	Q4334	Amnioplast 1, per square centimeter
	Q4335	Amnioplast 2, per square centimeter
	Q4336	Artacent c, per square centimeter
	Q4337	Artacent trident, per square centimeter
	Q4338	Artacent velos, per square centimeter
	Q4339	Artacent vericlen, per square centimeter
	Q4340	Simpligraft, per square centimeter
	Q4341	Simplimax, per square centimeter
	Q4342	Theramend, per square centimeter
	Q4343	Dermacyte ac matrix amniotic membrane allograft, per square centimeter
	Q4344	Tri-membrane wrap, per square centimeter
	Q4345	Matrix hd allograft dermis, per square centimeter
	Q4346	Shelter dm matrix, per square centimeter
	Q4347	Rampart dl matrix, per square centimeter
	Q4348	Sentry sl matrix, per square centimeter
	Q4349	Mantle dl matrix, per square centimeter
	Q4350	Palisade dm matrix, per square centimeter
	Q4351	Enclose tl matrix, per square centimeter
	Q4352	Overlay sl matrix, per square centimeter
	Q4353	Xceed tl matrix, per square centimeter
	Q4354	Palingen dual-layer membrane, per square centimeter
	Q4355	Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter
	Q4356	Abiomend membrane and abiomend hydromembrane, per square centimeter
	Q4357	Xwrap plus, per square centimeter
	Q4358	Xwrap dual, per square centimeter
	Q4359	Choriply, per square centimeter
	Q4360	Amchoplast fd, per square centimeter
	Q4361	Epixpress, per square centimeter
	Q4362	Cygnus disk, per square centimeter
	Q4363	Amnio burgeon membrane and hydromembrane, per square centimeter
	Q4364	Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter
	Q4365	Amnio burgeon dual-layer membrane, per square centimeter
	Q4366	Dual layer amnio burgeon x-membrane, per square centimeter
	Q4367	Amniocore sl, per square centimeter

Date of Origin: *December 2018*

Regence

Medical Policy Manual Medicine, Policy No. 175

Digital Therapeutic Products

Effective: January 1, 2025

Next Review: September 2025
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease.

MEDICAL POLICY CRITERIA

Note:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker. See Cross References).
  - Applications operated by a health care practitioner for remote health monitoring.
  - Products not meeting the definition of a digital therapeutic (see Policy Guidelines).

- Products for which coverage is required by a particular health plan under state or federal law (see Policy Guidelines).

The following general Criteria are applied to digital therapeutic products not already addressed in any other Medical Policy (see Cross References).

I. The use of a digital therapeutic product in the treatment or prevention of any health condition is considered **medically necessary** when all of the following Criteria are met:
   A. The digital therapeutic product has been prescribed by a healthcare practitioner providing medical oversight; and
   B. The digital therapeutic product has been approved by the Food and Drug Administration (FDA) for the requested indication; and
   C. High-quality evidence demonstrates the digital therapeutic product improves clinically meaningful net health outcomes as much or more than an established alternative; and
   D. The improved net health outcome provided by the digital therapeutic product is attainable outside of investigational settings.

II. The use of a digital therapeutic product in the treatment or prevention of any health condition is considered **investigational** when Criterion I. is not met.

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

POLICY GUIDELINE

When a digital health product is a software that delivers evidence-based therapeutic intervention to prevent, manage, or treat a medical disorder or disease, it may be considered as a digital therapeutic product. Digital therapeutics are distinguished from digital medicine and digital health products, such as mobile health products or wearable devices, in that clinical evidence of effectiveness and regulatory oversight are required for digital therapeutic products.[1, 2]

How Digital Therapeutics Differ From Digital Health, adapted from[1-4]

	Digital Health	Digital Medicine	Digital Therapeutics
Definition	Technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes; capture, store or transmit health data; and/or support life science and clinical operations.	Evidence-based software and/or hardware products that measure and/or intervene in the service of human health.	Delivers evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease.

	Digital Health		
		Digital Medicine	
			Digital Therapeutics
Clinical Evidence Required?	NO	**YES**	**YES**
Real-World Outcomes required?	NO	NO	**YES**
Regulatory Oversight Required?	NO Do not meet the regulatory definition of a medical device.	VARIES **YES** if classified as medical device.	**YES** As required to support product claims of risk, efficacy, and intended use.

Health Resources and Services Administration Women's Preventive Services Guidelines (HRSA Guidelines) ensure women's access to the full range of FDA-approved contraceptive methods including, but not limited to barrier methods, hormonal methods, and implanted devices, as well as patient education and counseling, as prescribed by a health care provider.[5]

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.

1. Name and manufacturer of the digital therapeutic product
2. Indication for which the digital therapeutic product is being prescribed
3. Relevant billing codes
4. Brief description of how the digital therapeutic product will improve net health outcomes for the patient
5. Medical records related to this request, including but not limited to history and physical exam, conventional testing and outcomes, and treatment provided, if any.

CROSS REFERENCES

1. Insulin Infusion Pumps, Automated Insulin Delivery and Artificial Pancreas Device Systems, DME, Policy No. 77
2. Digital Therapeutic Products for Attention Deficit Hyperactivity Disorder, Medicine, Policy No. 175.01
3. Digital Therapeutic Products for Substance Use Disorders, Medicine, Policy No. 175.02
4. Digital Therapeutic Products for Chronic Low Back Pain, Medicine, Policy No. 175.03
5. Digital Therapeutic Products for Amblyopia, Medicine, Policy No. 175.04
6. Digital Therapeutic Products for Post-traumatic Stress Disorder and Panic Disorder, Medicine, Policy No. 175.05
7. Digital Therapeutic Products for Gait Modulation, Medicine, Policy No. 175.06

BACKGROUND

DIGITAL HEALTH

In 2020 alone, more than 90,000 new digital health applications, an average of more than 250 apps per day, were introduced, bringing the total number of digital health applications available to consumers to over 350,000. Among these applications almost half (47%) focus on the management of a specific disease or health condition.[3] Examples of digital health products currently available include applications that purport to perform cognitive behavior therapy, support weight loss goals, distinguish normal cardiac sinus rhythm and potentially dangerous arrhythmias, and to identify a suspicious mole. In addition, over 80% of adults in the United States own a smartphone.[6] The ability to utilize a personal mobile device, such as a smartphone, as a medical device has substantial potential to impact clinical care and to promote general health and wellness. However, despite the rapid influx of digital health products into the market, there remains no widely accepted framework for the evaluation of efficacy of these products. The use of a digital health product to prevent, manage, or treat a medical disorder or disease must be evaluated in the setting of existing evidence frameworks, as discussed below.

DEFINING DIGITAL THERAPEUTICS

The field of digital health is broad and rapidly changing. Digital therapeutic products fall under the umbrella term of digital health, however, digital therapeutic products are distinguished from digital medicine and digital health products in that clinical evidence of effectiveness and regulatory oversight are required for digital therapeutic products.[1]

The Academy of Managed Care Pharmacy (AMCP) published a review in 2020 which provides the definition of digital therapeutics as: software that delivers a clinical mechanism of action, either alone or in combination with other standard-of-care treatments to improve outcomes.[2]

This review also states, “Digital therapeutics represents one segment of digital health products and can be distinguished from other products, such as mobile health products or wearable devices, specifically by their demonstrated impact on measurable clinical outcomes.” The AMCP provides examples of products that do not meet the definition of a digital therapeutic product, as summarized in Table 1.

Table 1. Products Not Considered Digital Therapeutics[2]

Class	Description	Examples
Mobile Health	The practice of medicine and public health supported by mobile devices	• Clinician-facing: Apps that are for displaying, storing, analyzing, or transmitting patient-specific medical device data • Consumer-facing: Lifestyle, fitness tracking, nutrition, and medication adherence apps
Health Information Technology	• Information technology applied to health and health care • Supports health information management across computerized systems and the secure exchange of health information	• Electronic Medical records • Electronic prescribing systems • Consumer health interface (e.g., MyChart
Devices,	• Devices that can be worn,	• Wearable and wireless devices, (e.g.,

Class	Description	Examples
sensors, wearables	attached on skin, or ingested to continuously and closely monitor an individual's activities • Supported by embedded technology for data communication and sensors to interact with both internal and external objects and the environment	Fitbit, Apple Watch) • Biometric sensors • Diagnostic products • Proprietary algorithms that control the function of physical devices, such as insulin pumps
Telehealth	Provision of health care remotely	• Telemedicine, telehealth platforms

The World Health Organization has developed a classification system to define various types of digital health products.[7] While this system categorizes the different ways digital and mobile technologies are used to support health system needs, it does not provide a definition of therapeutic digital health products, specifically.

The Digital Therapeutics Alliance (DTA) is a global non-profit trade association of industry leaders and stakeholders engaged in the evidence-driven advancement of digital therapeutics.[1] The DTA provides the following definition of digital therapeutics:

> Digital therapeutics (DTx) deliver evidence-based therapeutic interventions that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.
>
> DTx products incorporate advanced technology best practices relating to design, clinical evaluation, usability, and data security. They are reviewed and cleared or certified by regulatory bodies as required to support product claims regarding risk, efficacy, and intended use.
>
> DTx empower patients, clinicians, and payers with intelligent and accessible tools for addressing a wide range of conditions through high quality, safe, and effective data-driven interventions.

Table 2. How Digital Therapeutics Differ From Digital Health, *adapted from*[1-4]

	Digital Health		
		Digital Medicine	
			Digital Therapeutics
Definition	Technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes; capture, store or transmit health data; and/or support life science and clinical operations.	Evidence-based software and/or hardware products that measure and/or intervene in the service of human health.	Delivers evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease.

	Digital Health		
		Digital Medicine	
			Digital Therapeutics
Clinical Evidence Required?	NO	**YES**	**YES**
Real-World Outcomes required?	NO	NO	**YES**
Regulatory Oversight Required?	NO Do not meet the regulatory definition of a medical device.	VARIES **YES** if classified as medical device.	**YES** As required to support product claims of risk, efficacy, and intended use.

REGULATORY STATUS

The US Food and Drug Administration (FDA) defines Software as a Medical Device (SaMD) as, "intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."[8]

The FDA notes the following regarding SaMD:

- SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device
- SaMD is capable of running on general purpose (non-medical purpose) computing platforms
- "Without being part of" means software not necessary for a hardware medical device to achieve its intended medical purpose
- Software does not meet the definition of SaMD if its intended purpose is to drive a hardware medical device
- SaMD may be used in combination (e.g., as a module) with other products including medical devices
- SaMD may be interfaced with other medical devices, including hardware medical devices and other SaMD software, as well as general purpose software
- Mobile apps that meet the definition above are considered SaMD.

SaMD are reviewed by the FDA under existing 510(k) and DeNovo pathways established for the review of medical devices.

- A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device.[9]
- The De Novo process provides a pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device. De Novo classification is a risk-based classification process. Devices that are classified into class I or class II through a De Novo classification request (De Novo request) may be marketed and used as predicates for future premarket notification [510(k)] submissions.[10]

The Digital Health Center of Excellence (DHCoE) is a resource under the Center for Devices and Radiological Health (CDRH) of the FDA. The DHCoE mission is to complement advances in digital health technology by "providing services to digital health stakeholders to translate digital advances into tools that benefit consumers."[11] The DHCoE notes they support the following:

Empowering Stakeholders

The Digital Health Center of Excellence empowers digital health stakeholders to advance health care by fostering responsible and high-quality digital health innovation by:

Setting and leading strategic direction in digital health technology at the Center for Devices and Radiological Health (CDRH)
Launching strategic initiatives that advance digital health technologies
Building new capacity to oversee and leverage digital health technologies
Providing scientific expertise across the FDA
Providing technological and policy advice to support the FDA decision-making processes
Promoting and showcase existing work across the FDA
Transparently share resources for developers

Connecting Stakeholders

The Digital Health Center of Excellence connects and builds partnerships to accelerate digital health advancements by:

- Fostering collaboration across the FDA in common interest areas
- Facilitating synergies in regulatory science research in digital health
- Facilitating and building strategic partnerships
- Communicating the FDA's research interests
- Advancing international harmonization on device regulatory policy
- Advancing digital health technology international standards
- Providing access to internal and external digital health experts

Sharing Knowledge

The Digital Health Center of Excellence shares knowledge to increase awareness and understanding, drive synergy, and advance best practices by:

- Sharing information to increase awareness of advancements in digital health
- Establishing and promoting best practices
- Creating and disseminating shared resources internally and externally
- Offering training opportunities for the FDA's staff and external stakeholders
- Communicating the FDA's research interests

Innovating Regulatory Approaches

The Digital Health Center of Excellence innovates regulatory approaches to provide efficient and least burdensome oversight by:

- Enabling efficient, transparent, and predictable product review with consistent evaluation quality
- Providing clarity on regulation by developing cross-cutting digital health guidance
- Developing novel, efficient medical device regulatory approaches that are least burdensome while meeting FDA standards

In 2017, the FDA announced the Software Pre-Cert Pilot Program as part of the Digital Health Innovation Action Plan "to develop a new regulatory paradigm that would focus first on the assessment of organizations that perform high-quality software design, testing, and monitoring."[12] In January 2019, the FDA released a Test Plan for the Pre-Cert program as well as a Regulatory Framework for conducting the pilot program.[13, 14] In September 2022, the Software Precertification (Pre-Cert) Pilot Program was completed with the issuance of the Report: The Software Precertification (Pre-Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and Key Findings.[12] This document includes the following statement:

> Ultimately, the approach to regulating novel, swiftly-evolving medical device software must foster, not inhibit, innovation, while continuing to provide reasonable assurance of safety and effectiveness. These aspects are not mutually exclusive. A flexible, risk based approach to regulation could allow FDA to tailor regulatory requirements more efficiently for devices based on the latest science, the benefits and risks posed by devices, their real-world performance, and their contribution to promoting health equity. It could leverage the capabilities of evolving medical device software so that health care providers, patients, and users can benefit from advancement and innovation, and so that risk for such devices can be reduced through swift software and cybersecurity updates throughout the total product lifecycle, when needed. New legislative authority establishing such an approach could be supplemental to, and not replace, the established regulatory pathways.

PRACTICE GUIDELINE AND POSITION STATEMENT SUMMARY

At this time, no single framework has been adopted by medical or regulatory bodies for evaluation of digital therapeutic products. However, several organizations, both global and national, have initiated efforts to develop a framework for evaluation of digital health products, including those summarized below.

DIGITAL THERAPEUTICS ALLIANCE

The Digital Therapeutics Alliance (DTA), a global non-profit trade association of industry leaders and stakeholders, provides a summary of Industry Core Principals to which all digital therapeutic products should adhere "to demonstrate product integrity and ensure patient safety."[15] These Principals include the statements that digital therapeutic products should:

- prevent, manage, or treat a medical disorder or disease; and
- produce a medical intervention that is driven by software; and
- publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals; and
- be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use; and
- make claims appropriate to clinical evaluation and regulatory status; and
- collect, analyze, and apply real world evidence and/or product performance data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

The National Institute for Health and Care Excellence (NICE) published an update to the Evidence Standards Framework for Digital Health Technologies (DHTs) in 2022.[4] The framework provides standards for evidence that should be available or developed for DHTs to demonstrate their value in the UK health and care system, specifically. The framework is broken into evidence tiers (minimum evidence standards) based on the functional classification of the technology. Per the definitions above, digital therapeutics fit primarily in the highest evidence tier, C interventions. In 2022, NICE changed evidence tier naming from tiers one, two, and three to A, B, and C to avoid confusion with the European Union's CE (Conformité Européene) marking categories.

Minimum evidence for effectiveness standards for tier C DHTs includes the following:

> High quality intervention study (experimental or quasi-experimental design) showing improvements in relevant outcomes, such as:
>
> - diagnostic accuracy
> - patient-reported outcomes (preferably using validated tools) including symptom severity or quality of life
> - other clinical measures of disease severity or disability
> - healthy behaviors
> - physiological measures
> - user satisfaction and engagement.
>
> Generic outcome measures may also be useful when reported alongside condition-specific outcomes. The comparator should be a care option that is reflective of the current care pathway, such as a commonly used active intervention.

XCERTIA

Xcertia, founded in December 2016 by representatives from groups including the American Medical Association, American Heart Association, Healthcare Information and Management Systems Society and digital health nonprofit DHX Group, published a guideline in 2019 that addressed "key areas of guidance to ensure mHealth apps deliver true value in a trusted environment."[16]

These guidelines include the following statement regarding documentation of evidence for the app:

- The app's public description should clearly state which type of research has been performed to validate its content. These can include the following levels of research:
  - I. Systematic review or meta-analysis of randomized control trials
  - II. Randomized control trial/s (number of trials if more than one)
  - III. Quasi-experimental study
  - IV. Case-control or cohort studies
  - V. Systematic reviews of descriptive and qualitative studies
  - VI. Single descriptive or qualitative study
  - VII. Expert medical or academic opinion
- If level of research performed on the opinion [sic] is based on expert or academic opinion (VII) or no study, the app's public description should clearly state, "The effectiveness of the app has not been studied."

THE AMERICAN MEDICAL ASSOCIATION

The American Medical Association Policy on Integration of Mobile Health Applications and Devices into Practice (2017) states; “Our AMA supports the establishment of coverage, payment and financial incentive mechanisms to support the use of mobile health applications (mHealth apps) and associated devices, trackers and sensors by patients, physicians and other providers that:

- support the establishment or continuation of a valid patient-physician relationship
- have a high-quality clinical evidence base to support their use in order to ensure mHealth app safety and effectiveness
- follow evidence-based practice guidelines, especially those developed and produced by national medical specialty societies and based on systematic reviews, to ensure patient safety, quality of care and positive health outcomes
- support care delivery that is patient-centered, promotes care coordination and facilitates team-based communication
- support data portability and interoperability in order to promote care coordination through medical home and accountable care models
- abide by state licensure laws and state medical practice laws and requirements in the state in which the patient receives services facilitated by the app
- require that physicians and other health practitioners delivering services through the app be licensed in the state where the patient receives services, or be providing these services as otherwise authorized by that state’s medical board
- ensure that the delivery of any services via the app be consistent with state scope of practice laws.”[17]

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	0770T	Virtual reality technology to assist therapy (List separately in addition to code for primary procedure)
	0771T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status; initial 15 minutes of intraservice time, patient age 5 years or older
	0772T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring

Codes	Number	Description
		the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status; each additional 15 minutes intraservice time (List separately in addition to code for primary service)
	0773T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; initial 15 minutes of intraservice time, patient age 5 years or older
	0774T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; each additional 15 minutes intraservice time (List separately in addition to code for primary service)
	98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
	99199	Unlisted special service, procedure or report [when specified as a digital health management software application]
HCPCS	A9291	Prescription digital behavioral therapy, FDA cleared, per course of treatment
	A9292	Prescription digital visual therapy, software-only, FDA cleared, per course of treatment
	E1399	Durable medical equipment, miscellaneous [when specified as a digital health management software application]
	E1905	Virtual reality cognitive behavioral therapy device (cbt), including pre-programmed therapy software
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *September 2021*

Regence

Medical Policy Manual Medicine, Policy No. 175.01

Digital Therapeutic Products for Attention Deficit Hyperactivity Disorder

Effective: January 1, 2025

Next Review: September 2025
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for attention-deficit/hyperactivity disorder (ADHD).

MEDICAL POLICY CRITERIA

Note:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).

- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of attention-deficit/hyperactivity disorder (ADHD), either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational,** including but not limited to EndeavorRx® (AKL-T01).

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition characterized by core symptoms of hyperactivity, impulsivity, and inattention, which are considered excessive for the person's age. Both the International Classification of Mental and Behavioral Disorders 10th edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) require that the symptoms are reported or observed in several settings and that the symptoms of ADHD affect psychological, social, and/or educational/occupational functioning. Prevalence estimates for ADHD vary from 7.2% to 15.5% of children.[1]

For children younger than 17 years of age, the DSM-5 requires at least six symptoms of hyperactivity-impulsivity or at least six symptoms of inattention. The combined type requires a minimum of six symptoms of hyperactivity-impulsivity plus at least six symptoms of inattention. The symptoms must 1) occur often, 2) be present in more than one setting, 3) persist for at least six months, 4) be present before 12 years of age, 5) impair function in academic, social, or occupational activities, and 6) be excessive for the developmental level of the child.

Treatment

Established treatments for ADHD in children include educational, environmental, psychological, and behavioral interventions, and medication. Almost two-thirds of children with ADHD take medication, and about one half receive behavioral treatment.[1]

- Educational intervention involves discussion with parents about symptoms and access to services, environmental modifications such as seating arrangements, changes to lighting and noise, reducing distractions, and the benefit of having movement breaks and teaching assistants at school.
- Parent-child behavioral therapy teaches parenting techniques within the principles of behavior therapy. The therapy programs typically last two to three months and includes rewarding positive behavior, identifying unintentional reinforcement of negative behaviors, limiting choices, and using calm discipline.
- Medication with stimulants, such as methylphenidate, are considered first-line therapy for ADHD in school-age children. However, adverse effects of stimulants may include

sleep disturbance, decreased appetite, and weight changes. Combination therapy with medication and behavioral interventions can improve both core ADHD symptoms and non-ADHD symptoms such as social skills and parent-child relations.

REGULATORY STATUS

In April 2020, EndeavorRx® (Akili Interactive Labs) received marketing clearance by the U.S. Food and Drug Administration (FDA) through the De Novo premarket review process (DEN200026).[2] EndeavorRx® is a prescription device that is indicated to "improve attention function as measured by computer-based testing in children ages 8 to 12 years old with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx® demonstrate improvements in a digitally assessed measure Test of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity." EndeavorRx® is intended to be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs. EndeavorRx® was referred to as "ProjectEvo" and in later evaluations as "AKL-T01."

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, two domains are examined: the relevance and the 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. Randomized controlled trials 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.

DIGITAL THERAPIES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Clinical Context and Therapy Purpose

The purpose of digital therapeutic products is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with attention-deficit/hyperactivity disorder (ADHD).

Attention-deficit/hyperactivity disorder is a syndrome that can include hyperactivity, impulsivity, and/or inattention, which in turn can affect cognitive, academic, behavioral, emotional, and

social functioning. The symptoms of the hyperactive-impulsive presentation typically occur together and are characterized by the inability to sit still or inhibit behavior. The inattentive presentation is characterized by reduced ability to focus attention and reduced speed of cognitive processing, which is exhibited by difficulty with maintaining attention, lack of follow through and organization, distraction, and forgetfulness. The combined presentation includes symptoms of both the hyperactive-impulsive presentation and the inattentive presentation.

Treatment may include environmental adjustments, behavioral and psychological interventions, and medications. In some children, these treatments do not sufficiently address symptoms. In others, there may be resistance by the parents to treat children with medications, or there may be other barriers to obtaining established therapies. EndeavorRx® is proposed to address these barriers with improved access to care and minimal side effects. The therapy is based on research showing that impairments in attention and cognitive control are associated with lower activation of frontal, frontoparietal, and ventral attention networks. Previously, a game-like intervention was shown to improve cognitive performance and alter the electroencephalogram in the prefrontal cortex in older adults.[3] The similarity between cognitive control in older adults and attention deficits in ADHD led to the development of EndeavorRx® for the treatment of ADHD in children.

ADHD-specific rating scales are described in Table 1.

Table 1. ADHD Rating Scales

Rating Scale	Description	Scoring
ADHD Rating Scale (ADHD-RS-IV)[4]	The ADHD-RS-IV is an 18-item, clinician-administered questionnaire for which a parent respondent rates the frequency of occurrence of ADHD symptoms and behaviors as defined by criteria outlined for ADHD in the DSM-IV. Each item is scored on a 4-point scale ranging from 0 (rarely or never) to 3 (very often) with total scores ranging from 0 to 54. The 18 items are grouped into 2 subscales: hyperactivity/impulsivity and inattentiveness.	Each subscale produces a subscale score ranging from 0 to 27. A higher score indicates more severe ADHD symptoms and behaviors and a negative change in total score indicates improvement.
The Clinical Global Impression Scale – Improvement (CGI-I)[5]	The CGI-I is a clinician's comparison of the participant's overall clinical condition at follow-up to the overall clinical condition at baseline. It includes an assessment of the change from the initiation of treatment with a rating from 1 to 7.	The 7-point scale is: 1 = Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, and 7=Very much worse. A score of 1, 2, or 3 would indicate overall improvement of ADHD severity.
Conners Comprehensive Behavior Rating Scales[6]	Parent and teacher forms are available in full (90-item, 59-item) and abbreviated (27-item, 28-item) versions.	Normative values are provided separately by gender and age.
The Vanderbilt Assessment Scales for parents and teachers[7, 8]	The Vanderbilt Assessment Scales are based on DSM-IV scales. The scale for parents has 55 questions that rate symptoms and their impact on family and school. The teacher scale includes 43 questions on symptoms and school performance.	Normative data and percentile ranks are provided for each subscale by grade and gender.

Rating Scale	Description	Scoring
Test of Variables of Attention (TOVA), Attention performance index[9]	TOVA® is a validated computerized continuous performance test that presents targets and non-targets as squares that either appear at the top or bottom of the screen. The task consists of two halves: the first half has a target-to-non-target ratio assessed sustained attention; the second half assesses inhibitory control. The program assesses attention consistency, attentional lapses, and processing speed.	Clinical meaningfulness for the pivotal trial was defined as: TOVA API improvement greater than 1.4 points, and post-test API score 0 or more (normative range), ADHD-RS improvement of two points or more, CGI-I post-score of one (very much improved) or two or less (very much or much improved), and any improvement in an Impairment Rating Scale.

ADHD: attention-deficit/hyperactivity disorder; ADHD-RS-IV: ADHD rating scale, version 4; CGI-I: clinical global impression scale-improvement; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; TOVA (API): test of variables of attention (attention performance index).

Follow-up after the treatment period (1 to 3 months), at six months, and annually for three years is of interest to monitor outcomes of the effect of EndeavorRx®.

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 randomized controlled trials (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.

REVIEW OF EVIDENCE

Systematic Reviews

Oh (2023) published a systematic review and meta-analysis of 20 RCT reports that assessed the effects of game-based digital therapeutics on inattention and hyperactivity/impulsivity as reported by assessors (e.g., parents and teachers).[10] Sample size of studies ranged from 6 to 17. Controls included placebo and different types of active controls. Game-based digital therapy improved inattention more than control treatments (standard mean difference [SMD] 0.28, 95% confidence interval [CI] 0.14 to 0.41 and SMD 0.21, 95% CI 0.03 to 0.39, respectively). Medication improved inattention more than game-based digital therapy (SMD -0.62, 95% CI -1.04 to -0.20) upon assessment by teachers. Game-based digital therapy improved hyperactivity/impulsivity more than control treatments (SMD 0.28, 95% CI 0.03 to 0.53 and SMD 0.30, 95% CI 0.05 to 0.55, respectively). Medication improved hyperactivity/impulsivity significantly more than game-based digital therapeutics (SMD 0.24, 95% CI 0.65 to 0.17. Limitations of included RCTs include small sample size and high heterogeneity among outcome endpoints, evaluation indicators, and type of control group. The authors noted that no included studies evaluated the safety of digital therapeutics for ADHD.

Randomized Controlled Trials

Key RCT characteristics and results are described in Tables 2 and 3. Limitations in study relevance and study design and conduct are described in Tables 4 and 5.

Kollins (2020) reported results of the STARS-ADHD (Software Treatment for Actively Reducing Severity of ADHD) randomized double blind trial, which compared treatment with EndeavorRx® (AKL-T01) to a digital control (EVO Words) that targets cognitive domains other than those targeted by AKL-T01.[11] AKL-T01 is a digital game played on a mobile device as described above. EVO Words requires the child to spell as many words as possible by connecting letters in a grid in a fixed amount of time. Parents and children were informed that the study was evaluating two different investigational interventions for ADHD, and only the study coordinator was aware of which video game that the children received. Compliance was monitored by study coordinators, who notified parents by email if the game was not played for more than 48 hours. After four weeks, patients were reassessed for attentional functioning, ADHD symptoms, and impairment. The primary outcome was the change in the computerized test of variable of attention, attention performance index (TOVA API). Secondary outcomes included a number of clinician and parent reported measures such as the ADHD rating scale, Impairment Rating Scale, and Clinical Global Impressions-Improvement. Out of 348 patients who were randomly assigned, five were lost to follow-up, four were withdrawn by the parent or investigator, and 10 had invalid test results, resulting in a final sample of 329 children for the primary outcome measure. The two children who received the incorrect allocation were included in the intention-to-treat population. The mean change from baseline on the TOVA API was 0.93 in the AKL-T01 group and 0.03 in the control group ($p<0.05$). However, there were no between-group differences for secondary measures, which included the clinician and parent ratings of ADHD symptoms; both groups showed improvement in ADHD ratings from baseline to post-treatment. Treatment-related adverse events in the AKL-T01 group included frustration (5 [3%] of 180) and headache (3 [2%] of 180) with a mean number of completed sessions of 83%, compared to 96% compliance in the EVO Words group. The study was well-designed and conducted, but there are a number of limitations in study relevance due to the limited age range, limited follow-up, and most importantly the uncertainty of the association of computerized tests with observable behavior. There are also questions regarding the most effective treatment schedule and characteristics of patients who might benefit from this intervention. The trial authors conclude "the results of the current trial are not sufficient to suggest that AKL-T01 should be used as an alternative to established and recommended treatments for ADHD." This study was funded by Akili Interactive Labs and multiple study authors have a financial interest in the funding company.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Kollins (2020); STARS-ADHD[11]	US	20	2016 to 2017	348 pediatric patients aged 8 to 12 years, with confirmed ADHD, TOVA API scores -1.8 and below, without or with washout of disorder-related medication.	AKL-T01 (EndeavorRx®) for 25 min a day on 5 days per week for 4 weeks (n=180)	EVO Words for 25 min a day on 5 days per week for 4 weeks (n=168)

ADHD: attention-deficit/hyperactivity disorder; RCT: randomized controlled trial; STARS-ADHD: Software Treatment for Actively Reducing Severity of ADHD; TOVA API: test of variables of attention, attention performance index.

Table 3. Summary of Key RCT Results

Study	TOVA API mean improvement (SD)	TOVA API Improvement >1.4 points n/N (%)	ADHD-Rating Scale Improvement ≥2 points n/N (%)	Impairment Rating Scale n/N (%)	Clinical Global Impressions ≤2 n/N (%)
Kollins (2020); STARS-ADHD[11]					
N	329	329	337	332	339
AKL-T01	0·93 (3.15)	79/169 (47%)	128/173 (74%)	82/171 (48%)	29/175 (17%)
EVO Words	0·03 (3.16)	51/160 (32%)	119/164 (73%)	60/161 (37%)	26/164 (16%)
p-value	<0.05	0.006	0.77	0.049	0.86

ADHD: attention deficit/hyperactivity disorder; RCT: randomized controlled trial; SD: standard deviation; STARS-ADHD: Software Treatment for Actively Reducing Severity of ADHD; TOVA API: test of variables of attention, attention performance index.

Tables 4 and 5 display notable limitations identified in each study.

Table 4. Title

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Kollins (2020)[11]	4. The study population was limited to children 8 to 12 years of age.			6. Improvement on computerized tests of attention is weakly associated with classroom attention.	1. There was no follow-up after the 4 week intervention period.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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 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. Title

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]
Kollins (2020)[11]				2. Missing data was not included in the intention-to-treat analysis.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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.

Nonrandomized Studies

Stamatis (2024) published results from two multi-center, single-arm studies which evaluated objective attention functioning and ADHD symptoms in response to EndeavorRx® treatment.[12] One study evaluated four weeks of EndeavorRx® treatment in adolescents aged 13 to 17 years, who were stably on or off medication (n=162). The second study evaluated six weeks of EndeavorRx® treatment in adults (n=221). Both studies reported improvements on the Test of Variables of Attention (TOVA®) Attention Comparison Score (ACS) of 2.6 (95% CI: 2.02 to 3.26; p<0.0001) in adolescents and 6.5 in adults (95% CI: 5.35 to 7.57; p<0.0001). 15 participants reported mild to moderate adverse events. This study is limited by lack of a control group and lack of blinding.

In 2021, Kollins published the results of an additional open-label study of the effectiveness of EndeavorRx® as an adjunct to pharmacotherapy in 8 to 14-year-old children with ADHD on stimulant medication (n=130) or not on any ADHD medication (n=76).[13] Study participants were instructed to use the EndeavorRx® (approximately 25 min per day, five days per week) followed by a treatment break of four weeks and a second treatment period of four weeks. The primary study outcome was change in ADHD-related impairment as assessed by the Impairment Rating Scale (IRS) after four weeks. Secondary outcomes included changes in IRS, ADHD Rating Scale (ADHD-RS) and Clinical Global Impressions Scale - Improvement (CGI-I) on days 28, 56, and 84. Significantly improved ADHD-related impairment as measured by clinician-rated IRS was found after the first 4-week treatment in both cohorts; mean changes from Baseline to Day 28 in IRS overall severity score was −0.7 (95% confidence interval (CI): [−0.86 to −0.50]; DOF: 127; Cohen's d: 0.65; p<0.001) in the On Stimulants cohort and −0.5 (95% CI: [−0.73 to −0.32]; DOF: 73; Cohen's d: 0.59; p<0.001) in the No Stimulants cohort. Participants with an improvement of ≥1 point on the IRS total score from Baseline to Day 28 were considered responders, and 55.5% of the On Stimulants cohort and 40.5% of the No Stimulants cohort were IRS responders. Significant improvement also was found in both cohorts for all secondary endpoints. Mean change from baseline to Day 56 in IRS overall severity score, ADHD-RS total score, and Inattention and Hyperactivity-Impulsivity subscale scores remained significantly improved for participants in both cohorts (all p<0.001), indicating stability of treatment effects over this timeframe. While this study provides valuable information regarding longer-term treatment effects and observations in an expanded population not available from the pivotal trial discussed above, there are considerable limitations to the study. This study was conducted without randomization did not include a blinded control condition, which precludes evaluation of a possible placebo effects. The manufacturer of the application, Akili Interactive Labs, provided research support and was involved in trial conceptualization. Multiple study authors have a financial interest in the study product. There was no clear effort to mitigate the potential for bias resulting from these possible conflicts of interest.

SUMMARY OF EVIDENCE

For individuals with ADHD who receive a prescription digital therapy, the evidence includes a systematic review, an RCT and an open-label, uncontrolled study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single

RCT that has been identified compared outcomes of the predecessor of the FDA-cleared EndeavorRx® (AKL-T01) to a word game that targeted different cognitive abilities. Although the experimental treatment group had significantly greater improvement on a computerized test of attention, both the experimental and control groups improved to a similar extent on parent and clinician assessments. The clinical significance of an improvement in a computerized test of attention without a detectable improvement in behavior by parents and clinicians is uncertain. A single-arm, open-label study evaluating EndeavorRx® in patients with ADHD with and without current pharmaceutical intervention provided additional information regarding the effectiveness of the intervention in a broader population. However, the lack of a control group or randomization limit interpretation of study findings. Several questions remain concerning the efficacy of this treatment. At this time, the digital therapy is not recommended as an alternative or adjunct to established treatments. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

In 2019, the American Academy of Pediatrics (AAP) updated their 2011 clinical practice guideline on the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.[1]

The guidelines were based on a systematic evidence review by the Agency for Healthcare Research and Quality. The AAP gave strong recommendations based on level A evidence for medications and training and behavioral treatment for ADHD implemented with the family and school.

SOCIETY FOR DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

In 2020, the Society for Developmental and Behavioral Pediatrics published a clinical practice guideline for the assessment and treatment of children and adolescents with complex ADHD.[14] Complex ADHD is defined by age (<4 years or presentation >12 years), presence of coexisting conditions, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment. The society gave a strong recommendation based on grade B evidence for psychoeducation and evidence-based behavioral and educational interventions (eg, parent training, classroom management, behavioral peer interventions, organizational skills training). The society gave a recommendation based on grade C to B evidence for the frequent need to combine behavioral approaches with pharmacological treatments, and that "treatment should focus on areas of functional impairment and not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of attention-deficit/hyperactivity disorder (ADHD) improves net health outcomes. No clinical guidelines based on research recommend digital therapeutic products for the treatment of attention-deficit/hyperactivity disorder (ADHD). Therefore, digital therapeutic products for the treatment of attention-deficit/hyperactivity disorder (ADHD) are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
	99199	Unlisted special service, procedure or report [when specified as a digital health management software application]
HCPCS	A9291	Prescription digital behavioral therapy, FDA cleared, per course of treatment
	E1399	Durable medical equipment, miscellaneous [when specified as a digital health management software application]
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *September 2021*

Regence

Medical Policy Manual Medicine, Policy No. 175.02

Digital Therapeutic Products for Substance Use Disorders

Effective: January 1, 2025

Next Review: September 2025
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace individual or group therapy and/or to deliver cognitive-behavioral therapy for the treatment of substance use disorders.

MEDICAL POLICY CRITERIA

Note:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).
  - Applications operated by a health care practitioner for remote health monitoring.

- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of a substance use disorder, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational,** including but not limited to reSET® and reSET-O®.

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

SUBSTANCE USE DISORDER

The American Psychiatric Association (APA) defines substance use disorder (SUD) as a complex condition "in which there is uncontrolled use of a substance despite harmful consequence. People with SUD have an intense focus on using a certain substance(s) such as alcohol, tobacco, or illicit drugs, to the point where the person's ability to function in day-to-day life becomes impaired."[1] The APA notes that individuals can become addicted to several substances including alcohol, marijuana, PCP, LSD and other hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, cocaine, methamphetamine and other stimulants, and tobacco. The Diagnostic and Statistical Manual of Mental Disorders (DSM) details 11 problematic patterns of use that lead to clinically significant impairment or distress. Mild substance use disorder (SUD) is defined as meeting 2 to 3 criteria, moderate as 4 to 5 criteria, and severe as 6 or more criteria.

1. Often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7. Important social, occupational, or recreational activities are given up or reduced because of use.
8. Recurrent use in situations in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance.
11. Withdrawal.

TREATMENT

Treatments for drug addiction include behavioral counseling, skills training, medication, treatment for withdrawal symptoms, treatment for co-occurring mental health issues, and long-term follow-up to prevent relapse. For patients with primary opioid use disorder (OUD), medication-assisted treatment is the most common approach. U.S. Food and Drug Administration (FDA) approved drugs for opioid use treatment include a full opioid agonist (methadone), a partial opioid agonist (buprenorphine), and an opioid antagonist (naltrexone). These are used to suppress withdrawal symptoms and reduce cravings and may be used in combination with counseling and behavioral therapies.

One common psychosocial intervention is cognitive-behavioral therapy (CBT). CBT is an established therapy based on social learning theory that addresses a patient's thinking and behavior. CBT has proven positive effects for the treatment of SUD.[2] There are two main goals of CBT: first, recognize thoughts and behaviors that are associated with substance abuse, and second, expand the repertoire of effective coping responses. Specific goals for SUD and OUD include a better understanding of risk factors for use, more accurate attributions of cause and effect, increased belief in the ability to address problems, and coping skills. Specific skills may include motivation, drink/drug refusal skills, communication, coping with anger and depression, dealing with interpersonal problems, and managing stress.

The community reinforcement approach is a form of CBT that has a goal of making abstinence more rewarding than continued use. Community reinforcement approach increases non-drug reinforcement by teaching skills and encouraging behaviors that help improve employment status, family/social relations and recreational activities. Community reinforcement approach was originally developed for alcohol dependence and cocaine use and has been shown to be more effective than usual care in reducing the number of substance use days.

Contingency management may also be a component of addiction treatment. Contingency management, also known as motivational incentives, provides immediate positive reinforcement to encourage abstinence and attendance. Positive reinforcement may range from a verbal/text acknowledgement of completion of a task to monetary payment for drug-negative urine specimens. Contingency management is based on the principles of operant conditioning as formulated by B.F. Skinner, which posits that rewarding a behavior will increase the frequency of that behavior. Contingency management is typically used to augment a psychosocial treatment such as community reinforcement approach.

The combination of community reinforcement approach plus contingency management was shown in a 2018 network meta-analysis of 50 RCTs to be the most efficacious and accepted intervention among 12 structured psychosocial interventions, including contingency management alone, in individuals with cocaine or amphetamine addiction.[3] Positive reinforcement with voucher draws (eg, from a fishbowl) of variable worth that range from a congratulatory message to an occasional high dollar value are as effective as constant monetary vouchers. Studies conducted by the National Drug Abuse Treatment Clinical Trials Network have shown that intermittent reinforcement with incentives totaling $250 to $300 over 8 to 12 weeks both increases retention in a treatment program and reduces stimulant drug use during treatment.[4]

SOFTWARE AS A MEDICAL DEVICE

The International Medical Device Regulators Forum, a consortium of medical device regulators from around the world, which is led by the FDA, distinguishes between 1) software in a medical device and 2) software as a medical device (SaMD). The Forum defines SaMD as "software

that is intended to be used for one or more medical purposes that perform those purposes without being part of a hardware medical device".[5]

FDA's Center for Devices and Radiological Health is taking a risk-based approach to regulating SaMD. Medical software that "supports administrative functions, encourages a healthy lifestyle, serves as electronic patient records, assists in displaying or storing data, or provides limited clinical decision support, is no longer considered to be and regulated as a medical device".[6]

Regulatory review will focus on mobile medical apps that present a higher risk to patients.

- Notably, FDA will not enforce compliance for lower risk mobile apps such as those that address general wellness.
- FDA will also not address technologies that receive, transmit, store, or display data from medical devices.

The agency has launched a software pre-cert pilot program for SaMD that entered its test phase in 2019. Key features of the regulatory model include the approval of manufacturers prior to evaluation of a product, which is based on a standardized "Excellence Appraisal" of an organization, and its commitment to monitor product performance after introduction to the U.S. market. Criteria include excelling in software design, development, and validation. Companies that obtain pre-certification participate in a streamlined pre-market review of the SaMD. Pre-certified organizations might also be able to market lower-risk devices without additional review. In 2017, FDA selected nine companies to participate in the pilot program, including Pear Therapeutics. In September 2022, the Software Precertification (Pre-Cert) Pilot Program was completed with the issuance of the Report: The Software Precertification (Pre-Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and Key Findings.[7] This document includes the following statement:

> Ultimately, the approach to regulating novel, swiftly-evolving medical device software must foster, not inhibit, innovation, while continuing to provide reasonable assurance of safety and effectiveness. These aspects are not mutually exclusive. A flexible, risk based approach to regulation could allow FDA to tailor regulatory requirements more efficiently for devices based on the latest science, the benefits and risks posed by devices, their real-world performance, and their contribution to promoting health equity. It could leverage the capabilities of evolving medical device software so that health care providers, patients, and users can benefit from advancement and innovation, and so that risk for such devices can be reduced through swift software and cybersecurity updates throughout the total product lifecycle, when needed. New legislative authority establishing such an approach could be supplemental to, and not replace, the established regulatory pathways.

REGULATORY STATUS

In 2017, reSET® (Pear Therapeutics), received De Novo marketing clearance from the FDA to provide CBT as an adjunct to contingency management, for patients with SUD who are enrolled in outpatient treatment under the supervision of a clinician (DEN160018). This was the first prescription digital therapeutic to be approved by the FDA. reSET® is indicated as a 12-week (90 days) prescription-only treatment intended to increase abstinence from a patient's substances of abuse during treatment and increase retention in the outpatient treatment. FDA product code: PWE.

In 2018, reSET-O® (Pear Therapeutics) was cleared for marketing by the FDA through the 510(k) pathway as a prescription-only digital therapeutic to “increase retention of patients with opioid use disorder (OUD) in outpatient treatment by providing cognitive behavioral therapy, as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management” (K173681). FDA determined that this device was substantially equivalent to existing devices. The predicate device was reSET®.

Vorvida® and Modia® (Orexo) provide support for individuals with problematic drinking and OUD. These digital technologies have not received marketing clearance by U.S. Food and Drug Administration and are not reviewed here.

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 a 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.

DIGITAL HEALTH TECHNOLOGIES FOR SUBSTANCE USE DISORDER

Clinical Context and Therapy Purpose

Substance abuse is a serious health problem in the U.S. A 2019 survey from the Substance Abuse and Mental Health Services Administration found that 20.4 million people age 12 or older in the U.S., or 7.4 percent of the U.S. population, had substance use disorder (SUD), but only 1.5 million people were enrolled in substance use treatment.[8] The most common substances reported in the survey are alcohol, followed by tobacco and marijuana. Illicit drug use and prescription drug misuse occur in a lower percentage of the population.

A computer-delivered cognitive-behavioral therapy (CBT) program named CBT4CBT (Computer-Based Training for Cognitive Behavioral Therapy) has been developed to provide therapy for patients with substance abuse. The program includes seven core CBT skills delivered by on-screen narration, graphic animation, quizzes, and interactive exercises. In a 2018 RCT, both clinician and computer delivery of CBT reduced the frequency of substance use more than treatment as usual.[9] In addition, patients who received the computer-based CBT with minimal monitoring had the best treatment retention, learning of CBT concepts, and

six-month outcomes compared to either clinician-delivered CBT or treatment as usual. A computer-based community reinforcement approach (CRA) plus vouchers was reported in a 2008 study to lead to similar levels of abstinence as patients who received clinician-guided CRA plus vouchers.[10] These results suggest that computerized CRA (CCRA) could potentially substitute for clinician-guided therapy and increase access to treatment.

In 2017 and 2018, the first prescription mobile apps (i.e., reSET® and reSET-O®) were cleared for marketing by the U.S. Food and Drug Administration (FDA). These have the potential to increase access to substance abuse treatments in patients who have SUD or OUD. These two apps are intended to provide CCRA as an addition to traditional therapy in the context of an outpatient program.

Evaluation of clinically meaningful outcomes

The outcome which is most frequently cited as the most important outcome for patients is abstinence from the substance of abuse.[11] This primary outcome should be measured during therapy, at the end of therapy, and at longer-term (e.g., 3, 6, and 12 months) follow-up to assess the durability of the treatment.

Other outcomes that have been reported as important to patients are drug craving, employment, and stable relationships. A semi-structured assessment of seven potential problem areas in substance-abusing patients is the Addiction Severity Index.[12] The domains are medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. The Addiction Severity Index provides severity ratings of the client's need for treatment and composite scores which measure problem severity during the prior 30 days.

The Maudsley Addiction Profile is a brief standardized interview that assesses treatment outcomes in domains of substance abuse, health risk behavior, physical and psychological health, and personal social functioning.[13]

Retention in a treatment program is commonly used in addiction research but is an indirect measure of treatment success. Although retention is necessary, it is not sufficient to assess effectiveness and additional outcome measures are needed. Observational data from the Drug Abuse Treatment Outcome Studies suggest that most addicted individuals need at least three months in treatment to significantly reduce or stop their drug use and that the best outcomes occur in patients who participate in longer treatment.[14]

REVIEW OF EVIDENCE

Randomized Controlled Trials

The two pivotal RCTs for the prescription digital apps for substance use disorder (SUD) (resSET) and opioid use disorder (OUD) (reSET-O®) are described below and in Tables 1 and 2. The technology was developed by the National Institute of Drug Abuse-funded Center for Technology and Behavioral Health as the Therapeutic Education System, which was subsequently submitted to the FDA for a mobile platform by Pear Therapeutics.

Campbell (2014) reported the pivotal multicenter trial for reSET®, in which patients with SUD or OUD completed 20 to 30 minute multimedia modules on a desktop while in the clinic or at home.[15, 16] The active treatment was the Therapeutic Education System, which combined CCRA plus contingency management, and was compared to treatment as usual (therapy

alone) at 10 community-based outpatient treatment programs as part of the National Drug Abuse Clinical Trials Network. Clinicians were able to access reports on computer activity and discussed module completion in the individual therapy sessions. Contingency management consisted of random selection of vouchers, which ranged from a congratulatory message to $100 cash, for module completion and negative urine drug results. The mean dollar earned was $277 (SD $226) over the 12 weeks. Although the study was intended to replace some of the hours of therapy, the Therapeutic Education System group received the same number of therapy session as the control group, so the combined program was effectively in addition to counseling alone.

The co-primary outcomes were abstinence from drug/heavy alcohol use in the last four weeks of treatment and retention in the treatment program. In the analysis by Campbell (2014),[15] the Therapeutic Education System reduced drop-out from the treatment program (hazard ratio = 0.72 [95% CI: 0.57 to 0.92], p=0.010), and the odds of achieving abstinence was 1.62 fold greater in the group with CCRA and contingency management group (p=0.010). However, the beneficial effect of the Therapeutic Education System was observed only in patients who were not abstinent at baseline. For patients who were abstinent at baseline, the Therapeutic Education System did not increase abstinence, and at three- and six-months follow-up, the effect of Therapeutic Education System was no longer significant. Subsequent analyses of the trial found that the Therapeutic Education System was not associated with improvements in social functioning compared to standard outpatient care.[17]

In the FDA analyses of the trial, results were analyzed for the entire cohort and for cohorts that excluded patients who reported opioid use.[16] Abstinence during weeks 9 to 12 and total abstinence with CCRA plus contingency management was significantly greater in the cohort as a whole and more so in the analyses that excluded primary opioid users. For example, abstinence during weeks 9 to 12 was 40.3% in the SUD subgroup who received CCRA plus vouchers compared to 17.6% in the group who received only therapy (p<0.001). Total abstinence, defined as the number of half weeks with a negative urine drug test, was 11.9 half weeks in the SUD subgroup who received the experimental treatment and 8.8 half weeks in controls (p=0.003).

In the pivotal study reported by Christensen (2014), CCRA was added to treatment as usual in patients who had opioids as the primary substance of abuse.[18, 19] Treatment as usual in this second trial included clinic visits three times per week with a reward for a negative urine drug screen (maximum of $997.50), sublingual buprenorphine/naloxone, and a clinician visit every two weeks. Patients who did not show up for any of the thrice weekly clinic visits were considered to have a positive drug screen and were considered drop-outs if they missed three visits in a row. The primary outcomes were the longest continuous abstinence and total abstinence. The study was powered to detect a three-week difference between groups in mean weeks of continuous abstinence. In the 84-day treatment program there were 9.7 more days of abstinence in the CCRA group (67.1 days) than in the control group (57.4 days, p=0.01). The trial did not meet one of the primary outcomes of a significant difference between the two groups in the longest abstinence (5.5 days p=0.214). The group using the computerized therapy had an increase in medication Addiction Severity Index scores (p=0.04) but did not show a significant improvement on the overall Addiction Severity Index (p>0.16). The data on abstinence and Addiction Severity Index was not reported in the 510(K) Summary for the U.S. FDA.[19]

Both trials reported a significant increase in retention during the 12-week program. The SUD subgroup had a 23.8% drop out rate compared to 36.8% in the control group (p=0.004). The addition of CCRA to treatment as usual in patients with OUD also increased retention, with a hazard ratio for dropping out of treatment of 0.47 (0.26 to 0.85).

Both trials had limitations in relevance and in design and conduct that preclude determination of the effect of the intervention on relevant health outcomes, as is summarized in Tables 3 and 4.

- Studies were conducted with desktop computers, used primarily during clinic visits. In the study by Christensen (2014), CCRA was only available in the clinic to avoid confounding the efficacy of the program with compliance issues. Regular use of a mobile app without close supervision and outside of the constraints of a trial setting is unknown. Although a proposed benefit of digital technology is to increase access to evidence-based treatments, particularly in rural areas or where there are other limitations to specialist care, consistent use of a mobile device in the home and the resources and expertise of local providers to supervise addiction treatment is uncertain.

- In the study by Campbell (2014), the experimental group received both the web-based CCRA and a reward for a negative drug test. The trial was designed to assess the combined treatment approach, and not specifically the CCRA program. Because a reward for a negative drug screen is known by itself to increase both retention and abstinence during a trial,[4] the contribution of the digital technology to the increase in abstinence in patients with SUD cannot be determined. Notably, abstinence was not improved at the three and six-month follow-up, raising further questions about whether the increase in abstinence during the trial was due to contingency management rather than the CCRA.

- The choice (e.g., retention) and timing (e.g., during treatment) of the outcome measures. Abstinence after a treatment program is a main objective of therapy. Abstinence was greater during the trial, but not improved at the three and six-month follow-up.

- The potential for performance bias inunblinded studies. Nearly half of patients who qualified for the study chose not to participate. There may have been greater motivation to use the new technology in patients who agreed to participate in the study. While acknowledging the difficulty of blinding with this type of intervention, providing a control intervention of similar intensity, such as computer time that is not based on CRA, is feasible.

Additional data from well-designed trials are needed to determine the effects of the technology on addiction.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Participants	Interventions	
				Active[a]	***Comparator***
Campbell (2014) FDA Submission DEN160018[15, 16]	U.S.	10	507 adult patients with self-report of drug use, with a subset of 305 who did not have primary use of opioids treated at community health centers	12 weeks of treatment as usual + CCRA (62 modules on a desktop) + contingency management for module completion and negative drug screen (n=255)	12 weeks of treatment as usual consisting ≥ 2 individual or group therapy sessions per week (n=252)
Christensen (2014) FDA summary K173681[18, 19]	U.S.	1	170 opioid-dependent adults	12 weeks of CCRA (69 modules on a desktop in the clinic) + contingency management + buprenorphine/ naloxone (n=92)	12 weeks of contingency management + buprenorphine/ naloxone (n=78)

CCRA: computer-based community reinforcement approach; RCT: randomized controlled trial.
[a]CCRA consisted of 20 to 30 min multimedia computer modules. Patients completed a mean of 36.6 (standard deviation, 18.1) out of 62 total CCRA modules in the study by Campbell et al. There were a total of 69 CCRA modules in the study by Christensen et al.

Table 2. Summary of Key RCT Results

Study	Abstinence		Total Abstinence		Retention		Dropping Out of Treatment		ASI overall	ASI Medication Subscale
Campbell (2014) FDA Submission DEN160018[15, 16]	Rate During Weeks 9-12		Half weeks							
	Entire Cohort (n=507)	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***	***Entire Cohort (n=507)***	***Excluding Primary Opioid Abusers (n=399)***		
Treatment as usual + CCRA + contingency management	29.7%	40.3%	10.9	11.9	72.2%	76.2%	27.8%	23.8%		
Treatment as usual	16.0%	17.6%	8.6	8.8	63.5%	63.2%	36.5%	36.8%		
p	0.008	<0.001	0.002	0.003			0.03	0.004		

Study	Abstinence	Total Abstinence	Retention	Dropping Out of Treatment	ASI overall	ASI Medication Subscale
Christensen (2014) K173681[18, 19]	Longest Abstinence in Days (+ SD)	Total Days + SD	Treatment Completion			
CRA + contingency management	55	67.1 + 19.3	80.4%	17.6%		
Contingency management	49.5	57.4 + 28.0	64.1%	31.6%		
HR/Diff/OR (95% CI)	Diff: 5.5	Diff: 9.7 (2.3 to 17.2)	OR: 2.30 (1.15 to 4.60)	HR: 0.47 (0.26 to 0.85)		
p	0.214	0.011		0.0224	>0.24	0.04

ASI: Addiction Severity Index; CI: confidence interval; (C)CRA: (computer-based) community reinforcement approach; HR: hazard ratio; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Campbell (2014); FDA Submission DEN16001[15, 16]	4. The study volunteers may not be representative of the general population with substance use disorder.	2. Was an earlier desktop technology and was conducted mostly in the clinic	3. The comparator did not include contingency management with vouchers. Delivery was not a similar intensity as the intervention.	1. Uncertain significance of retention as an outcome. 5. The minimal clinically important difference for abstinence was not pre-specified	1. Duration of follow-up not sufficient to assess durability.
Christensen (2014) K173681[18, 19]		2. Was an earlier desktop technology and was conducted in the clinic	3. Delivery was not a similar intensity as the intervention.	1. Uncertain significance of retention as an outcome. 5. The minimal clinically important difference for abstinence was not pre-specified.	1. The study did not extend after 12 week treatment period, limiting inferences on efficacy for abstinence.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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 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 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Campbell (2014); FDA Submission DEN160018[15, 16]		1. Participants and investigators were not blinded to treatment assignment.	2. Subgroup analyses in the FDA Summary were not pre-specified			
Christensen (2014) K173681[18, 19]		1. Participants and investigators were not blinded to treatment assignment.	2. Data on abstinence was not included in the FDA Summary			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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.

OBSERVATIONAL STUDIES

Xiong (2023) published the results of an industry-funded analysis of reSET® data from 602 patients with substance use disorder who filled a 12-week prescription of the software.[20] Patients were prescribed 61 therapy sessions and contingency management rewards (e.g., positive reinforcement message or monetary gift cards) based on lesson completion and negative urine drug screens. The reSET® application collected data on engagement (defined as any activity in the prescription digital therapeutic), retention (any activity in weeks 9 to 12), and self-reported substance use data. Participants were included in data analysis if they completed at least one therapy session. 52% of patients completed all core modules, and median lessons completed was 33 (out of 61 possible). Retention during treatment in the last four weeks of treatment was 74%. Substances used by patients, as reported by clinicians, were alcohol (46.7%), opioids (17.9%), stimulants other than cocaine (13.3%), cannabis (7.8%), cocaine (6.5%), and other/unknown (7.8%). 434 patients (72%) provided at least one substance use self-report during weeks 9 to 12. 92 patients (15%) had at least one clinician-reported urine drug screening during weeks 9 to 12. Abstinence was calculated as a combined measure of urine drug screening and self-reporting. Based on this metric, the authors reported that 434 patients (86%) were abstinent.

In a retrospective analysis of data from the Campbell pivotal trial, Luderer (2022) reported an association between engagement with the app (i.e., total number of modules completed) and abstinence during weeks 9 to 12 among the157 study completers (OR = 1.11; 95% CI 1.08-1.14).[21]Maricich (2022) published the results of a secondary analysis of data from the trial, excluding participants with OUD. The data included were from 399 individuals with SUD related to alcohol, cannabis, cocaine, or other stimulants; 206 were in the digital therapeutic group and were 193 in the treatment as usual group.[22] Abstinence was significantly higher than treatment as usual in the reSET® group (40.3% vs. 17.6%; p<0.001) as was retention in therapy (76.2% vs. 63.2%; p=0.004).

Marichich (2021) performed an industry-funded analysis of reSET-O® data from 3144 patients with OUD who had filled a 12-week prescription of the software.[23] Participants were instructed to complete at least four modules per week with a total possible of 31 core modules and 36 supplemental modules. Analysis of the software's data showed that about half of the patients completed all 31 modules, 66% completed half of the modules, and 74% of patients actively participated through 12 weeks. Use decreased from 100% in the first week to 55% of individuals completing 4 modules in week 12. (Retention in the pivotal study by Christensen was 80% for the software compared to 64% for contingency management alone).

Abstinence during the last four weeks of treatment was determined by either urine drug screening or self-report recorded on reSET-O®. With a conservative estimate of missing data considered to be a positive drug screen, 66% of patients were estimated to be abstinent during the last four weeks of the prescription. For patients who completed 3 to 5 modules in the first week, abstinence in the final four weeks ranged from 83% to 89%. A limitation of this study is that patients who completed more modules in the first week may have been more motivated to remain abstinent, and cause and effect cannot be determined from this non-comparative observational study.

Marichich (2021) also published data from a subset of 643 individuals from the above cohort who completed the 12-week prescription and were then prescribed a second 12-week refill

prescription.[24] At the end of the second prescription period, 86.0% of the cohort were abstinent and 91.4% were retained in treatment through 24 weeks.

SUMMARY OF EVIDENCE

For individuals with SUD other than OUD who receive a prescription digital therapeutic, the evidence includes one pivotal RCT and secondary analyses of data from the trial. Relevant outcomes are symptoms, morbid events, change in disease status, quality of life, and medication use. Mobile digital technology is proposed as an adjunct to outpatient treatment; however, there are several limitations in the current evidence base that limit any conclusions regarding efficacy. The RCT assessed the combined intervention of computer-based learning and a reward for abstinence. Since reward for abstinence alone has been shown to increase both abstinence and retention, the contribution of the web-based program to the overall treatment effect cannot be determined. The treatment effect on abstinence was not observed at follow-up, raising further questions about the relative effects of the rewards and the web program. While the RCT reported a positive effect on the intermediate outcome of retention, the relationship between retention and relevant health outcomes in this trial is uncertain. A secondary analysis of data from the trial reported an association between engagement with the app and abstinence at 9 to 12 weeks, but study design limitations preclude drawing conclusions from this study. Given these limitations, further study in well-designed trials is needed to determine the effects of prescription digital therapeutics on relevant outcomes in individuals with SUD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with OUD who receive a prescription digital therapeutic, the evidence includes one pivotal RCT and analysis of data of more than 3000 patients from the mobile app. Relevant outcomes are symptoms, morbid events, change in disease status, quality of life, and medication use. Mobile digital technology is proposed as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management; however, there are a number of limitations in the current evidence base that limit any conclusions regarding efficacy. The RCT did not meet a primary objective of longest days of abstinence. While there was a positive effect on the intermediate outcome of retention, the relationship between retention and relevant health outcomes in this trial is uncertain. Retrospective observational studies found that participants who completed more modules with the mobile app had greater abstinence during weeks 9 to 12 and, in a subgroup of individuals who received a refill prescription, during weeks 21 to 24, but the retrospective design and lack of a control group with comparable motivation limits interpretation of these results. Given these limitations, further study in well-designed trials is needed to determine the effects of prescription digital therapeutics on relevant outcomes in individuals with OUD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF ADDICTION MEDICINE

In 2020, the American Society of Addiction Medicine (ASAM) published a focused update of their National Practice Guideline for the Treatment of Opioid Use Disorder.[25] The guideline recommends that psychosocial treatment be considered in conjunction with pharmacological treatment for opioid use disorder and notes, "At a minimum, the psychosocial treatment component of the overall treatment program should include assessment of psychosocial needs; individual and/or group counseling; linkages to existing support systems; and referrals

to community-based services." The guideline also notes that "psychosocial treatment may also include more intensive individual counseling and psychotherapy, contingency management, and mental health services" and, "while questions remain about which specific psychosocial therapies work best with which pharmacological treatments, there is widespread support for recommending psychosocial treatment as an important component of a patient's opioid use disorder treatment plan." The guideline does not address digital therapies.

NATIONAL INSTITUTE ON DRUG ABUSE

The 2018 Principles of Drug Addiction and Treatment from the National Institute on Drug Abuse describes evidence-based approaches to drug addiction treatment.[14] Behavioral therapies include cognitive-behavioral therapy (alcohol, marijuana, cocaine, methamphetamine, nicotine), contingency management (alcohol, stimulants, opioids, marijuana, nicotine), community reinforcement approach plus vouchers (alcohol, cocaine, opioids), motivational enhancement therapy (alcohol, marijuana, nicotine), the matrix model (stimulants), 12-step facilitation therapy (alcohol, stimulants, opiates) and family behavior therapy. The guideline does not address digital therapies for substance use disorders.

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of substance use disorders improves net health outcomes. No clinical guidelines based on research recommend digital therapeutic products for the treatment of substance use disorders. Therefore, digital therapeutic products for the treatment of substance use disorders are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
	99199	Unlisted special service, procedure or report [when specified as a digital health management software application]
HCPCS	A9291	Prescription digital behavioral therapy, fda cleared, per course of treatment
	E1399	Durable medical equipment, miscellaneous [when specified as a digital health management software application]
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *September 2021*

Regence

Medical Policy Manual Medicine, Policy No. 175.03

Digital Therapeutic Products for Chronic Low Back Pain

Effective: January 1, 2025

Next Review: September 2025
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for chronic low back pain.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).

- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of chronic low back pain either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational**, including but not limited to the RelieVRx device.

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

REGULATORY STATUS

In March 2021, RelieVRx (formerly EaseVRx) received FDA Breakthrough Device designation through the De Novo premarket review pathway. No other virtual reality devices have been FDA authorized or approved. RelieVRx is a prescription device intended to treat chronic low back pain.

EVIDENCE SUMMARY

Systematic Reviews

Henríquez-Jurado (2024) published a systematic review and meta-analysis of 25 RCTs on the effect of virtual reality based therapy (VRBT) on reducing pain intensity, kinesiophobia, associated disability, and health-related quality of life in patients with chronic neck pain or chronic low back pain.[1] VRBT was compared to therapeutic exercise, sham, or no intervention. Data from 19 RCTs (n=1,415) showed a large immediate effect in pain response with VRBT for chronic low back pain (Standard Mean Difference [SMD]=−1.27, 95% CI: −1.45 to −0.8, p<0.001). Heterogeneity was high (I^2=63.9%; Q=66.5; df=24; p=0.87). For chronic neck pain, five RCTs (n=417) showed a large immediate effect in pain response (SMD=−0.45, 95% CI: −0.68 to −0.21, p<0.001) in favor of VRBT with low risk of publication bias or heterogeneity (I^2=0%; Q=4.4; df=6; p=0.62). Improvements in kinesiophobia, associated disability, and health-related quality of life were also reported. On average, the reviewers concluded that risk of bias was moderate across studies; two RCTs were of high quality and low risk of bias, and nine RCTs were of moderate quality and medium risk of bias. Limitations of this study include high heterogeneity in pain intensity analysis and VR treatment type, lack of long-term follow-up, and not all outcomes were reported for control groups.

Brea-Gomez (2021) published a systematic review for the use of virtual reality for the treatment of chronic low back pain which included 14 studies, 11 of which were included in the meta-analysis.[2] Significant differences were found in favor of VR compared to no VR in pain intensity postintervention (p< 0.00001) and follow-up (p< 0.00001); and kinesiophobia postintervention (p=0.04) and follow-up (p=0.006). No significant differences were found in disability. The authors concluded that VR can significantly reduce pain intensity and

kinesiophobia in patients with chronic low back pain. There was significant heterogeneity in the included studies. Additionally, the studies had small sample sizes and the interventions provided in the studies had a broad range of type, duration, and frequency which makes it difficult to interpret meaningful differences and make generalizable conclusions.

Randomized Controlled Trials

Groenveld (2023) published a single-center pilot RCT of 40 adult participants with non-specific chronic low back pain, reporting an average pain score of 4 and higher on an 11 point Likert scale in the week before enrollment.[3] Participants were randomized to receive self-administered behavioral therapy with a novel virtual reality application (Reducept) for at least 10 minutes per day for 4 weeks (n=20) or standard care (n=20). The primary outcome was quality of life measured by the short form-12 at four weeks. Secondary outcomes were short form-12 scores at four months and daily pain scores and analgesic use at four weeks and four months. Six patients did not complete the questionnaires and were lost to follow-up. Short form-12 scores did not differ between treatment groups at four weeks for the physical scale (mean difference -2.56, 95% confidence interval [CI] -5.60 to 0.48, p=0.96) or mental scale (mean difference -1.75, 95% CI -6.04 to 2.53, p=0.41). A significant treatment effect was observed for daily worst pain score (F [1, 91.425] = 33.3, p<0.001) and daily least pain score (F [1, 30.069] = 11.5, p=0.002). Due to low sample size, most secondary outcomes could not be measured due to insufficient statistical power.

Garcia (2021) published a double-blind RCT with 179 participants chosen from a national online convenience sample.[4] The participants had self-reported low back pain with duration of six months or more with average pain intensity of four or greater (out of 10) and were randomized to a 56-day EaseVRx program or a Sham VR. The sham VR group was exposed to a 2D nature content delivered through a VR headset. The primary outcome was the effects of EaseVRx versus the Sham VR representing change in average pain intensity and pain-related interference with activity, stress, mood, and sleep from baseline to end of treatment at 56 days. Change was measured using the Defense and Veterans Pain Rating Scale (DVPRS) and the DVPRS interference scale (DVPRS-II). Twice-weekly surveys were obtained with a final survey at treatment completion. EaseVRx was superior to Sham VR for all primary outcomes with greater reductions in average pain intensity and pain-related interferences with activity, mood, and stress. Between-group comparisons for physical function and sleep disturbance demonstrated superiority for the EaseVRx versus the Sham VR (p=0.022 and 0.012, respectively). However, pain catastrophizing, pain self-efficacy, pain acceptance, and prescription opioid use did not reach statistical significance for either group. Use of over-the-counter analgesic use was reduced for EaseVRx but not for Sham VR (p<0.01).

A three-month follow-up study by Garcia (2022) analyzed data for 188 participants who were surveyed at one, two, and three months after the original 56-day trial.[5] 168 of the participants from the original trial completed the 56-day treatment and remained blinded during the follow-up period. The authors reported that the EaseVRx had lower pain intensity, lower pain-interference with activity, sleep, and stress than the Sham VR through three months. There was no significant difference between EaseVRx and Sham VR for sleep disturbance at three months. A six-month follow-up study by Garcia (2022) demonstrated similar results.[6]

A 24-month follow-up study of the Garcia (2021) RCT was published by Maddox (2023).[7] The Defense and Veterans Pain Rating Scales (DVPRS, DVPRS-II) were used to collect 24-month post-treatment data among VR- and sham-treated participants. 127 out of 168 participants

(76%) completed the 24-month post-treatment survey (81% of the VR group and 70% of the sham group). Skills-Based VR participants had lower pain intensity ratings (p=0.04, ES=0.28) and overall pain interference (p=0.002, ES=0.54) compared to sham participants. Pain interference subcomponents, including activity, sleep, mood, and stress, were also significantly lower for Skills-Based VR participants. At the end of treatment, 62% of VR participants achieved a clinically meaningful reduction in both pain intensity and pain interference, compared to 37% of sham participants. Similar results were reported in an 18-month follow-up study.[8]

The original trial and the follow-up studies are limited in their recruitment protocol, collection of self-reported data including the inclusion criteria (e.g., self-reported back pain and medication usage), lack of diversity in the sample collected, and lack of generalizability. Additional high-quality randomized trials are needed to establish the effectiveness of virtual reality as a treatment of chronic low back pain.

Section Summary

The evidence for those with chronic low back pain who receive virtual reality as a treatment modality includes systematic reviews and one randomized controlled trial with four follow-up studies at three months, six months, 18 months, and 24 months, and one randomized controlled trial with a four-week follow-up. Relevant outcomes are pain scores, quality of life, and medication utilization. Several questions remain concerning the efficacy of this treatment based on the limitations of the included trials which demonstrates a need for high-quality randomized trials with long-term follow-up to establish the effectiveness and durability of the treatment. At this time, the digital therapy is not recommended as an alternative or adjunct to established treatments. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

No clinical practice guidelines were identified which addressed the use of a digital therapeutic for the treatment of chronic low back pain.

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of chronic low back pain improves net health outcomes. No clinical guidelines based on research recommend digital therapeutic products for the treatment of chronic low back pain. Therefore, digital therapeutic products for the treatment of chronic low back pain are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
	99199	Unlisted special service, procedure or report [when specified as a digital health management software application]
HCPCS	A9291	Prescription digital behavioral therapy, FDA cleared, per course of treatment
	E1399	Durable medical equipment, miscellaneous [when specified as a digital health management software application]
	E1905	Virtual reality cognitive behavioral therapy device (cbt), including pre-programmed therapy software
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Codes	Number	Description
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *March 2023*

Regence

Medical Policy Manual Medicine, Policy No. 175.04

Digital Therapeutic Products for Amblyopia

Effective: January 1, 2025

Next Review: September 2025
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.

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DESCRIPTION

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for amblyopia.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or pacemaker).

- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

The use of a digital therapeutic product for the treatment of amblyopia either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational** including but not limited to CureSight™, Luminopia One™, and RevitalVision.

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

AMBLYOPIA

Amblyopia is reduced vision without a cause detected by physical eye examination. Amblyopia is also known as lazy eye and occurs in one, or less often, both eyes and is caused by abnormal visual system development in infancy and childhood.[1] In early childhood, the brain's visual system learns to interpret images from both eyes. The brain relies more heavily on the non-amblyopic eye and suppresses poor images from the amblyopic eye, which worsens vision in the amblyopic eye. Amblyopia can also cause loss of stereopsis and depth perception, reduced reading speed, impaired motor skills, and lower self-confidence in children.

Amblyopia is the leading cause of preventable monocular vision loss and is prevalent among children. Amblyopia can be caused by multiple factors including myopia, hyperopia, astigmatism, strabismus, or cloudiness in the crystalline lens. Amblyopia and its associated risk factors are more common in children who are premature, small for their gestational age, have a developmental delay, or have a first-degree relative with amblyopia. If untreated or inadequately treated, amblyopia can cause lifelong vision loss, and the risk of bilateral vision impairment is doubled for individuals with amblyopia.

Treatment

Timely amblyopia treatment decreases the likelihood of vision loss later in life, usually improves visual acuity, and sometimes improves binocularity.[1] Success rates of amblyopia treatment decline as age increases. Many strategies are used to improve visual acuity in amblyopia, and the goal of treatment is to achieve equal visual acuity between both eyes although this is not always possible. Treatment steps include correction of any cause of visual deprivation, correction of refractive errors likely to cause blur, and promotion of amblyopic eye use by occluding, fogging, or reducing contrast of images detected by the stronger eye.

According to the American Academy of Ophthalmology's (AAO) evidence-based Preferred Practice Pattern, recommended treatment is based on age, visual acuity, and adherence and response to previous treatment as well as the child's physical, social, and psychological status. Recommended treatments for amblyopia in children include[1]:

- ***"Refractive correction with eyeglasses is recommended as the initial step in care of children 0-17 years of age."*** Occlusion of the non-amblyopic eye with eye patching or pharmacological treatment with blurring atropine eye drops are each recommended *as "an appropriate choice for amblyopia treatment in children who do not improve with refractive correction alone or who have incomplete resolution of their visual acuity deficit."*

- Surgery is indicated when amblyopia is caused by opacity issues in the ocular media, e.g., cataract, nonclearing vitreous opacity, cornmeal opacities, that are severe enough to prevent successful amblyopia therapy without surgical correction.

Success of current treatments varies due to severity of amblyopia and issues with therapy adherence.[2] Vision improvement is typically greatest for the first four months and beyond with eyeglasses. Success with patching and atropine eye drops is similar; both result in statistically and clinically significant improvements in visual acuity and stereopsis. Issues with patching and blurring eye drops include poor adherence to treatment and suboptimal treatment outcomes. Lack of adherence to patching is common with adherence ranging from 41% to 57%. With current treatments, approximately 25% of eyes with severe amblyopia and 58% of eyes with moderate amblyopia improve to a level of 0.20 Logarithm of the Minimum Angle of Resolution (logMAR), an improvement of two lines of letters on the LogMAR visual acuity chart. Common goals of digital therapeutics for amblyopia are to promote use of both eyes with binocular visual stimulation and to increase adherence to therapy using appealing visuals such as movies, television shows, or video games.

REGULATORY STATUS

The RevitalVision system (Talshir Guy Medical Technologies) received U.S. Food and Drug Administration (FDA) 510(k) approval in August 2001, then known as the AA-1 System (K012530).[3] RevitalVision is software for at-home use on the patient's personal computer and is customized to match the patient's visual acuity. The technology is designed to improve visual acuity by facilitating neural connections in the visual cortex through a visual training regime using interactive visual tasks and Gabor patches, grate-like images that stimulate neurons in the visual cortex. RevitalVision is indicated for the treatment of amblyopia in patients nine years or older when prescribed by a vision care provider. Use of RevitalVision does not require simultaneous use of eyeglasses. A minimum of 12 training sessions per month are recommended, three to four times per week for approximately 30 minutes. Total training sessions vary by condition and eye care provider.

In October 2021, Luminopia One™ (Luminopia, Inc.) received marketing clearance by the U.S. FDA through the De Novo premarket review process (DEN210005).[4] Luminopia One™ is a prescription software-only digital therapeutic indicated for the improvement of visual acuity in patients 4 to 7 years old who have amblyopia associated with anisometropia and/or with mild strabismus. The application incorporates dichoptic presentations into displays of digital content, e.g., movies and television shows, via therapeutic algorithms designed to strengthen visual processing and increase use of the amblyopic eye. Luminopia One™ is to be used with commercially available head-mounted displays which are compatible with the software application in an at-home environment. Luminopia One™ is intended for previously treated and untreated patients, but patients with greater than 12 months prior treatment, other than refractive correction, have not been studied. Luminopia One™ is indicated as an adjunct to full-time refractive correction with glasses, which should also be warn under the head-mounted

display during therapy. One hour viewing sessions, six days per week for at least three months are recommended.

In September 2022, the CureSight-CS100™ (Nova-Sight) device received U.S. FDA 510(k) approval, listing Luminopia One™ as the predicate device.[5] CureSight-CS100™ is a prescription device and software indicated for the improvement of visual and stereo acuity in amblyopia patients 4 to 9 years old, with anisometropia and/or with mild strabismus. The system uses digital content, real-time eye tracking, and separation of visual stimuli presented on a monitor into two separate digital channels for each eye. Refractive correction glasses are to be warn underneath the CureSight-CS100 device, a dichoptic anaglyph (red-blue glasses). During treatment, patients wear anaglyph glasses and interact with the interface touchscreen by selecting digital content. Gaze and eye position are tracked, and the software blurs images for the non-amblyopic eye and sharpens images for the amblyopic eye. This system is designed to force the patient's visual system to use information from the central vision area of the amblyopic eye. CureSight-CS100™ is intended for both previously treated and untreated patients as an adjunct to full-time refractive correction. CureSight-CS100™ is intended for at-home use under remote supervision of an eye-care provider and NovaSight's Monitoring Center. Treatment requires a minimum of 90 minutes per day, five days per week. Duration of treatment is determined by an eye care provider.

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 a 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.

DIGITAL THERAPIES FOR AMBLYOPIA

Clinical Context and Therapy Purpose

The purpose of digital visual therapeutic products is to provide a treatment option that is an alternative to, or an improvement on, existing therapies for patients with amblyopia. Issues with established amblyopia therapies include discomfort, low adherence, stigmatization among peers, and failure to restore normal visual function in some children.[6] Digital visual therapeutics for amblyopia use dichoptically presented images such that each eye receives an

altered version of the same image in order to balance input from each eye to the brain. This technique is referred to as balanced binocular viewing, or binocular therapy. Binocular therapies present a range of visual stimuli (e.g., Gabor patches, movies, television shows, or video games) and exist in a range of platforms such as computer or tablet screens, specialized glasses, or virtual reality systems. These digital therapeutics have been designed to be child-friendly with the goal of increasing adherence to therapy. In contrast to conventional patching or pharmacological treatments, binocular therapies are designed to promote the two eyes working together instead of occluding the non-amblyopic eye.

REVIEW OF EVIDENCE

Systematic Reviews

Tsani (2024) conducted a systematic review of digital binocular treatment for amblyopia across 20 RCTs published between 2014 and 2024.[7] Included studies compared digital binocular therapy to standard amblyopia treatment or placebo. The reviewers concluded that binocular amblyopia treatment has shown promising results in improving visual acuity in patients with unilateral amblyopia. However, the reviewers also concluded that additional RCTs are needed to establish the optimal dosage, type, and duration of binocular therapy as a standard component of amblyopia care. The review also found that binocular therapy did not have a significant advantage in enhancing stereoscopic vision compared to established approaches and did not identify any safety concerns or evidence of induced reverse amblyopia. The reviewers noted that the evidence is limited by lack of long-term outcomes, which makes it difficult to determine the incidence of recurrent amblyopia.

A 2022 Cochrane Systematic Review compared binocular treatment to conventional patching or pharmacological blurring treatment to determine whether binocular treatments result in better visual outcomes.[2] The inclusion criteria were RCTs that enrolled children between the ages of 3 and 8 years old with unilateral amblyopia and any type of binocular viewing intervention on any device (e.g. computer monitors viewed with liquid-crystal glasses, hand-held screens, or virtual reality displays). The review excluded children who had received any previous treatment other than optical correction and studies with a follow-up time of less than eight weeks. The authors identified one eligible RCT by Holmes 2016, discussed below, that compared conventional patching to binocular treatment and analyzed a subset of 68 children from the study who met the age criterion of this review. The review authors concluded with moderate certainty that 16 weeks of binocular treatment is likely comparable to conventional patching treatment. The authors noted that due to the limited sample size and absence of long-term (e.g. 52 week) follow-up data, it is not yet possible to draw robust conclusions on the overall effectiveness and safety of binocular treatment for amblyopia.

Roda (2021) performed a systematic review and meta-analysis of five RCTs to compare efficacy of binocular treatment for amblyopia, including digital dichoptic training methods, to patching in children with unilateral amblyopia.[8] Primary outcome measures were visual acuity and stereopsis. No significant difference in visual acuity between patients treated with patching or binocular treatment was observed (standardized difference in means [SDM] = -0.07; 95% confidence interval [CI]: -0.45-0.20; p=0.464). Similarly, no significant difference in stereopsis was demonstrated between patients treated with patching or binocular treatment. The authors concluded that this meta-analysis did not reveal substantial evidence to support binocular treatment as an alternative treatment to traditional patching therapy but that it may be considered as a complementary therapy in unusual cases. The authors note that future studies

are required to draw conclusions as to whether more engaging digital therapies are more effective than standard treatments.

Chen (2021) conducted a systematic review and meta-analysis to evaluate the efficacy of binocular therapy versus patching and to determine whether binocular therapy could be an affective supplementary treatment for children with amblyopia.[9] The review included six RCTs in which a total of 304 participants received binocular therapy and 332 received conventional patching therapy. Mean best corrected visual acuity improvement in the binocular group was determined to be 0.13±0.14 logMAR and 0.16±0.14 logMAR in patching group. The combined effect analysis result was Z=3.01 (p=0.003). The authors reported severe heterogeneity among studies (I^2=56.8%, p=0.04) which they attribute to small sample size and diversity of binocular therapies. The authors concluded that binocular therapy may be an effective treatment for amblyopia but that a more statistically significant improvement was obtained with patching. The authors note that limitations of this study include the small sample size of six trials, lack of statistical analysis of masked data, inadequate randomization in one trial, and multiple trials demonstrated low adherence in binocular therapy groups which could influence treatment outcomes. Overall, the authors concluded that additional RCTs with larger sample sizes and longer treatment durations are necessary to assess the efficacy of binocular therapy for amblyopia.

In 2020, the AAO conducted a technology assessment of the efficacy of binocular therapy for the treatment of amblyopia compared to standard treatments.[10] The review also assessed whether binocular treatment confers sensory benefits, such as improved stereoacuity or reduced suppression to dichoptic treatment of amblyopia compared to conventional treatments which occlude the non-amblyopic eye. 20 studies were included in the review and were assigned a level of evidence rating: level I was assigned to well-designed and well-conducted RCTs (n=6); level II was assigned to well-designed case-control and cohort studies and lower-quality randomized studies (n=1); and level III was assigned to case series, case reports, and lower-quality cohort and case-control studies (n=13). Two level I and II studies reported a significant improvement in visual acuity in the binocular-treated group versus standard patching treatment (n=147 participants). Five studies failed to show a visual improvement from binocular therapy compared to standard treatments, and these studies were larger and more rigorously designed (n=813 patients). Level I and II studies did not show significant improvement over baseline in sensory status, including depth of suppression and stereopsis in participants treated with binocular therapy. 13 small, level III case series (n=163 participants) reported more improvements with binocular therapy than the level I and II studies. The review authors note that multiple level III studies included therapies deemed to be more engaging and therefore associated with better therapy adherence. The authors concluded that there is no level I evidence to support the use of binocular treatment as a substitute for standard treatments for amblyopia. Additionally, two large RCTs yielded inferior performance of binocular therapy compared to standard treatments. The authors suggest that more research is necessary to determine the potential benefits of binocular treatments for amblyopia.

Randomized Controlled Trials

Wygnanski-Jaffe (2024) published an evaluator-masked, multi-center RCT that compared the efficacy of CureSight-CS100™ (n=75) to eye patching (n=74) in children with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia (ages four to nine years).[11] CureSight-CS100™ treatment occurred for 90 minutes per day, five days per week, for 16 weeks, and eye patching occurred for two hours per day, five days per week, for 16 weeks.

The primary outcome was the mean improvement from baseline in amblyopic eye visual acuity to week 16 in both groups, with a non-inferiority margin of less than or equal to 0.10 logMAR. Mean improvement from baseline at week 16 in the binocular treatment group was non-inferior to the patching group in the modified intent-to-treat dataset, with a least squares mean difference between groups of 0.034 logMAR (95% CI -0.009 to 0.076). Both groups showed significant median improvement in stereoacuity at week 16, with no significant between-group difference in the magnitude of improvement. Binocular visual acuity improved in both groups ($p<0.0001$). Notably, median adherence in the CureSight-CS100™ group was significantly higher than in the patching group (94.0% vs 83.9%, $p=0.0038$). Limitations of this study include that most participants had anisometropic amblyopia (82%) and lack of long-term follow-up.

Wygnanski-Jaffe (2023) published a multi-center RCT that compared visual outcomes of digital CureSight-CS100™ treatment to conventional patching treatment.[12] 103 participants ages 4 to 8 years with amblyopia received either digital (n=51) or eye patch (n=52) therapy. CureSight™ participants used the treatment for 90 minutes per day, 5 days per week for 16 weeks. Eye patch participants wore their patch for two hours per day, seven days per week. The primary outcome was mean improvement of visual acuity from baseline at 16 weeks (a non-inferiority of no more than 0.10 logMAR). Participants were assessed at 4, 8, 12, and 16 weeks. The baseline mean amblyopic eye visual acuity in the digital treatment group was 0.37±0.15 logMAR and 0.37±0.14 logMAR in the eye patch group. At 16 weeks, the mean change from baseline was 0.26 logMAR in the CureSight-CS100™ group and 0.23 logMAR in the eye patch group (standard error 0.02). Overall, the percentage of patients with a 2-line or more improvement in the binocular treatment group was 79% (34/43 patients) versus 61% (30/49 patients) in the patching group. A significantly greater median adherence was observed for the CureSight™ group (91%) compared to the patching group (83%). No serious adverse events were reported, and headaches occurred at a lower incidence in the CureSight™ group (4%) than the patching group (8%). Study limitations include the use of subjective self-logging compliance diaries for the patching group and that most patients had anisometropic amblyopia (90% of the patients in this study versus 50% to 60% in comparable RCTs). The authors note that a more conservative noninferiority limit, more similar to other studies, should have been used and that future studies are necessary to explore longer treatment durations, dosing, and effectiveness compared to other types of amblyopia treatments.

Xiao (2022) conducted a phase 3 RCT to evaluate the safety and efficacy of the Luminopia One™ (Luminopia, Inc.) dichoptic digital therapeutic for amblyopia.[13] 105 children 4 to 7 years old with amblyopia were randomized to receive either Luminopia One™ therapy or conventional optical correction with glasses. Participants in the treatment group (n=51) used Luminopia One™ at home for one hour per day, six days per week, and wore glasses full-time. Participants in the control group continued to wear glasses full-time (n=54). The primary outcome was change in visual acuity from baseline at 12 weeks, measured by masked examiners. 12 weeks after treatment, visual acuity improved by 1.8 lines (95% CI 1.4–2.3 lines; n=45) in the treatment group and by 0.8 lines (95% CI 0.4–1.3 lines; n=45) in the control group. Upon 12-week interim analysis, the difference between the treatment and control groups was significant (1.0 lines; $p=0.0011$; 96.14% CI 0.33-1.63 lines), and the authors stopped the study for early success, according to the study protocol. No serious adverse events were reported. Limitations of this study include lack of comparison to standard treatments, such as eye patching or blurring drops, and lack of long-term follow-up. Future studies are needed to assess the treatment's long-term effects and to compare to current standard treatments.

Manny (2022) published a multi-center RCT that compared treatment of children ages 4 to 6 years with the dichoptic iPad game, Dig Rush (Ubisoft, not yet commercially available), in addition to glasses (n=92) versus continued treatment with glasses only (n=90).[14] Participants in the video game group were prescribed to play one hour per day, five days per week. Participants in the glasses group were prescribed to wear glasses during all waking hours. At the four-week visit, there were 85 participants (92%) in the video game group and 84 participants (93%) in the glasses group available for analysis. Parents reported adherence of greater than 75% for 74 glasses group participants (95%) and 66 (78%) video game participants. At eight weeks, 75% adherence was reported for 78 (95%) in the glasses-wearing group and 69 participants (78%) in the video game group. At four weeks, mean visual acuity improved by 1.1 lines in the video game group and 0.6 lines in the group who wore glasses. At eight weeks, the mean visual acuity improvement for the video game group was 1.3 lines and 1.0 lines in the glasses group. Additional studies are necessary to compare this treatment to eye patching and to assess the long-term effectiveness of this treatment.

Elhusseiny (2021) published a double-masked, single-center RCT that assessed best-corrected visual acuity and stereoacuity gains in 20 children greater than 7 years old and adults with unilateral anisometropic and/or strabismic amblyopia treated with a prototype virtual reality-based binocular amblyopia therapy.[15] Participants had a history of prior amblyopia treatment failure and were randomized to either a full-treatment group (eight weeks of binocular treatment using therapeutic software on a virtual reality headset) or a sham-crossover group (four weeks of sham treatment followed by four weeks of binocular treatment). The full treatment group included 11 participants, and the sham group included 9 participants. Amblyopic eye visual acuity and stereoacuity were evaluated at 4, 8, and 16 weeks. In the full-treatment group, the mean amblyopic eye logMAR visual acuity at 16 weeks was 0.49 ± 0.26, compared with 0.47 ± 0.20 at baseline. In the sham-crossover group, it was 0.51 ± 0.18 at 16 weeks, compared with 0.53 ± 0.21 at baseline. The improvement in visual acuity was not significantly different between treatment groups. Stereoacuity (log arcsec) was significantly improved, from 7.3 ± 2 at baseline to 6.6 ± 2.3 at 8 weeks (< 0.001) and 6.7 ± 2.6 at 16 weeks ($p<0.001$). No significant adverse events (diplopia, asthenopia, or worsening strabismus) were noted in either group. The authors noted that larger studies are necessary to confirm these results.

In a double-masked RCT, Gao (2018) evaluated efficacy of a home-based digital therapy video game compared to a placebo video game to improve visual function.[16] The study included children 7 years old and older and adults. Participants were prescribed video game play for a minimum of one hour per day for six weeks. The primary outcome was the change in visual acuity from baseline to six weeks. Treatment compliance was recorded by the video game software as well as a written diary completed by study participants. 56 participants were randomized to the active group and 59 participants to the placebo video game. At the six-week follow-up, there were 50 participants available for analysis in the active group and 57 participants in the placebo group. In the active group, there were 36 participants (64%) who met the study definition of compliance compared to 49 (83%) in the placebo group. At six weeks, the mean improvement of visual acuity from baseline was 0.06 lines (3 letters on a vision chart) in the active group and 0.07 lines (3.5 letters) in the placebo group. No significant differences were found between the two groups.

An RCT by Manh (2018) compared improvement of visual acuity in participants with amblyopia by following either treatment with a binocular video game or eye patching.[17] Participants were 13 to 16 years old and were followed for 16 weeks after treatment. Those in the binocular

video game group (n=40) were prescribed one hour of game play each day for seven days per week. Those in the eye patch group (n=60) were prescribed to wear the patch two hours per day. Parents or participants recorded the number of hours of treatment each day, and the video game device recorded the duration of game play. There were 39 participants (98%) in the video game group and 58 participants (97%) in the eye patch group who completed the 16 weeks of treatment. Adherence after 16 weeks was assessed to be adequate in 24 video game participants (62%) and 42 eye patch participants (75%). However, in the video game group, the game device recorded only 13% of participants who completed 75% of their prescribed treatments. At 16 weeks, mean visual acuity in the amblyopic eye improved by 3.5 letters (2-sided 95% CI 1.3 to 5.7 letters) in the binocular group and by 6.3 letters (2-sided 95% CI 4.4 to 8.5 letters) in the eye patch group. While a major limitation of this study is poor treatment adherence, the authors reported more improvement in VA in the eye patch group compared to the binocular vision treatment group.

Holmes (2016) conducted a multi-center RCT to compare visual acuity improvement in children with amblyopia treated with a binocular iPad game versus part-time patching.[18] Visual acuity was measured at baseline and after 16 weeks of treatment. 195 participants wore an eye patch for two hours per day, seven days per week. 190 participants played the binocular video game for one hour per day, seven days per week. Parents reported compliance by recording the number of hours spent using either treatment. 172 participants (92.5%) in the eye patch group completed over 75% of the prescribed treatments. 176 participants (66.7%) in the video game group were available for evaluation at the 16-week follow-up. Only 39 video game participants (22.2%) completed more than 75% of their prescribed treatments, as measured by the video game log file data. Mean visual acuity improved from 1.08 lines from baseline in the video game group and by 1.32 lines in the eye patch group. There were no significant between-group differences found for changes in amblyopic eye visual acuity. Limitations include lack of occlusion dose monitors, adherence data reliance on parental report (particularly for eye patch wearing), low adherence among the video game participants, and no monitoring of wearing the red-green glasses required to play the video game.

Nonrandomized Studies

Wygnanski-Jaffe (2024) published a prospective, non-randomized, one-year follow-up study that evaluated the efficacy of CureSight-CS100™ in 27 children (ages four to nine years) with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia.[19] At one-year, there was a partial reduction in visual acuity gain in the amblyopic eye, but a significant residual gain of 0.20 logMAR remained compared to baseline. Additionally, gains in stereoacuity and binocular visual acuity were maintained at both 12 weeks and one year post-treatment, with no significant change compared to end of treatment. However, amblyopia recurrence, defined as a worsening of ≥2 logMAR levels, occurred in 5.3% of patients at 12 weeks and 20.4% at one year post-treatment. Limitations of this study include small sample size and lack of comparison with eye patching for long-term follow-up.

Zhu (2023) conducted a prospective study of CureSight-CS100™ that included 34 participants ages 4 to 9 years with unilateral anisometropic amblyopia who had not received prior treatment.[20] The study included a full treatment group in which participants used CureSight-CS100™ for 90 minutes per day, five days per week (n=12); a part-time treatment group who used CureSight-CS100™ for 90 minutes per day, three days per week (n=8); and a control group who received standard patching treatment for two hours per day, seven days per week (n=14). Participants were evaluated at 4, 8, and 12 weeks. At 12 weeks, mean amblyopic eye

distance visual acuity improved by 1.8 lines (95% CI 1.1 to 2.5) in the full treatment group, 1.5 lines (95% CI, 0.4-2.7) in the part-time treatment group, and 3.0 lines in the patching group. Stereoacuity improved 0.38 log-arcseconds (95% CI, 0.24-0.53) in the full-time treatment group, 0.59 log-arcseconds (95% CI, 0.36-0.82) in the part-time treatment group, and 0.40 log-arcseconds (95% CI, 0.13-0.67) in the patching group. Limitations of this study are small sample size and lack of long-term outcomes assessment.

Wygnanski-Jaffe (2023) published the results of the first-in-human prospective study of 23 amblyopic children 4 to 15 years of age, 20 of whom completed 6 months of treatment with the CureSight-CS100™ system.[21] Three participants left the study before the four-week follow-up. 13 participants had been previously treated with patching. At the primary endpoint of 24 weeks, amblyopic eye visual acuity (VA) significantly improved by 0.19 ± 0.11 logMAR for distance crowded VA, 0.27 ± 0.13 logMAR for near crowded VA, and by 0.22 ± 0.15 logMAR for distance single letter VA ($p<0.001$ for each). Stereoacuity improved by 198 ± 218 arcsec ($p=0.001$). Binocular VA improved 0.09 ± 0.13 logMAR for distance crowded VA ($p=0.007$), 0.12 ± 0.11 logMAR for near crowded VA ($p<0.001$) and 0.07 ± 0.12 logMAR for distance single letter VA ($p=0.018$). At 52 weeks, distance crowded visual acuity, distance single letter visual acuity, and stereoacuity were not significantly different from the 24-week measurements.

Abdal (2022) conducted a retrospective study of 161 children, 4 to 13 years old, with unilateral or bilateral amblyopia, who received dichoptic digital treatment with the Bynocs® platform (Kanohi Eye Pvt. Ltd.), an artificial intelligence-based video game that is used in-office or at-home via an online eye care appointment.[22] Participants used the therapy 30 minutes per day, 5 times per week, for 6 weeks. Best corrected mean visual acuity in the amblyopic eye improved by 0.39 logMAR ($p<0.001$), and binocular function score improved by a mean change of 1.55 ($p<0.001$). Study limitations include lack of control or comparison group and a short, six-week, treatment period.

Magdalene (2022) published the results of a prospective, observational study that measured visual outcomes in 45 patients with unilateral or bilateral amblyopia.[23] Participants received RevitalVision therapy after at least six months of no improvement with part-time occlusion therapy (e.g., with eye patching or atropine eye drops). Participants completed 40 training sessions within 3 months. Mean best-corrected visual acuity improved by approximately 2 logMAR lines ($p<0.001$) in 3 months. Issues with this study include lack of a comparison group, small sample size, and a large age range among participants (8 to 48 years of age).

Murali (2022) performed a prospective study of 29 adults ages 18 to 40 years with anisometropic amblyopia who were treated with the binocular video game, VisuoPrime (Visuoprime Neurapy, Ltd.) for 30 minutes per day, 7 days per week, for 6 weeks.[24] Participants had the option of completing game training in an eye care office (n=5) or at home (n=24). The video game included a tracking mechanism to determine therapy compliance. 14 subjects were compliant with therapy, and 15 subjects were noncompliant, playing less than 80% of prescribed therapy. Best corrected visual acuity and binocularity were assessed at one and three months. Best corrected visual acuity of the amblyopic eye improved from 0.60 ± 0.40 logMAR to 0.45 ± 0.29 logMAR and 0.38 ± 0.23 logMAR at one and three months, respectively ($p=0.0001$). Near acuity improved from 0.21 ± 0.14 to 0.14 ± 0.08 logMAR and 0.1 ± 0.04 logMAR at one and three months respectively ($p<0.0001$). The authors reported that stereopsis improved in 24% of subjects at one month, and this change persisted at three months. Study limitations included lack of a control or comparison group, small sample size, and lack of long-term follow-up.

Xiao (2021) published the results of a single-arm, multicenter prospective pilot study that evaluated the efficacy of Luminopia One™ in 90 children 4 to 12 years old with anisometropic, strabismic, or mixed amblyopia.[25] Digital therapy was prescribed for 1 hour per day, 6 days per week, for 12 weeks of at-home use. Of the 90 participants, 73 (81%) had prior treatment beyond refractive correction with glasses. Adherence to therapy was 86%. 74 participants (82%) completed the 12-week follow-up. Mean amblyopic eye best corrected visual acuity improved from 0.50 logMAR to 0.35 logMAR (1.5 logMAR lines; 95% CI, 1.2-1.8 lines; p<0.0001). Mean stereoacuity improved by 0.28 log arcsec (95% CI, 0.14-0.42 log arcsec; p<0.0001). Median adherence was 86% (interquartile range, 70%-97%). This study is limited by lack of a comparison group. The authors noted that visual improvement in this study was less than the improvement observed in their previous study, Xiao (2020), discussed below, possibly due to the larger sample size in this study.

Xiao (2020) assessed visual acuity improvement and therapy adherence to the Luminopia One™ technology in 10 amblyopia patients ages 4 to 7.[26] Researchers monitored participants for adverse effects, such as double vision, new or worsening eye misalignment, worsening visual acuity, or other unanticipated adverse events. Therapy was prescribed for at-home use 1 hour per day, 7 days per week for 12 weeks. Follow-up visits occurred at 2, 4, 8, and 12 weeks. Adherence to therapy was recorded automatically by Luminopia One™. Amblyopic eye best-corrected visual acuity improved by 0.29 logMAR (2.9 logMAR lines, p<0.01) from baseline to 12 weeks. Six patients experienced resolution of amblyopia, defined by a difference in visual acuity between the two eyes of less than 0.3 logMAR. Therapy adherence over the 12-week study was 78% ± 27%. No serious adverse events were reported. This study is limited by small sample size, lack of a comparison group, and lack of long-term outcomes.

A prospective study by Yalcin (2014) evaluated the efficacy of the RevitalVision neural vision therapy in improving best corrected visual acuity and contrast sensitivity in patients with amblyopia, aged 9 to 50 years.[27] 53 participants received RevitalVision therapy, and 46 participants were in the control group. The active treatment group completed 45 training sessions with perceptual vision therapy of approximately 30 minutes during which the participant responded to visual perception tasks on a computer screen. Initial sessions were supervised in the clinic, and additional sessions were performed at home. The control group received 30 minutes of eye patching three times per week and played a placebo computer games at home. All participants were followed for up to four months. At follow-ups within four to eight months, a mean improvement of 2.6 logMAR lines in visual acuity was observed in the treatment group. Contrast sensitivity function improved at 1.5, 3, 6, 12, and 18 cycles per degree spatial frequencies. The control group did not experience a significant change in visual acuity or contrast sensitivity function. Study limitations include lack of a control group that received standard eye patch treatment only.

Section Summary

The evidence for digital visual therapy for the treatment of amblyopia includes four systematic reviews, seven RCTs, and several uncontrolled cohort studies and case series. Relevant outcomes are visual acuity, stereoacuity, and adherence to therapy. Several questions remain regarding the efficacy of, and adherence to, this treatment based on the limitations of the included studies. Additional high-quality randomized trials with comparison to standard treatments and long-term follow-up and are needed to establish the effectiveness and durability of digital visual therapeutics. Currently, the evidence is insufficient to determine that

digital visual therapeutics improve health outcomes as much as or more than established treatments for amblyopia.

PRACTICE GUIDELINE SUMMARY

American Academy of Ophthalmology (AAO)

In 2024, the AAO published a limited update to the Amblyopia Preferred Practice Pattern based on a literature review by the Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel. Selected studies used to form a recommendation for care were graded for strength of evidence individually, and grades were listed with the study citation.

The recommendation section of these guidelines includes evidence ratings for each treatment. Regarding binocular (dichoptic) digital therapy, the guidelines state:

"Research with this technology is ongoing, which will be used to delineate use of binocular therapy for treatment of amblyopia."

- This recommendation was rated as *I+, Good, Discretionary*: "the evidence for this recommendation includes well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; further research is unlikely to change our confidence in the estimate of effect; and trade-offs of therapy are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of amblyopia improve net health outcomes as much as or more than established treatments. No clinical guidelines based on research recommend digital visual therapeutic products for the treatment of amblyopia. Therefore, digital visual therapeutics for the treatment of amblyopia are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	0687T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session
	0688T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and assessment of patient performance and program data by physician or other qualified health care professional, with report, per calendar month
	0704T	Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment
	0705T	Remote treatment of amblyopia using an eye tracking device; surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days
	0706T	Remote treatment of amblyopia using an eye tracking device; interpretation and report by physician or other qualified health care professional, per calendar month
HCPCS	A9292	Prescription digital visual therapy, software-only, fda cleared, per course of treatment

Date of Origin: *September 2023*

Regence

Medical Policy Manual Medicine, Policy No. 175.05

Digital Therapeutic Products for Post-traumatic Stress Disorder and Panic Disorder

Effective: January 1, 2025

Next Review: December 2024
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for post-traumatic stress disorder, panic disorder, and depression.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or

pacemaker).
- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

I. The use of a digital therapeutic product for the treatment of panic disorder and/or post-traumatic stress disorder, including but not limited to Freespira®, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational**.

II. The use of a digital therapeutic product for the treatment of nightmare disorder or nightmares from post-traumatic stress disorder, including but not limited to NightWare™, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational.**

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

PANIC DISORDER

Panic disorder is defined by recurrent, untriggered panic attacks with one month or more of worry about future attacks, or a maladaptive change in behavior related to the attacks.[1] Although other symptoms such as headache, tinnitus, and uncontrollable crying are common, they do not help define panic attacks. The most common symptom of a panic attack is heart palpitations. Panic disorder evaluation should be considered in patients who express recurrent, pervasive worry or present with somatic symptoms not attributed to underlying medical conditions. The Patient Health Questionnaire for Panic Disorder (PHQ-PD) is used to screen for panic disorder.

Treatment

Initial therapies for panic disorder include cognitive behavior therapy and anti-depressants, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[1] Benzodiazepines are not recommended for first-line treatment or long-term use due to adverse reactions, risk of dependence, and higher mortality. No consistent evidence currently supports a specific prevention strategy for panic disorder, but exercise may be beneficial. Despite limited evidence, beta blockers are frequently used to treat acute symptoms on panic attacks. The effectiveness of buspirone for panic disorder is uncertain. Antipsychotics or sedating antihistamines are not recommended for panic disorder due to limited evidence of effectiveness and adverse effects.

POST-TRAUMATIC STRESS DISORDER (PTSD)

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)* defines a traumatic event as an event, or series of events, in which an individual has

been personally or indirectly exposed to actual or threatened death, serious injury, or sexual violence.[2] There is a wide spectrum of psychological responses to traumatic events, including transient, non-debilitating symptoms; transient, acute stress response; acute, time-limited, and clinically significant acute stress disorder; and symptoms that persist beyond one month (PTSD) that might become chronic, if untreated. PTSD symptoms include intrusive thoughts, nightmares and flashbacks of past traumatic events, avoidance of reminders of trauma, hypervigilance, and sleep disturbance, all of which lead to considerable social, occupational, and interpersonal dysfunction.

Diagnosis of PTSD is challenging due to heterogeneous symptoms and patient resistance to discuss past trauma.[3] Comprehensive psychological assessment is used for PTSD screening. Example screening assessments include the PTSD checklist (PCL-5), a 20-item self-report measure used to screen patients for PTSD and monitor the severity of symptoms over time, and the Clinician Administered PTSD Scale (CAPS), a 30-item, structured interview used to diagnose PTSD in the past week, past month, or lifetime, and to assess the severity of PTSD symptoms. DSM-5 criteria are used to diagnose PTSD.

Treatment

A 2023 systematic review conducted by The Department of Veteran's Affairs and Department of Defense reported that psychotherapy and pharmacotherapy are effective at treating PTSD.[2] Clinical guidelines based on this evidence review recommend trauma-focused psychotherapy over pharmacotherapy if both treatment types are available and feasible. The following individual, manualized, or trauma-focused psychotherapies are recommended for the treatment of PTSD: Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing, Prolonged Exposure, Ehlers' Cognitive Therapy for PTSD, Present-Centered Therapy, or Written Exposure Therapy. Regarding pharmacotherapy, selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) (e.g., paroxetine, sertraline, or venlafaxine) are recommended for the treatment of PTSD.

The following approaches are currently used to treat PTSD-associated nightmares: medications; image rehearsal therapy; cognitive behavioral therapy; cognitive behavioral therapy for insomnia; eye movement desensitization and reprocessing; exposure, relaxation, and rescripting therapy.[4] Current treatments for nightmare disorder include image rehearsal therapy; cognitive behavioral therapy; exposure, relaxation, and rescripting therapy; hypnosis; lucid dreaming therapy; progressive deep muscle relaxation; sleep dynamic therapy; self-exposure therapy; systematic desensitization; and the testimony method.

REGULATORY STATUS

The Freespira® Canary Breathing System (Freespira, previously PaloAlto Health Sciences) received United States (US) Food and Drug Administration (FDA) 510(k) premarket approval on July 23, 2018 and was previously approved as the Canary Breathing™ System in 2013 (K131586, K180173).[5, 6] Freespira capnometry-assisted respiratory therapy is intended for use as a relaxation treatment for the reduction of stress by leading the user through guided and monitored breathing exercises. The device is indicated as an adjunctive treatment of symptoms associated with panic disorder and/or PTSD, to be used under the direction of a healthcare professional, together with other pharmacological and/or non-pharmacological interventions. It is a small breathing sensor with a tablet that is used twice a day for 17 minutes. Individuals are trained to use the sensor with the mobile application to measure and

display their end-tidal carbon dioxide ($EtCO_2$) level, respiratory rate, and how different breathing habits affect $EtCO_2$ levels. Product code: HCC, CCK.

The NightWare™ Kit (NightWare, Inc.) received US FDA breakthrough device designation on May 27, 2023 (DEN200033).[7] The NightWare™ digital therapeutic provides vibrotactile feedback on an AppleWatch® based on an analysis of heart rate and motion during sleep. NightWare™ is indicated for the temporary reduction of sleep disturbance related to nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from PTSD. It is intended for home use. The NightWare™ therapeutic platform uses a proprietary AppleWatch® and Apple iPhone application. The application learns the wearer's sleep patterns and customizes treatment to the individual. The application monitors the wearer's heart rate and movement during sleep and provides a vibration alert when a stress threshold is reached, intended to interrupt the nightmare but not awaken the patient. Users wear the watch only while sleeping and not during the day. Product code: QMZ.

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 a 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.

DIGITAL THERAPIES FOR PANIC DISORDER AND PTSD

Clinical Context and Therapy Purpose

Panic disorder is an anxiety disorder associated with marked impairment in social and occupational functioning, significant impact on quality of life, and high utilization of health care services.[8] Fearful interpretation of bodily symptoms such as tachycardia, shortness of breath, chest tightness, and dizziness with catastrophic beliefs is the core of the diagnosis and differentiates it from other anxiety disorders. Many individuals with panic disorder hyperventilate, and it has been suggested that respiratory abnormality associated with panic disorder may be due to a hypersensitivity to carbon dioxide (CO_2). Based on the recognition of subtle respiratory irregularities associated with hyperventilation in individuals with panic disorder, and CO_2 sensitivity, Meuret (2008) developed a breathing intervention focused on normalizing both exhaled carbon dioxide levels ($EtCO_2$) and respiratory rate.[9] The protocol

provided breath-to-breath feedback of $EtCO_2$, while modeling paced breathing at four different respiratory rates. Administered as twice daily, 17-minute sessions over a four-week period, the authors reported that by study end, 86% of subjects reported zero weekly panic attacks; an improvement that was durable over time, as 73% reported zero weekly attacks 1-year post-treatment. Freespira® incorporates this protocol in their approach to managing panic disorder.

PTSD is marked by symptoms of hyperarousal, difficulties with emotional regulation, negative affect, and autonomic dysfunction.[3] Carbon dioxide hypersensitivity may be responsible for mediating some PTSD symptoms as CO_2 challenge tests in individuals with established PTSD have been shown to provoke a panic attack.[10, 11] Since the characteristic of CO_2 hypersensitivity is shared by both PTSD and panic disorder, extending the use of Freespira® to a population with PTSD is a logical and potentially valuable clinical tool given the lack of medication-free treatment options for PTSD.

The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to, or an improvement on existing therapies, for individuals with panic disorder and PTSD. Panic symptoms may be associated with more shallow and rapid breathing. Freespira® addresses rapid and shallow breathing that may contribute to panic symptoms through training of respiratory control.

Freespira®

Nonrandomized Studies

Ostacher (2021) assessed Freespira® in a single-center, single-arm study of 55 adults with a primary DSM-5 diagnosis of PTSD (CAPS-5 score greater than or equal to 30 and Clinical Global Impressions Scale [CGI-S] score greater than or equal to four).[12] Participants were excluded if they were using any concurrent evidenced-based therapy for PTSD or had concurrent psychotic disorder, alcohol or drug use disorder requiring acute medical treatment, epilepsy or recent seizures; or cardiovascular or pulmonary disease. Participants were treated for four weeks with twice-daily, 17-minute, at-home Capnometry Guided Respiratory Intervention (CGRI) sessions. The primary efficacy outcome was 50% of participants achieving a greater than or equal to six-point decrease in CAPS-5 score at two-month follow-up. 88% (95% Confidence Interval [CI] 74 to 96%) of participants met the primary endpoint. Mean CAPS-5 scores decreased from 49.5 [±9.2] at baseline to 27.1 [±17.8] at two months, and mean CAPS-5 scores were 26.2 (±18.4) at six-month follow-up. Respiratory rate decreased, and $EtCO_2$ levels increased. All participants completed the treatment, and 48 (87%) participants completed the post-treatment assessment. 42 (76%) participants completed two-month follow-up, and 38 (69%) of participants completed six-month follow-up. No clear description of reasons for missingness, characteristics of missing observations, or sensitivity analyses of missing data assumptions were provided. In addition to significant loss to follow-up, this study is limited by lack of a comparison group or placebo control.

Kaplan (2020) published a single-arm, payer-funded (Highmark) multi-center single-arm study of Freespira® among 52 adults with a primary diagnosis of panic disorder (“moderately ill” on the CGI-S, score greater than or equal to four). Participants were either off medications or stable on medications prior to, during, or immediately after the four-week Freespira® treatment. Participants were excluded if they were receiving other psychological treatment or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Treatment was delivered in the same manner as in Ostacher (2021), and participants completed weekly

check-ins with a therapist. This study investigated whether treating panic disorder with Freespira® would reduce medical costs and improve outcomes over one year. Panic symptoms were assessed using the Panic Disorder Severity Scale (PDSS). Pre-and post-treatment insurance claims determined costs. Post-treatment, PDSS scores improved from 14.4 (±3.8) at baseline to 4.9 (±3.4). At six-month follow-up, mean PDSS was 4.1 (±4.3), and at 12-month follow-up, mean PDSS was 4.4 (±4.5).

Tolin (2017) evaluated Freespira® in a multi-site, single-arm study that enrolled 69 adults with a primary diagnosis of panic disorder.[13] Participant diagnoses were based on the Mini International Diagnostic Interview, and participants were rated as “moderately ill” or greater on the CGI-S. Participants were excluded if they were receiving other psychological treatment; unresponsive to cognitive-behavioral therapy; or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Participants received four weeks of CGRI using Freespira®. The intervention was delivered in an at-home setting after initial training by a clinician and provided remote monitoring of participant adherence and progress. The primary outcome was score on the PDSS. 53 (77%) participants completed the treatment, and 48 (70%) patients completed the post-treatment assessment. 46 (67%) participants completed two-month follow-up, 42 (61%) completed six-month follow-up, and 33 (48%) completed 12-month follow-up. Mean PDSS was 14.8 (±3.6) at baseline and 5.4 (±4.4) post-treatment, with a mean change of 9.4. At two months, mean PDSS was 6.0 (±5.2), with a mean change from baseline of 8.8. At 12 months, mean PDSS was 5.0 (±6.2) with a mean change from baseline of 9.4. This study is limited by significant dropout rates of 3%, 39%, and 52% at two, six, and 12 months of follow-up, and consequently data is missing for over 30% of study participants. This study is also limited by small sample size and lack of a comparison group or placebo control.

Section Summary

The evidence for digital therapeutic products for the treatment of panic disorder and PTSD with capnometry guided respiratory intervention (Freespira®) includes multiple single-arm studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several questions remain regarding the efficacy of, and adherence to, these treatments based on the limitations of the included studies. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments or sham controls, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD.

NightWare™

Randomized Clinical Trials

Davenport (2023) published results from a double-blind, sham-controlled RCT that evaluated efficacy of the NightWare™ System among veterans with impaired sleep secondary to trauma-related nightmares.[14] The trial was designed to enroll 240 participants with PTSD and nightmares, however, only 70 were enrolled. Patients with high suicide risk; cardiovascular comorbidities; current use of varenicline, beta-blockers, non-dihydropyridines; regular Circadian rhythm disruption; sleep-related comorbidities; and active substance abuse were excluded. Data from 63 trial participants were included on the primary and secondary outcome measures. The primary outcome was the difference in the Pittsburgh Sleep Quality Index (PSQI). The change from baseline was numerically higher for the NightWare™ group compared to sham, but the difference did not achieve statistical significance. There was no

statistical difference observed in multiple other secondary endpoints such as change from baseline to day 30 in the active treated arm versus sham in the following outcome measures: PCL-5, Patient Health Questionnaire 9-item depression scale (PHQ-9), Trauma-Related Nightmare Survey (TRNS), Functional Outcomes of Sleep Questionnaire (FOSQ-10), and Veterans RAND 12 Item Health Survey (VR-12). This study is limited by unclear blinding and lack of accessor blinding, statistical power not calculated for the primary outcomes, lack of power calculations, and inadequate control for selection bias. Further, the trial failed to achieve recruitment goals and was likely underpowered.

Section Summary

For individuals with nightmare disorder or PTSD-associated nightmares who receive NightWare™, the evidence includes a single trial. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single pivotal trial did not meet the primary efficacy endpoint and was likely underpowered. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD. Currently, there is not enough evidence to determine whether digital therapeutics improve health outcomes for panic PTSD-related nightmares.

PRACTICE GUIDELINE SUMMARY

Department of Veteran's Affairs and Department of Defense (VA/DoD)

The VA/DoD published evidence-based clinical practice guidelines for management of post-traumatic stress disorder and acute stress disorder in 2023.[2]

Regarding non-pharmacological treatments for PTSD, including digital therapeutics, the guidelines state:

"There is insufficient evidence to recommend for or against the following somatic therapies for the treatment of PTSD: capnometry-assisted respiratory therapy, hyperbaric oxygen therapy, neurofeedback, NightWare™, repetitive transcranial magnetic stimulation, stellate ganglion block, or transcranial direct current stimulation."

Regarding treatments for nightmares, the guidelines state:

"There is insufficient evidence to recommend for or against the following treatments for nightmares associated with PTSD: Imagery Rehearsal Therapy, Exposure Relaxation and Rescripting Therapy, Imaging Rescripting and Reprocessing Therapy, or NightWare."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of post-traumatic stress disorder (PTSD), panic disorder, or nightmare disorder improve net health outcomes as much as or more than established treatments. No clinical guidelines based on research recommend digital therapeutic products for the treatment of PTSD, panic disorder, or nightmare disorder. Therefore, digital therapeutics for the treatment of PTSD, panic disorder, and nightmare disorder are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
HCPCS	A9291	Prescription digital cognitive and/or behavioral therapy, FDA cleared, per course of treatment
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *December 2023*

Regence

Medical Policy Manual Medicine, Policy No. 175.05

Digital Therapeutic Products for Post-traumatic Stress Disorder and Panic Disorder

Effective: February 1, 2025

Next Review: December 2025
Last Review: December 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

Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. A digital therapeutic product is a specific type of digital health product that is practitioner-prescribed software that delivers evidence-based therapeutic intervention directly to a patient to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace established treatments for post-traumatic stress disorder and panic disorder.

MEDICAL POLICY CRITERIA

Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy.
- This policy addresses the use of practitioner-prescribed software applications for therapeutic intervention.
- This policy does not address:
  - Software that is used for the function or control of an FDA-cleared or approved stand-alone medical device (e.g., external insulin pump or

pacemaker).
- Applications operated by a health care practitioner for remote health monitoring.
- Products not meeting the definition of a digital therapeutic (see Policy Guidelines in Digital Therapeutic Products, Medicine, Policy No. 175).

I. The use of a digital therapeutic product for the treatment of panic disorder and/or post-traumatic stress disorder, including but not limited to Freespira®, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational**.

II. The use of a digital therapeutic product for the treatment of nightmare disorder or nightmares from post-traumatic stress disorder, including but not limited to NightWare™, either as a stand-alone treatment or as an adjunct to standard treatment, is considered **investigational.**

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

CROSS REFERENCES

1. Digital Therapeutic Products, Medicine, Policy No. 175

BACKGROUND

PANIC DISORDER

Panic disorder is defined by recurrent, untriggered panic attacks with one month or more of worry about future attacks or a maladaptive change in behavior related to the attacks.[1] Although other symptoms such as headache, tinnitus, and uncontrollable crying are common, they do not define panic attacks. The most common symptom of a panic attack is heart palpitations. Panic disorder evaluation should be considered in patients who express recurrent, pervasive worry or present with somatic symptoms not attributed to underlying medical conditions. The Patient Health Questionnaire for Panic Disorder (PHQ-PD) is used to screen for panic disorder.

Treatment

Initial therapies for panic disorder include cognitive behavioral therapy and anti-depressants, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[1] Benzodiazepines are not recommended for first-line treatment or long-term use due to adverse reactions, risk of dependence, and higher mortality. No consistent evidence currently supports a specific prevention strategy for panic disorder, but exercise may be beneficial. Despite limited evidence, beta blockers are frequently used to treat acute symptoms of panic attacks. The effectiveness of buspirone for panic disorder is uncertain. Antipsychotics or sedating antihistamines are not recommended for panic disorder due to limited evidence of effectiveness and adverse effects.

POST-TRAUMATIC STRESS DISORDER (PTSD)

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)* defines a traumatic event as an event, or series of events, in which an individual has

been personally or indirectly exposed to actual or threatened death, serious injury, or sexual violence.[2] There is a wide spectrum of psychological responses to traumatic events, including transient, non-debilitating symptoms; transient, acute stress response; acute, time-limited, and clinically significant acute stress disorder; and symptoms that persist beyond one month (PTSD) that might become chronic, if untreated. PTSD symptoms include intrusive thoughts, nightmares and flashbacks of past traumatic events, avoidance of reminders of trauma, hypervigilance, and sleep disturbance, all of which lead to considerable social, occupational, and interpersonal dysfunction.

Diagnosis of PTSD is challenging due to heterogeneous symptoms and patient resistance to discuss past trauma.[3] Comprehensive psychological assessment is used for PTSD screening. Example screening assessments include the PTSD checklist (PCL-5), a 20-item self-report measure used to screen patients for PTSD and monitor the severity of symptoms over time and the Clinician Administered PTSD Scale (CAPS), a 30-item, structured interview used to diagnose PTSD in the past week, past month, or lifetime, and to assess the severity of PTSD symptoms. DSM-5 criteria are used to diagnose PTSD.

Treatment

A 2023 systematic review conducted by The Department of Veteran's Affairs and Department of Defense reported that psychotherapy and pharmacotherapy are effective at treating PTSD.[2] Clinical guidelines based on this evidence review recommend trauma-focused psychotherapy over pharmacotherapy if both treatment types are available and feasible. The following individual, manualized, or trauma-focused psychotherapies are recommended for the treatment of PTSD: Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing, Prolonged Exposure, Ehlers' Cognitive Therapy for PTSD, Present-Centered Therapy, or Written Exposure Therapy. Regarding pharmacotherapy, selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) (e.g., paroxetine, sertraline, or venlafaxine) are recommended for the treatment of PTSD.

The following approaches are currently used to treat PTSD-associated nightmares: medications; image rehearsal therapy; cognitive behavioral therapy; cognitive behavioral therapy for insomnia; eye movement desensitization and reprocessing; exposure, relaxation, and rescripting therapy.[4] Current treatments for nightmare disorder include image rehearsal therapy, cognitive behavioral therapy, exposure, relaxation, and rescripting therapy, hypnosis, lucid dreaming therapy, progressive deep muscle relaxation, sleep dynamic therapy, self-exposure therapy, systematic desensitization, and the testimony method.

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display their end-tidal carbon dioxide ($EtCO_2$) level, respiratory rate, and the effects of different breathing habits on $EtCO_2$. Product code: HCC, CCK.

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The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to, or an improvement on existing therapies, for individuals with panic disorder and PTSD. Panic symptoms may be associated with more shallow and rapid breathing. Freespira® addresses rapid and shallow breathing that may contribute to panic symptoms through training of respiratory control.

Freespira®

Nonrandomized Studies

Ostacher (2021) assessed Freespira® in a single-center, single-arm study of 55 adults with a primary DSM-5 diagnosis of PTSD (CAPS-5 score greater than or equal to 30 and Clinical Global Impressions Scale [CGI-S] score greater than or equal to four).[12] Participants were excluded if they were using any concurrent evidenced-based therapy for PTSD or had concurrent psychotic disorder, alcohol or drug use disorder requiring acute medical treatment, epilepsy or recent seizures; or cardiovascular or pulmonary disease. Participants were treated for four weeks with twice-daily, 17-minute, at-home Capnometry Guided Respiratory Intervention (CGRI) sessions. The primary efficacy outcome was 50% of participants achieving a greater than or equal to six-point decrease in CAPS-5 score at two-month follow-up. 88% (95% Confidence Interval [CI] 74 to 96%) of participants met the primary endpoint. Mean CAPS-5 scores decreased from 49.5 [±9.2] at baseline to 27.1 [±17.8] at two months, and mean CAPS-5 scores were 26.2 (±18.4) at six-month follow-up. Respiratory rate decreased, and $EtCO_2$ levels increased. All participants completed the treatment, and 48 (87%) participants completed the post-treatment assessment. 42 (76%) participants completed two-month follow-up, and 38 (69%) of participants completed six-month follow-up. No clear description of reasons for missingness, characteristics of missing observations, or sensitivity analyses of missing data assumptions were provided. In addition to significant loss to follow-up, this study is limited by lack of a comparison group or placebo control.

Kaplan (2020) published a single-arm, payer-funded (Highmark) multi-center single-arm study of Freespira® among 52 adults with a primary diagnosis of panic disorder (“moderately ill” on the CGI-S, score greater than or equal to four). Participants were either off medications or stable on medications prior to, during, or immediately after the four-week Freespira® treatment. Participants were excluded if they were receiving other psychological treatment or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Treatment was delivered in the same manner as in Ostacher (2021), and participants completed weekly check-ins with a therapist. This study investigated whether treating panic disorder with

Freespira® would reduce medical costs and improve outcomes over one year. Panic symptoms were assessed using the Panic Disorder Severity Scale (PDSS). Post-treatment, PDSS scores improved from 14.4 (±3.8) at baseline to 4.9 (±3.4). At six-month follow-up, mean PDSS was 4.1 (±4.3), and at 12-month follow-up, mean PDSS was 4.4 (±4.5).

Tolin (2017) evaluated Freespira® in a multi-site, single-arm study that enrolled 69 adults with a primary diagnosis of panic disorder.[13] Participant diagnoses were based on the Mini International Diagnostic Interview, and participants were rated as "moderately ill" or greater on the CGI-S. Participants were excluded if they were receiving other psychological treatment; unresponsive to cognitive-behavioral therapy; or had evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures. Participants received four weeks of CGRI using Freespira®. The intervention was delivered in an at-home setting after initial training by a clinician and provided remote monitoring of participant adherence and progress. The primary outcome was score on the PDSS. 53 (77%) participants completed the treatment, and 48 (70%) patients completed the post-treatment assessment. 46 (67%) participants completed two-month follow-up, 42 (61%) completed six-month follow-up, and 33 (48%) completed 12-month follow-up. Mean PDSS was 14.8 (±3.6) at baseline and 5.4 (±4.4) post-treatment, with a mean change of 9.4. At two months, mean PDSS was 6.0 (±5.2), with a mean change from baseline of 8.8. At 12 months, mean PDSS was 5.0 (±6.2) with a mean change from baseline of 9.4. This study is limited by significant dropout rates of 3%, 39%, and 52% at two, six, and 12 months of follow-up, and consequently data is missing for over 30% of study participants. This study is also limited by small sample size and lack of a comparison group or placebo control.

Section Summary

The evidence for digital therapeutic products for the treatment of panic disorder and PTSD with capnometry guided respiratory intervention (Freespira®) includes multiple single-arm studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several questions remain regarding the efficacy of, and adherence to, these treatments based on the limitations of the included studies. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments or sham controls, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD.

NightWare™

Randomized Clinical Trials

Davenport (2023) published results from a double-blind, sham-controlled RCT that evaluated efficacy of the NightWare™ System among veterans with impaired sleep secondary to trauma-related nightmares.[14] The trial was designed to enroll 240 participants with PTSD and nightmares, however, only 70 were enrolled. Patients with high suicide risk; cardiovascular comorbidities; current use of varenicline, beta-blockers, non-dihydropyridines; regular Circadian rhythm disruption; sleep-related comorbidities; and active substance abuse were excluded. Data from 63 trial participants were included on the primary and secondary outcome measures. The primary outcome was the difference in the Pittsburgh Sleep Quality Index (PSQI). The change from baseline was numerically higher for the NightWare™ group compared to sham, but the difference did not achieve statistical significance. There was no statistical difference observed in multiple other secondary endpoints such as change from baseline to day 30 in the active treated arm versus sham in the following outcome measures:

PCL-5, Patient Health Questionnaire 9-item depression scale (PHQ-9), Trauma-Related Nightmare Survey (TRNS), Functional Outcomes of Sleep Questionnaire (FOSQ-10), and Veterans RAND 12 Item Health Survey (VR-12). This study is limited by unclear blinding and lack of accessor blinding, statistical power not calculated for the primary outcomes, lack of power calculations, and inadequate control for selection bias. Further, the trial failed to achieve recruitment goals and was likely underpowered.

Section Summary

For individuals with nightmare disorder or PTSD-associated nightmares who receive NightWare™, the evidence includes a single trial. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single pivotal trial did not meet the primary efficacy endpoint and was likely underpowered. Additional high-quality randomized trials with a clear design for testing a pre-specified hypothesis, comparison to standard treatments, and long-term follow-up and are needed to establish the effectiveness and durability of digital therapeutic products for panic disorder and PTSD. Currently, there is not enough evidence to determine whether digital therapeutics improve health outcomes for panic PTSD-related nightmares.

PRACTICE GUIDELINE SUMMARY

Department of Veteran's Affairs and Department of Defense (VA/DoD)

The VA/DoD published evidence-based clinical practice guidelines for Management of Post-traumatic Stress Disorder and Acute Stress Disorder in 2023.[2]

Regarding non-pharmacological treatments for PTSD, including digital therapeutics, the guidelines state:

"There is insufficient evidence to recommend for or against the following somatic therapies for the treatment of PTSD: capnometry-assisted respiratory therapy, hyperbaric oxygen therapy, neurofeedback, NightWare™, repetitive transcranial magnetic stimulation, stellate ganglion block, or transcranial direct current stimulation."

Regarding treatments for nightmares, the guidelines state:

"There is insufficient evidence to recommend for or against the following treatments for nightmares associated with PTSD: Imagery Rehearsal Therapy, Exposure Relaxation and Rescripting Therapy, Imaging Rescripting and Reprocessing Therapy, or NightWare™."

SUMMARY

There is not enough research to show that digital therapeutic products for the treatment of post-traumatic stress disorder (PTSD), panic disorder, or nightmare disorder improve net health outcomes as much as or more than established treatments. No clinical guidelines based on research recommend digital therapeutic products for the treatment of PTSD, panic disorder, or nightmare disorder. Therefore, digital therapeutics for the treatment of PTSD, panic disorder, and nightmare disorder are considered investigational.

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CODES

NOTE: Not all digital health products will have a specific code. These are examples of codes that may be relevant.

Codes	Number	Description
CPT	None	

Codes	Number	Description
HCPCS	A9291	Prescription digital cognitive and/or behavioral therapy, FDA cleared, per course of treatment
	G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
	G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the dmht device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
	G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (dmht) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the dmht device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month

Date of Origin: *December 2023*

Regence

Medical Policy Manual Medicine, Policy No. 177

Laser Interstitial Thermal Therapy

Effective: April 1, 2025

Next Review: December 2025
Last Review: February 2025

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

Laser interstitial thermal therapy (LITT) involves the introduction of a laser fiber probe to deliver thermal energy for the targeted ablation of diseased tissue. The goal of therapy is selective thermal injury through the maintenance of a sharp thermal border, as monitored via the parallel use of real-time magnetic resonance (MR) thermography and controlled with the use of actively cooled applicators. In neurological applications, LITT involves the creation of a transcranial burr hole for the placement of the laser probe at the target brain tissue. Probe position, ablation time, and intensity are controlled under MRI guidance. LITT has been proposed as a less invasive treatment option for patients with neurological conditions compared to surgery.

MEDICAL POLICY CRITERIA

I. Laser interstitial thermal therapy (LITT) may be considered **medically necessary** for the treatment of refractory epilepsy when both of the following Criteria (A. and B.) are met:

   A. There is documentation of disabling seizures despite use of two or more antiepileptic drug regimens (i.e., medically refractory epilepsy), and

B. There is a well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus accessible by LITT.

II. Laser interstitial thermal therapy (LITT) is considered **investigational** for all other neurological indications, including but not limited to the treatment of refractory epilepsy when Criterion I. is not met and for the treatment of primary or metastatic brain tumors or radiation necrosis.

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.

1. Medical records related to:
    - History and physical/chart notes including those documenting disabling seizures
    - Conservative treatment provided, including documentation of two or more antiepileptic drug regimens
    - Documentation of well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus *that is accessible by LITT.*

CROSS REFERENCES

1. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213
2. Focal Laser Ablation of Prostate Cancer, Surgery, Policy No. 222

BACKGROUND

LASER INTERSTITIAL THERMAL THERAPY

Laser interstitial thermal therapy (LITT) involves the introduction of a laser fiber probe to deliver thermal energy for the targeted ablation of diseased tissue. Thermal destruction of tissue is mediated via DNA damage, necrosis, protein denaturation, membrane dissolution, vessel sclerosis, and coagulative necrosis.[1] The goal of therapy is selective thermal injury through the maintenance of a sharp thermal border, as monitored via the parallel use of real-time magnetic resonance (MR) thermography and controlled with the use of actively cooled applicators.[2] In neurological applications, LITT involves the creation of a transcranial burr hole for the placement of the laser probe at the target brain tissue. Probe position, ablation time, and intensity are controlled under MRI guidance.

The majority of neurological LITT indications described in the literature involve the ablation of primary and metastatic brain tumors, epileptogenic foci, and radiation necrosis in surgically inaccessible or eloquent brain areas.[2] LITT may offer a minimally invasive treatment option for patients with a high risk of morbidity with traditional surgical approaches. The most common complications following LITT are transient and permanent weakness, cerebral edema, hemorrhage, seizures, and hyponatremia.[3] Delayed neurological deficits due to brain edema are temporary and typically resolve after corticosteroid therapy. Contraindications to MRI are

also applicable to the administration of LITT.

REGULATORY STATUS

In August 2007, the Visualase™ Thermal Therapy System (Medtronic; formerly Biotex, Inc.) received initial marketing clearance by the FDA through the 510(k) pathway (K071328). In January 2022 (K211269), the system (software version 3.4) was classified as a neurosurgical tool with narrowed indications for use, including "to ablate, necrotize or coagulate intracranial soft tissue including brain structures (for example, brain tumor, radiation necrosis and epileptic foci as identified by non-invasive and invasive neurodiagnostic testing, including imaging) through interstitial irradiation or thermal therapy in medicine and surgery in the discipline of neurosurgery with 800 nm through 1064 nm lasers." The device is contraindicated for patients with medical conditions or implanted medical devices contraindicated for MRI and for patients whose physician determines that LITT or invasive surgical procedures in the brain are not acceptable. Data from compatible MRI sequences can be processed to relate imaging changes to relative changes in tissue temperature during therapy. The Visualase™ cooling applicator utilizes saline.

In April 2013, the NeuroBlate® System (Monteris Medical) received initial clearance for marketing by the FDA through the 510(k) pathway (K120561). As of August 2020, the system is indicated for use “to ablate, necrotize, or coagulate intracranial soft tissue, including brain structures (e.g., brain tumor and epileptic foci as identified by non-invasive and invasive neurodiagnostic testing, including imaging), through interstitial irradiation or thermal therapy in medicine and surgery in the discipline of neurosurgery with 1064 nm lasers” (K201056). The device is intended for planning and monitoring of thermal therapy under MRI guidance, providing real-time thermographic analysis of selected MRI images. The NeuroBlate® system utilizes a laser probe with a sapphire capsule to promote prolonged, pulsed laser firing and a controlled cooling applicator employing pressurized CO2.

On April 25, 2018, the FDA issued a safety alert on MR-guided LITT (MRgLITT) devices with a letter to healthcare providers stating that the FDA is currently evaluating data suggesting that potentially inaccurate MR thermometry information can be displayed during treatment which may contribute to a risk of tissue overheating and potentially associated adverse events, including neurological deficits, increased intracerebral edema or pressure, intracranial bleeding, and/or visual changes. Several risk mitigation strategies were recommended. In an updated letter released on November 8, 2018, risk mitigation recommendations specific to the Visualase™ and NeuroBlate® systems were issued.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, two domains are examined: the relevance and the 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 is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

PRIMARY OR METASTATIC BRAIN TUMORS

Clinical Context and Therapy Purpose

The purpose of MRgLITT is to use a focused thermal therapy technique to ablate primary or metastatic brain tumors and to avoid potential complications associated with alternative surgical interventions.

Review of Evidence

Systematic Reviews

Pandey (2024) conducted a meta-analysis of 22 studies (n=206) that reported use of LITT for primary brain tumors (glioblastoma [n=185] and *IDH*-mutated astrocytoma [n=21]).[4] Among patients with glioblastoma, overall survival (OS) was 9.3 months (range, 7.1 to 11.4 months) and progression-free survival (PFS) was 4.8 months (range, 2.0 to 7.9 months). Neurologic complications occurred in 10.3% and non-neurologic complications occurred in 4.8% of patients with glioblastoma. Among patients with astrocytoma, OS and PFS could not be determined due to a lack of data. Neurologic complications occurred in 33% and non-neurologic complications occurred in 8.3% of patients with astrocytoma.

Zhao (2024) performed a systematic review and meta-analysis of eight studies (n=128) in patients with recurrent glioblastoma multiforme (rGBM).[5] At six months, PFS was 25% (95% CI 15% to 37%, I^2=53%) and OS was 92% (95% CI 83% to 100%, I^2=0%). At 12 months, PFS was 9% (95% CI 4% to 15%, I^2=24%) and OS was 42% (95% CI 13% to 73%, I^2=67%). Complication rates were low overall, and most complications were mild to moderate in severity.

Alkazemi (2023) published a systematic review of comparative and descriptive studies (excluding case reports) assessing the evidence for LITT in primary and metastatic brain tumors. A total of 45 studies (n=826) were included. Lesions were categorized as high-grade gliomas (n=361), low-grade gliomas (n=116), metastatic brain tumors (n=337), or nonglial tumors (n=15). Most studies offered LITT for patients with inaccessible or deep tumors (n=12), after failed radiosurgery (n=9), or were nonspecific (n=12). One-year PFS was 19.6% (95% confidence interval [CI] 11.3% to 29.0%, I^2=0%) in high-grade gliomas, 16.9% (95% CI 11.6% to 24.0%, I^2=0%) in grade 4 astrocytomas, and 51.2% (95% CI 36.7% to 65.5%, I^2=0%) in brain metastases. One-year OS was 43.0% (95% CI 36.0% to 50.0%, I^2=7.6%) in high-grade glioma, 45.9% (95% CI 37.9% to 54%, I^2=0%) in grade 4 astrocytomas, 93.0% (95% CI 42.3% to 100%, I^2=not applicable) in low-grade gliomas, and 56.3% (95% CI 47.0% to 65.3%, I^2=not applicable) in brain metastases. The incidence of major procedure-related adverse events (AEs) was 30% (95% CI 27% to 40%) with a 16% incidence (95% CI 12% to 22%) of major or minor neurological deficits. This study is limited by lack of comparator data.

Viozzi (2021) published a systematic review of data from 11 studies (n=111) of patients treated with LITT for newly diagnosed glioblastoma reported in 11 studies.[6] All included studies were conducted in the US predominantly (81%) using the Neuroblate system. Median OS ranged from 4.1 to 32 months and PFS from 2 to 31 months. No randomized studies were identified for inclusion. All studies had serious or critical risk of bias, and the quality of evidence was graded as very low according to the GRADE criteria. The mean complication rate was 33.7%. No quality-of-life outcomes were reported. The low quality of available evidence regarding LITT for newly diagnosed glioblastoma precluded the author's ability to draw conclusions regarding the net impact of the technology on health outcomes.

Alattar (2019) published a systematic review of stereotactic laser ablation (SLA, also known as LITT) for the treatment of brain metastases recurring after radiosurgery.[7] Thirteen publications were included. Median survival ranged from 5.8 to 19.8 months. About two-thirds of treated lesions showed pos-tablation expansion of contrast-enhancing volume and fluid-attenuated inversion recovery volume, which reached up to three times the pre-operative lesion volume, typically resolved within six months. Median hospital stay was one to two days (range one to five days), and most treated patients were discharged home (range 59.5% to 100%). The incidence of SLA-related permanent neurologic injuries was <10%. The most common complications were hemorrhage, thermal injury causing neurologic deficit, and malignant cerebral edema.

Chen (2021) published a systematic review and meta-analysis of retrospective studies and case series investigating the efficacy of LITT for brain metastases with in-field recurrence or radiation necrosis following treatment with stereotactic radiosurgery (SRS).[8] A meta-analysis of 14 studies (470 patients with 542 lesions) was performed. The overall 12-month local control rate ranged between 56.0% and 84.7% with a pooled rate of 69.0% (95% CI 60.0% to 76.7%, I^2 = 50.584%, p=0.048) and pooled overall survival of 17.15 months (95% CI 13.27 to 24.8). Among 153 recurrent brain metastasis lesions across five studies, the 12-month local control rate was 59.9% (95% CI 47.9% to 70.9%). Among 75 radiation necrosis lesions across four studies, the 12-month local control rate was 76.3% (95% CI 65.0% to 84.8%). Thus, LITT provided more favorable local control efficacy in patients with radiation necrosis compared to those with brain metastasis recurrence. No significant difference in median overall survival at one year was determined between radiation necrosis and brain metastasis groups (66.5% vs. 66.8%, p=0.978). Survival outcomes were not stratified by pathology and safety outcomes were not reported. Compared to previously reported estimates for surgical resection with a local control rate ranging from 62% to 93% and a median overall survival of 8.7 months, the authors concluded that LITT demonstrates comparable local control but a more satisfactory survival benefit. The analysis is limited by study heterogeneity, small sample sizes, and the lack of a standardized definition for local disease control.

A systematic review by Montemurro (2020) evaluated data on LITT in the treatment of recurrent glioblastoma and included data from 17 studies (n=203,219 LITT sessions).[9] The median age was 57.4 years (65.8% male). Treatment location was most commonly frontal lobe (29%), followed by temporal (23.9%), parietal (21.4%) and occipital lobes (2.6%). Thalamus, corpus callosum and cerebellum also were treated (23.1%). Morbidity was 6.4% with a median hospital stay of 3.5 days. The most common complications were seizures (2%), motor deficits (1.5%), wound infection (1.5%), transient hemiparesis (1%) and hemorrhage (0.5%). All patients underwent adjuvant chemotherapy after treatment. The median PFS and the median OS after laser interstitial thermal therapy was 5.6 months and 10.2 months, respectively. The median OS from diagnosis was 14.7 months.

A meta-analysis by de Franca (2020) evaluated LITT as a therapy for brain tumors compared to SRS based on data from 25 studies.[10] Patient populations included patients with brain metastasis and recurrent glioblastoma multiforme. A significant improvement in median overall survival was observed in patients treated with LITT compared to SRS among patients with brain metastasis (12.8 versus 9.8 months, p<0.02) and was associated with a 15% reduction in risk of adverse events overall. The authors concluded that "there is no evidence that LITT can be used as a treatment of choice when compared to SRS," and note specifically there is a “lack of systematic data that were reported in our pooled studies.” The authors do indicate the use of LITT may have a role in lowering the risk of adverse events. The analysis was limited by inclusion of heterogeneous populations, small number of patients treated with LITT (n=39), and a lack of reporting on prior treatments. Patients treated with SRS varied in their degree of radiosensitivity and prior radiation exposure, which may have influenced the higher rate of adverse events observed in this group.

A meta-analysis by Barnett (2016) compared LITT (eight studies with 77 patients) to open craniotomy (12 studies with 1,036 patients) for the treatment of high-grade gliomas in or near areas of eloquence, with a focus on adverse events.[11] Proportions of major complications occurred in 5.7% (95% CI 1.8 to 11.6) and 13.8% (95% CI 10.3 to 17.9) of patients treated via LITT and craniotomy, respectively. Studies were rated at high risk of bias due to lack of randomization and blinding. The analysis was also limited by heterogeneous patient populations (e.g., age, Karnofsky score, recurrent vs. primary disease) and lack of reporting on health outcomes.

Comparative Observational Studies

Grabowski (2022) published a multicenter, retrospective study of patients undergoing treatment for biopsy-proven brain metastasis recurrence after stereotactic radiotherapy (SRT).[12] Patients were stratified into three groups: planned LITT plus SRT (n=21), LITT alone (n=25), or repeat SRT alone (n=9). Mean patient age was 60 years (range 37 to 86) and median follow-up duration was 7.3 months (range 1.0 to 30.5). No patients in the LITT plus SRT group received prior surgery or WBRT, compared to 20% and 28% treated with LITT alone and 11% and 56% treated with SRT alone (p=0.05 and 0.01, respectively). Median time to index lesion progression for LITT plus SRT, LITT alone, and repeat SRT alone was 29.8, 7.5, and 3.7 months, respectively (p=0.022). A univariate analysis found a significantly increased risk of tumor progression among patients receiving prior surgery (hazard ratio 5.33, 95% CI 1.41 to 16.93, p=0.007). The authors noted that future prospective studies are required to validate these findings.

Fadel (2022) retrospectively reviewed an institutional database to identify patients with unifocal, lobar, surgically accessible recurrent glioblastoma who were treated with LITT or resection between 2013 and 2020.[13] Of 744 patients identified, a LITT cohort of 17 patients was compared with 23 surgical patients. Baseline characteristics were similar between groups except for average lesion size, which was smaller in patients treated with LITT (4.37 cm^3 vs. 7.54 cm^3, p=0.017). Overall survival (14.1 vs. 13.8 months, p=0.578) and PFS (3.7 vs. 3.3 months, p=0.004) were not significantly different between groups. Significantly shorter hospital stays were observed in patients treated with LITT (2.2 vs. 3.0 days, p=0.004).

Mohammadi (2019) conducted a multicenter retrospective review of survival outcomes in patients with deep seated newly diagnosed glioblastoma treated with upfront MRgLITT prior to chemo/radiotherapy (n=24, median age of 54 years, 50% male) compared to a matched cohort

of biopsy-only patients (n=24, median age of 64 years, 58% male).[14] Patients were matched based on age, gender, tumor location (deep versus lobar), and tumor volume. Median follow-up was 9.3 months (range 2 to 43 months) and 14.7 months (range 2 to 41 months) in LITT and biopsy-only cohorts, respectively. Overall median estimates of overall survival and progression-free survival in the LITT cohort was 14.4 and 4.3 months compared to 15.8 and 5.9 months for the biopsy-only cohort. Age <70 y and tumor volume <11 cm3 were identified as favorable prognostic factors for overall survival. The study was limited by its retrospective design, lack of randomization, small sample size, and short follow-up durations. Additionally, concurrent chemotherapy and radiotherapy regimens were not specified.

Single-Arm Studies

The Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN) registry is an ongoing industry-sponsored, multicenter, multinational prospective registry of the NeuroBlate device enrolling patients with primary and metastatic brain tumors, epileptic foci, and movement disorders (NCT02392078). Rennert (2019) reported procedural safety outcomes for the first 100 patients enrolled in the LAANTERN registry (42% male, 86% white), including 48 and 34 patients with primary or metastatic intracranial tumors, respectively.[15] The majority of patients (81.2%) had undergone prior surgical or radiation treatment and received LITT for a single lesion (79%). The average length of intensive care and overall hospital stays were 38.1 and 61.1 hours, respectively. A total of 11 adverse events among nine patients were observed. Five adverse events were attributed to energy deposition from laser ablation, including neurological deficits (n=2), postoperative seizures (n=2), and delayed intraparenchymal hemorrhage (n=1). One mortality occurring within 30 days of laser ablation was reported and was not attributed to LITT.

Kim (2020) reported 12-month survival and quality of life outcomes among 223 patients enrolled in the LAANTERN registry with primary (n=131) or metastatic (n=92) brain tumors who received treatment with the NeuroBlate device.[16] The majority of patents with primary tumors had high-grade glioma (n=90) and patients with metastatic disease had recurrent tumors (n=43) or radionecrosis (n=34). The one year estimated overall survival rate was 73% (95% CI 65.3% to 79.2%), which was not found to be significantly different between primary or metastatic tumors (74.6% vs. 70.7%, respectively). Quality of life assessments with the Functional Assessment of Cancer Therapy - Brain (FACT-Br) questionnaire did not meet the criteria for a clinically meaningful change (>10%) and EQ-5D questionnaires indicated an overall decline of 0.1 points from baseline. A subgroup analysis of LAANTERN data published by de Groot (2022) focused on new (n=29) and recurrent (n=60) cases of IDH wild-type glioblastoma.[17] Median OS was 9.73 months (95% CI 5.16 to 15.91) for newly diagnosed patients and 8.97 months (95% CI 6.94 to 12.36) for recurrent patients. Median OS in newly diagnosed patients receiving post-LITT chemo/radiation was 16.14 months (95% CI 6.11 to not reached).

Ahluwalia (2018) reported results from the multicenter, prospective Laser Ablation After Stereotactic Radiosurgery (LAASR) study, which assessed the efficacy and safety of LITT as salvage treatment in patients with radiographic progression after SRS for brain metastasis.[18] Forty-two patients were enrolled, including 20 patients with recurrent brain tumors, 19 patients with biopsy-proven radiation necrosis, and three patients with no diagnosis. PFS rates for patients with recurrent tumors was 54% at 12 weeks and 62% at 26 weeks. Corresponding OS rates were 71% at 12 weeks and 64.5% at 26 weeks. Of four tumor lesions that received total ablation, 3/4 achieved a complete response, compared to 0/8 that received subtotal ablation.

Patient Karnofsky performance, quality of life, and neurocognitive scores did not change significantly over the duration of survival. Overall, 35/42 (83%) patients developed adverse events, including five cases of immediate LITT-related neurological complications and 14 surgery-related adverse events.

Patel (2016) conducted a retrospective analysis of patients who underwent MRgLITT with the Visualase system at a single center in the United States between 2010 and 2014.[19] The majority of patients (87/102) were treated for intracranial tumors. Fourteen (13.7%) developed new neurological deficits following treatment, of which nine achieved complete resolution within one month, one achieved partial resolution within one month, two had no resolution at most recent follow-up, and two died without resolution of symptoms. The authors concluded that LITT, albeit minimally invasive, must be used with caution as unintended thermal damage to critical and eloquent structures may occur despite MRI guidance.

Section Summary: Primary or Metastatic Brain Tumors

Evidence for the use of LITT in primary or metastatic brain tumors includes systematic reviews and meta-analyses, one retrospective matched-cohort study (in newly diagnosed glioblastoma comparing LITT to biopsy only), and several single-arm studies. Overall survival estimates ranged from 12.8 to 14.8 months. Among patients with metastatic tumors receiving LITT following prior SRS, overall survival rates have ranged between 72% and 76% at six months and between 63% and 65% at 12 months. In a more heterogenous population of patients with primary and metastatic brain tumors who received LITT, 12-month OS rates were slightly lower in patients with brain metastases (56.3%) and high-grade glioma (43.0%) than other analyses. Systematic reviews comparing LITT to open craniotomy with resection or SRS suggest a reduced incidence of adverse events with LITT; however neurological deficits attributable to LITT-induced thermal damage have been observed despite concurrent MRI guidance. Studies are limited by high risk of bias, predominantly retrospective designs, small sample sizes, and population heterogeneity, with study subjects varying by performance status, lesion volume and location, extent of prior therapies, and extent of ablation. Prospective comparative studies in well-defined and -controlled patient populations are required to assess net health outcomes.

RADIATION NECROSIS

Systematic Reviews

Gecici (2024) conducted a systematic review and meta-analysis of 24 studies (n=547) that compared bevacizumab and LITT in patients with radiation necrosis.[20] Most of the included studies were retrospective. Symptomatic improvement or stability occurred in 87.7% and 71.2% of patients, respectively (p=0.02). Radiologic improvement or stability occurred in 86.2% and 64.7%, respectively (p=0.27). Steroid discontinuation occurred in 45% and 62.4%, respectively (p=0.90). Heterogeneity for all comparisons was high (I^2>70%). Adverse event rates were similar between groups (11.2% vs. 14.9%, p=0.66).

Vellayappan (2024) conducted a systematic review of treatments for radiation necrosis in patients who had previously undergone SRS.[21] The review was conducted on behalf of the International Stereotactic Radiosurgery Society. Of the 21 included studies, only five included LITT (n=151); one LITT study was prospective, and the rest were retrospective. The pooled radiologic improvement/stability rate was 88% (95% CI 82% to 93%) with LITT compared to 94% with bevacizumab. Symptom improvement was only reported in two studies and could not

be pooled for analysis. Toxicity results were not consistently reported, and no conclusions could be made. The authors concluded that the role of LITT is evolving and that prospective comparative studies are needed.

The meta-analysis published by Chen (2021), described previously, included 168 (35.7%) patients with radiation necrosis (RN) who received LITT following prior treatment with SRS.[8] The local control rate for patients with RN at 6 and 12 months was 83.1% (95% CI 68.4% to 91.8%) and 66.8% (95% CI 49.1% to 80.8%), respectively, and was more satisfactory compared to patients with recurrent brain metastasis. OS was 83.1% versus 69.2% at six months and 66.8% versus 66.5% at 12 months for RN and recurrent brain metastasis groups, respectively. Pre-ablation biopsy, which can accurately diagnose RN, was not routinely performed in all analyzed studies, highlighting a major limitation of this meta-analysis given that it can be quite challenging to accurately distinguish RN from brain metastases based on radiographic evidence alone.

Palmisciano (2021) published a systematic review and meta-analysis of bevacizumab versus LITT for the treatment of RN in patients with brain metastases previously treated with radiotherapy.[22] Eighteen studies were included for analysis, including 143 patients treated with bevacizumab and 148 treated with LITT. Compared to LITT, a higher proportion of patients treated with bevacizumab experienced symptomatic improvement (73.3% vs. 60.8%) and ability to wean off steroids (66.7% vs. 44.1%), but these differences were not significantly different between groups (p=0.187, I^2=54.8%, and p=0.614, I^2=25.5%, respectively). At 18 months, median OS was significantly higher for patients treated with LITT (46.4% vs. 25%, p=0.038, I^2=73.7%). Rates of adverse events were similar between bevacizumab (14.7%) and LITT (12.2%) cohorts. This analysis is limited by inclusion of primarily retrospective studies, heterogeneous study populations and treatment centers, and limited patient-level data.

Comparative Observational Studies

Sankey (2022) published a multicenter, retrospective study of SRS-treated patients with brain metastases who developed biopsy-proven RN who were treated with LITT (n=57) or medical management (n=15).[23] Median follow-up was 10.0 months (range 4.2 to 25.1 months). There was no significant difference in median OS (15.2 vs. 11.6 months, p=0.60) or freedom from local progression (13.6 vs. 7.06 months, p=0.40) in LITT or medical management cohorts, respectively. Patients were able to discontinue steroid therapy earlier in the LITT cohort at a median of 37 versus 245 days (p<0.001). The authors note that prospective trials should be designed to validate the utility of LITT for radiation necrosis, including its impact on steroid-induced morbidity.

Sujijantarat (2020) conducted a retrospective chart review comparing outcomes for patients with biopsy-confirmed RN treated with LITT (n=25) or bevacizumab (n=13) at a single center between 2011 and 2018.[24] The LITT group had a significantly longer OS compared to bevacizumab (median 24.8 versus 15.2 months, p=0.003). Time to local recurrence was not statistically significant between groups (p=0.091) but trended longer in the LITT cohort. Among 13 patients with pre-treatment symptoms in the LITT group, nine (69%) achieved symptom relief. Among 11 patients with pre-treatment symptoms in the bevacizumab group, four (36%) achieved symptom relief. No significant difference was noted between groups for the ability to wean off concurrent steroids. Given that only 50% of lesions treated with LITT were symptomatic compared to 80% of lesions treated with bevacizumab, the authors suggest that LITT treatment may be more successful before radiation necrosis lesions become

symptomatic. The study is limited by its retrospective design, small samples size, and population heterogeneity.

Hong (2019) conducted a single-center retrospective chart review of patients treated with LITT or craniotomy for previously irradiated brain metastasis, including 42 patients with recurrent brain tumors and 33 patients with RN.[25] Among the 33 RN patients, 15 received craniotomy and 18 received LITT, of which 20% and 38.9% received adjuvant post-operative bevacizumab, respectively. No significant differences for mean length of hospital stay, symptom improvement, ability to wean off steroids, or rate of perioperative complications were observed between LITT and craniotomy groups. Overall PFS for patients with RN was 73.2% and 86.7% at 24 months or patients treated with LITT and craniotomy, respectively. OS for patients with RN at 24 months was 64.6% for those receiving craniotomy and 63.2% for those receiving LITT. Study interpretation is limited by its retrospective nature and heterogeneity of prior and adjuvant treatments.

Single-Arm Studies

The LAASR study by Ahluwalia (2018), described previously,[18] included 19 patients with biopsy-confirmed radiation necrosis who received LITT following prior treatment with SRS for brain tumors. PFS and OS survival was 100% and 91%, respectively, at 12 weeks, and 100% and 82.1%, respectively, at 26 weeks. PFS was significantly higher at 12 weeks for patients with radiation necrosis compared to patients with recurrent tumors (p=0.016) but was not significantly different at 12 weeks (p=0.166). Similar trends were seen for OS in patients with radiation necrosis at 12 weeks (p=0.02) and 26 weeks (p=0.09). Thirty percent of subjects were able to stop or reduce steroid usage by 12 weeks after surgery. For patients with RN, regardless of whether a lesion was totally or subtotally ablated, LITT resulted in close to 100% lesion control and >80% survival at six months. No significant differences in Karnofsky performance status, quality of life, or neurocognitive scores were detected between subgroups.

Section Summary: Radiation Necrosis

Evidence on the use of LITT in patients with radiation necrosis includes one meta-analysis, two nonrandomized comparative studies, and one single-arm study. Studies have reported improved local control and survival outcomes in patients with radiation necrosis compared to those with brain metastases. One study comparing LITT to bevacizumab suggested that LITT treatment may be more successful among patients before radiation necrosis lesions become symptomatic. One study comparing LITT to craniotomy did not report significant survival differences between groups. One retrospective study of patients treated with LITT or medical management reported earlier steroid discontinuation with LITT but no significant differences in median OS or freedom from local progression. Studies are limited by retrospective designs, small sample sizes, population heterogeneity, and unclear relevance, as symptomatic status was not consistently reported. Prospective comparative studies in well-defined and -controlled patient populations are required to assess a net health outcome.

DRUG-RESISTANT EPILEPSY

Systematic Reviews

Ekman (2024) performed a systematic review and meta-analysis of MRgLITT compared to temporal lobe resection in patients with drug-resistant mesial temporal lobe epilepsy (mTLE).[26] Only cohort studies with a follow-up of at least 24 months were considered for

inclusion (randomized trials were excluded). Of the 55 studies in the review, 14 studies assessed MRgLITT (n=534) and 41 studies assessed temporal lobe resection (n=4,606). The primary outcome (seizure freedom, defined as the proportion of patients achieving Engel I status) was reported in six of the MRgLITT studies. A random effects model found that the proportion of patients with seizure freedom after MRgLITT was 57.1% (95% CI 51.2% to 62.7%) versus 72.5% (95% CI 65.6% to 78.5%) after temporal lobe resection (p<0.01). The overall rate of complications was 6.5% (95% CI 3.3% to 12.3%) after MRgLITT and 11.4% (95% CI 7.4% to 17.2%) after temporal lobe resection (p=0.15). There was no difference in major complications (2.7% vs. 2.0%, respectively, p=0.54) but minor complications were more common with temporal lobe resection (9.9%) than with MRgLITT (4.1%, p=0.04).

Hect (2023) conducted a systematic review of MRgLITT corpus callosum ablation for drug-resistant epilepsy.\\slcnas10\datapdx7\groups\1. Policy Work\Medicine\med177\Policy Drafts\2024 12_blank Sixteen observational reports were included (n=85 patients).[27] Seizure freedom at six months was evaluable in 53 patients and occurred at a rate of 18.87%. The rate of freedom from atonic seizures postoperatively was 46.28%. Overall, the rate in average number of seizures per day decreased by 80.12%. The complication rate was 12.94% and permanent neurologic deficits occurred in 4.71% of patients. The authors concluded that most patients experienced a meaningful decrease in seizure frequency and that LITT with an acceptable rate of complications.

Barot (2022) published a systematic review with meta-analysis of outcomes following LITT for the treatment of drug-refractory epilepsy, comparing outcomes between temporal, extratemporal epilepsies and hypothalamic hamartoma.[28] Twenty-eight studies (n=559) were included. The overall prevalence of Engel class I outcome was 56% (95% CI 0.52% to 0.60%). Hypothalamic hamartomas patients had the highest seizure freedom rate of 67% (95% CI 0.57% to 0.76%) and outcome was overall comparable between mTLE (56%, 95% CI 0.50% to 0.61%) and extratemporal epilepsy (50%, 95% CI 0.40% to 0.59%). The postoperative adverse event rate was 19% (95% CI 0.14% to 0.25%) and the most common adverse event was visual field deficits. The reoperation rate was 9% (95% CI 0.05% to 0.14%), which included repeat ablation and open resection.

Marathe (2021) conducted a systematic review and meta-analysis comparing open surgical resection, SRS, LITT, and radiofrequency ablation (RFA) in drug-resistant mTLE.[29]\\pdxnas01\DataPdx1\Saturn\Groups\MedPol\1. Policy Work\Medicine\med177\Policy Drafts\2022 12_blank Forty-one publications were included in the analysis, including 19 studies on open surgery, 11 on LITT, four on RFA, and seven on radiosurgery. The pooled seizure-free rate per person-year was 0.72 (95% CI 0.66 to 0.79) with trans-sylvian selective amygdalohippocampectomy (sAHE), 0.70 (95% CI 0.64 to 0.77) with anterior temporal lobe resection (ATL), 0.60 (95% CI 0.49 to 0.73) with transcortical sAHE, 0.59 (95% CI 0.53 to 0.65) with LITT, 0.50 (95% CI 0.34 to 0.73) with SRS, and 0.38 (95% CI 0.14 to 1.00) with radiofrequency ablation. The authors concluded that while there is no evidence to suggest that LITT is less effective than open surgical resection in the short term, long-term data are lacking and an RCT comparing LITT to open surgical methods is needed. Additionally, reporting of secondary neuropsychological and treatment-related morbidity outcomes is inconsistent and lacks standardization.

Kohlhase (2021) published a meta-analysis evaluating outcomes and complications following temporal lobe MRgLITT, RFA, and conventional surgical approaches (i.e., ATL or sAHE) for the treatment of drug-refractory mTLE.[30] Forty-three studies (13 MRgLITT, 6 RFA, and 24

surgery studies) of 554, 123, 1,504, and 1,326 patients treated by MRgLITT, RFA, ATL, or sAHE, respectively, were included in the review. Engel Class I (Engel-I) outcomes were achieved after MRgLITT in 57% (315/554, range 33.3% to 67.4%), RFA in 44% (54/123, range 0% to 67.2%), ATL in 69% (1,032/1,504, range 40% to 92.9%), and sAHE in 66% (887/1,326, range 21.4% to 93.3%). No significant difference in seizure outcome between MRgLITT and RFA (Q=2.74, p=0.098) was found, however, ATL and sAHE were both superior to MRgLITT (ATL: Q=8.92, p=0.002; sAHE: Q=4.33, p=0.037) with better outcomes in patients at follow-up of 60 months or more. The rate of major complications was 3.8% for MRgLITT, 3.7% for RFA, 10.9% for ATL, and 7.4% for sAHE; none of these frequencies were statistically significantly different. While the severity of cognitive impairment was not evaluated across treatment groups directly, the authors note that cognitive impairment following intervention appears to increase with the invasiveness of the respective intervention. The authors conclude “patients undergoing MRgLITT may experience fewer major complications compared to ATL or sAHE and might have a more beneficial neuropsychological outcome.”

Kerezoudis (2021) published a meta-analysis aimed at quantifying the relationship of LITT ablation volume with postoperative outcomes in temporal lobe epilepsy.[31] A total of 13 studies (551 patients) were analyzed. Meta-regression of seizure freedom rate for the overall cohort and mesial temporal sclerosis subset (n=384) was performed adjusting for overall ablation volume as well as percentage of hippocampal and amygdala ablation. Overall seizure freedom rate was 58% (95% CI 54% to 62%) and was not significantly associated with total ablation volume (p=0.42), hippocampal ablation (p=0.67), or amygdala ablation (p=0.33). Seizure freedom rate for patients with mesial temporal sclerosis was 66% (95% CI 58% to 74%) and was also not found to be significantly associated with total ablation volume (p=0.15), hippocampal ablation (p=0.73), or amygdala ablation (p=0.43). Overall complication rate was 17% (95% CI 13% to 22%).

Wang (2021) published a systematic review of data on LITT, SRS, radiofrequency thermocoagulation (RF-TC), and focused ultrasound for the treatment of mTLE.[32] Data from 19 publications were included with 1094 patients (LITT: 434, SRS: 81, RF-TC: 402, cortico-amygdalohippocampectomy (CAH): 153, and selective amygdalohippocampectomy (SelAH): 24). At six months postoperatively, LITT (9/19) Engel I outcomes ranged from 52% to 80%. Seizure freedom was similar between LITT studies and to rates achieved by CAH and SelAH, however, no direct comparisons were available. Common complications included transient postprocedure headaches (LITT: 0.4% to 27%, SRS: 15% to 70%, and RF-TC: 23%) and visual field deficits (LITT: 3% to 40%, SRS: 34% to 50%, and RF-TC: 2% to 5%).

Brotis (2021) conducted a meta-analysis to estimate the efficacy of LITT for mTLE.[33] Sixteen retrospective case series published between 2012 and 2019 representing 575 patients (range 1 to 231) were identified. Overall, seizure freedom was achieved in 54.7% (95% CI 50.6% to 58.8%, I^2=18.7%) of patients undergoing LITT with a median follow-up duration of 18 months (IQR 12 to 26 months). Sensitivity analyses yielded similar results. Four studies representing 150 patients indicated that the prevalence of Engel Class IA outcomes decreased with time, estimated at 64.2%, 46.9%, and 42.4% at 12-, 24-, and 36-month follow-up, respectively. The overall quality of evidence was regarded as 'very low' according to GRADE recommendations, with only four studies included more than 20 patients. The authors concluded that while mTLE resective surgeries are invasive and irreversible, they offer better seizure control rates, with previously reported seizure-free rates ranging from ranging from 60% to 90% for mTLE.

Grewal (2019) published a meta-analysis comparing MRgLITT versus SRS for medically intractable temporal lobe epilepsy.[34] A total of 19 studies published between 2008 and 2018 representing 404 patients (range 5 to 58) were identified, including nine retrospective studies on LITT (n=239). The overall seizure freedom rate was not found to be significantly different between LITT (50%, 95% CI 44% to 56%) and SRS (42%, 95% CI 27% to 59%; p=0.39), nor was it significantly different for patients with lesional conditions (62%, 95% CI 48% to 74% vs. 50%, 95% CI 37% to 64%, p=0.23). While LITT was associated with a significantly lower procedural complication rate (20% vs. 26%, p=0.06), reoperation rates were not significantly different (15% vs. 27%, p=0.31). The authors noted that the quality of evidence was low and that large-scale comparative studies directly comparing LITT and SRS are required to validate findings.

Xue (2018) reported postoperative outcomes for MRgLITT in the treatment of drug-resistant epilepsy.[35] Sixteen nonrandomized studies published between 2014 and 2018 representing 269 patients (range 5 to 30) were included in the meta-analysis. The prevalence of Engel Class I, II, III, and IV outcomes was 61%, 12%, 16%, and 15%, respectively. The prevalence of postoperative complications was 24% (95% CI 16% to 32%). Interpretation of outcomes is limited by small study size and short follow-up durations (range 7 days to 51 months).

Comparative Observational Studies

Hale (2019) reported postsurgical outcomes in 26 pediatric patients with insular epilepsy treated with LITT (n=14) or open resection (n=12).[36] Mean follow-up was 2.43 years. Engel Class I outcomes were achieved in 43% of patients treated with LITT compared to 50% who underwent open insular resection at one year post-surgery. Postoperative complications occurred in six patients treated with LITT and seven patients treated with resection, all of which resolved within three to four months. The authors conclude that further studies are needed to determine the noninferiority of LITT with respect to resection in terms of complication rates and seizure freedom, especially in cases of cortical dysplasia that may involve extensive regions of the brain.

Petito (2018) published a retrospective, single center analysis of 100 consecutive neurosurgeries performed between 2013 and 2015 in patients with drug-resistant epilepsy, representing 33 LITT procedures and 21 open resections with mean follow-up durations of 21.7 and 21.3 months, respectively.[37] A discrete lesion was radiographically identified in 85% of patients treated with LITT and 65% of patients treated with resection. The mean post-operative hospital length of stay was significantly shorter for LITT compared to resection (1.18 versus 3.43 days, p=0.0002). Patients treated with resection were significantly younger, with a mean age of 35.4 years (p=0.001). At 12 months, seizure freedom was achieved in 56.3% (95% CI 39.3% to 71.8%) and 60% (95% CI 38.7% to 78.12%) of patients treated with LITT and resection, respectively (p=0.79). Among patients with focal lesions, the seizure freedom outcomes were not significantly different between groups (p=0.21). For non-lesional patients, LITT treatment trended towards a better outcome, but did not achieve statistical significance (p=0.05). Study interpretation is limited by small sample size, retrospective analysis, and population heterogeneity.

Single-Arm Studies

Esmaeili (2023) published a prospective observational study of consecutive LITT-treated patients with drug-resistant epilepsy from 2013 to 2021.[38] The primary outcome was sudden unexpected death in epilepsy (SUDEP). There were four SUDEP cases among 135 patients

over a median duration of 3.5 years (range 0.1 to 9.0) for an estimated SUDEP incidence of 8 per 1,000 person-years. Among a historical control group, the incidence of SUDEP was estimated to be 2 per 1,000 person-years in patients who underwent resection surgery and 6.1 per 1000 years in patients who did not receive surgical intervention but were candidates. Thus, LITT-treated patients had significantly higher SUDEP incidence compared with surgery (p=0.02), but similar rates compared with those without intervention (p=0.55).

Kanner (2022) conducted a retrospective review of long-term seizure and psychiatric outcomes among patients who underwent LITT for drug-resistant mTLE between 2013 and 2019 at a single academic center.[39] Forty-eight patients (mean age 43 years) were identified with a mean follow-up duration of 50 ± 20.7 months (range 18 to 81). Engel class I outcomes were achieved in 29 (60.4%) subjects and 11 (22.9%) reported one to three seizures per year. The seizure-freedom rate was 77.8% among patients with 24-month follow-up which decreased to 50% among patients with >61-month follow-up data. Seizure freedom was associated with mesial temporal sclerosis, no pre-treatment focal to bilateral tonic-clonic seizures, and no psychopathology in the last follow-up year. Mood and/or anxiety orders were identified in 30 (62.5%) of patients pre-surgery, of which 19 (62%) remitted following LITT.

Landazuri (2020) reported one-year outcomes following LITT of epileptogenic foci with the NeuroBlate system in patients with drug resistant epilepsy enrolled in the previously described LAANTERN registry study by Rennert (2019).[15, 40] Engel Class I outcomes were achieved in 27/42 (64.3%, 95% CI 48.0% to 78.5%) patients at one year. No significant difference was observed in patients with mTLE (70.8%) versus other etiologies. Five adverse events were reported, with one categorized as serious. Median baseline QOLIE-31 was 51.7 (range 8.7 to 77.3). Median scores increased by 14.1 points reflecting a 72.4% improvement (95% CI 52.8% to 87.3%) in quality-of-life measures. However, the total score change was not statistically significant (p=0.217). Seizure worry and social functioning sub-scores were considered statistically significant (p=0.0219 and p=0.0175, respectively). The authors note that the primary success of LITT remains in well localized lesions/localizations, such as those seen in mTLE/mesial temporal sclerosis, cortical dysplasia, and hypothalamic hamartoma.

Wu (2019) published the results of a multicenter, retrospective cohort study of 234 patients with drug-resistant mTLE who underwent LITT between 2011 and 2017.[41] At both one and two years after LITT, 58% of patients achieved Engel I outcomes. Engel I outcomes were associated with ablations involving more anterior, medial, and inferior temporal lobe structures, which tended to involve greater amygdalar volume. Presence or absence of hippocampal sclerosis did not have a significant effect on seizure outcomes. Overall, Engel I or II outcomes were achieved by 76.9% patients at the time of last follow-up. A total of 42 complications were observed in 35 patients, of which 34 persisted at last follow-up.

Section Summary: Drug-Resistant Epilepsy

The evidence for the use of LITT in drug-resistant epilepsy includes several large systematic reviews (n>500 patients treated with LITT) and meta-analyses, nonrandomized comparative studies, and single-arm studies. Meta-analyses have reported seizure freedom rates ranging from 50 to 61% and six months postoperatively, Engel I outcomes have been observed between 52% to 80%. Nonrandomized studies comparing outcomes following LITT to open resection or radiofrequency ablation have reported comparable outcomes in patients with drug-refractory mTLE. A subsequent meta-analysis concluded that while there is no evidence to suggest LITT is less effective than open surgical resection in the short term, long-term data are

lacking. Total quality of life scores reported in the ongoing LAANTERN registry study increased by 72.4%, however this change did not reach statistical significance (p=0.2173).

PRACTICE GUIDELINE SUMMARY

AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS

In September 2021, the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) Joint Section on Tumors issued a position statement regarding the use of LITT for brain tumors and radiation necrosis.[42] The statement concludes that "LITT is an appealing option because it offers a method of minimally invasive, targeted thermal ablation of a lesion with minimal damage to healthy tissue. There is a growing body of evidence to demonstrate that LITT is an effective and well tolerated cytoreductive option for treatment of [newly diagnosed gliobastoma multiforme (GBM), recurrent GBM, and primary or recurrent brain metastases.] Intracranial LITT is also an effective option for addressing radiation necrosis with an overall reduction in steroid dependence for these patients. Especially in instances where the therapeutic window is narrowed such that craniotomy is not a viable option, LITT can play an important role in treatment for glioma or metastatic brain cancer."

AMERICAN SOCIETY OF SURGICAL ONCOLOGY, SOCIETY FOR NEURO-ONCOLOGY, AND AMERICAN SOCIETY FOR RADIATION ONCOLOGY

In 2021, the American Society of Clinical Oncology (ASCO) issued a joint evidence-based guideline on the treatment of brain metastases with the Society for Neuro-Oncology (SNO) and the American Society for Radiation Oncology (ASTRO).[43] The guideline stated that "no recommendation can be made for or against laser interstitial thermal therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: none)."

AMERICAN SOCIETY FOR STEREOTACTIC AND FUNCTIONAL NEUROSURGERY

In September 2021, the American Society for Stereotactic and Functional Neurosurgery (ASSFN) issued a position statement on the use of LITT in drug-resistant epilepsy.[44] The statement recommends consideration of MRgLITT as a treatment option when all of the following criteria are met:

- "Failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling, localization-related epilepsy AND
- Well-defined epileptogenic foci or critical pathways of seizure propagation accessible by MRgLITT."

CONGRESS OF NEUROLOGICAL SURGEONS

The Congress of Neurological Surgeons (CNS) guidelines for the treatment of adults with metastatic brain tumors (2019) state that "there is insufficient evidence to make a recommendation regarding the routine use of laser interstitial thermal therapy (LITT), aside from use as part of approved clinical trials."[45]

INTERNATIONAL STEREOTACTIC RADIOSURGERY SOCIETY

In 2024, the International Stereotactic Radiosurgery Society published recommendations for managing radiation necrosis after stereotactic radiosurgery.[21]\\slcnas10\datapdx7\groups\1. Policy Work\Medicine\med177\Policy Drafts\2024 12_blank Patients with corticosteroid-refractory symptoms can be considered for LITT based on low quality evidence (weak recommendation). The suggested management flowchart includes LITT as a treatment option for patients with refractory symptoms after noninvasive therapy such as bevacizumab or hyperbaric oxygen therapy, and as first-line or second-line therapy for patients with more severe symptoms who require invasive treatment.

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for central nervous system cancers (v.4.2024) states that MRgLITT "may be considered for patients who are poor surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases, radiation necrosis, glioblastomas and other gliomas." (Category 2B)[46]

SUMMARY

Studies comparing laser interstitial thermal therapy (LITT) to open resection or radiofrequency ablation have found comparable outcomes in the treatment of drug-resistant epilepsy. In addition, there is evidence that this treatment approach may be associated with fewer major complications and improved cognitive outcomes than open approaches. Evidence-based clinical practice guidelines recommend LITT for the treatment of drug-resistant epilepsy when criteria are met. Therefore, LITT for the treatment of drug-resistant epilepsy may be considered medically necessary when there is documentation of disabling seizures despite use of two or more antiepileptic drug regimens (i.e., medically refractory epilepsy) and there is a well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus. The evidence for the use of LITT for all other neurological indications is limited by retrospective designs, small sample sizes, and population heterogeneity. In addition, neurological deficits attributable to LITT-induced thermal damage have been observed despite concurrent MRI guidance. The evidence is insufficient to determine that the use of LITT results in an improvement in the net health outcome for these patients. Therefore, LITT is considered investigational for all other neurological indications, including but not limited to treatment of primary or metastatic brain tumors or radiation necrosis.

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CODES

Codes	Number	Description
CPT	61736	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion
	61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; multiple trajectories for multiple or complex lesion(s)
	64999	Unlisted procedure, nervous system
HCPCS	None	

Date of Origin: *December 2021*

Regence

Medical Policy Manual Radiology, Policy No. 38

Wireless Capsule Endoscopy for Gastrointestinal (GI) Disorders

Effective: October 1, 2024

Next Review: January 2025
Last Review: September 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 wireless capsule endoscopy (CE) uses a noninvasive device to visualize segments of the gastrointestinal (GI) tract. Patients swallow a capsule that records images of the intestinal mucosa as it passes through the GI tract. The capsule is collected after being excreted and images interpreted.

MEDICAL POLICY CRITERIA

I. Wireless capsule endoscopy of the ***small bowel*** may be considered **medically necessary** for one or more of the following:

   A. Evaluation of suspected small bowel bleeding when both of the following Criteria (1. and 2.) are met:

      1. Prior upper and lower gastrointestinal (GI) endoscopic studies performed during the current episode of illness are inconclusive; and

      2. Clinical documentation of suspected gastro-intestinal bleeding including anemia (e.g., iron-deficiency anemia and/or positive fecal occult blood test, or visible bleeding) is provided.

   B. Evaluation of Crohn's disease when either of the following are met:

      1. Re-evaluation in diagnosed Crohn's disease, when there are unexpected

change(s) in the course of disease or response to treatment, suggesting the initial diagnosis may be incorrect and reexamination may be indicated.

2. Initial diagnosis in suspected Crohn's disease when both of the following Criteria (a. and b.) are met:

   a. Clinical documentation of abdominal pain or diarrhea, plus 1 or more signs of inflammation (e.g., fever, elevated white blood cell count, elevated erythrocyte sedimentation rate, elevated C reactive protein, bleeding, terminal ileitis, or other signs of inflammation that are non-diagnostic on conventional tests) is provided; and

   b. The diagnosis has not been previously confirmed by conventional diagnostic tests. Conventional tests may include one or more of the following: small bowel follow-through, upper and lower endoscopy, MR enterography or CT enterography.

C. Surveillance of the small bowel in patients with hereditary GI polyposis syndromes, including familial adenomatous polyposis and Peutz-Jeghers syndrome.

D. Evaluation of celiac disease when either of the following are met:

1. Individuals with clinical evidence of celiac disease and positive celiac-specific serology when upper endoscopy with biopsy is not indicated.

2. Re-evaluation of individuals with celiac disease who remain symptomatic despite treatment.

II. Wireless capsule endoscopy is considered **investigational** for evaluation of the small bowel not meeting Criterion I. and for all other indications, including but not limited to:

A. Evaluation of the extent of involvement of known Crohn's disease or ulcerative colitis.

B. Evaluation of the esophagus, including in patients with gastroesophageal reflux or other esophageal pathologies.

C. Evaluation of other GI diseases and conditions not presenting with GI bleeding, including but not limited to the following: irritable bowel syndrome, hereditary *non*polyposis syndromes (including but not limited to Lynch syndrome), small bowel neoplasm, portal hypertensive enteropathy, and unexplained chronic abdominal pain.

D. Evaluation of the colon, including but not limited to detection of colonic polyps or colon cancer.

E. Initial evaluation of patients with acute upper GI bleeding.

F. Evaluation of patients with evidence of lower GI bleeding, including in the context of major risks for colonoscopy or moderate sedation.

G. Evaluation of patients following incomplete colonoscopy.

III. The patency capsule is considered **investigational** for all indications, including to evaluate patency of the GI tract before wireless capsule endoscopy.

IV. Magnetic capsule endoscopy is considered **investigational** for all indications including but not limited to the evaluation of patients with unexplained upper abdominal

complaints.

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.

1. Medical records related to Criterion I. above:
    - History and physical/chart notes
    - Description of suspected disorder

2. Additional medical records related to Criterion I. above, examples include:
    - Previous imaging or diagnostic testing results, if any
    - Documentation of signs of inflammation that are non-diagnostic on conventional tests, if relevant
    - Conservative treatment provided, if any
    - Genetic syndrome testing, if relevant.

CROSS REFERENCES

1. Ingestible pH and Pressure Capsule Medicine, Medicine, Policy No. 117

BACKGROUND

WIRELESS CAPSULE ENDOSCOPY

Capsule endoscopy (CE) is performed using a disposable imaging capsule which is ingested by the patient. The capsule measures 11 by 30 mm and contains video imaging, self-illumination, and image transmission modules, as well as a battery supply that lasts up to eight hours. The indwelling camera takes images at a rate of up to 35 frames per second as peristalsis carries the capsule through the gastrointestinal tract. The average transit time from ingestion to evacuation is 24 hours. The device uses wireless radio transmission to send the images to a receiving recorder device that is worn around the waist. This receiving device also contains sensors that can roughly gauge where the image was taken over the abdomen. Images are then downloaded onto a workstation for viewing and processing.

Capsule endoscopy has been proposed as a method for identifying Crohn's disease. There is no single criterion standard diagnostic test for Crohn's disease; rather, diagnosis is based on a corroboration of findings.[1] Thus it is difficult to identify a unique reference standard for the diagnosis of CD.

Gastrointestinal tract obstruction is a contraindication for CE. Patients who are at risk for obstruction, have swallowing disorders, pacemakers or other implanted cardiac devices, or are pregnant and should have careful evaluation by a specialist before undergoing a CE procedure. In addition, contraindications to capsule endoscopy are also noted by manufacturers and may include, but are not limited to, known or suspected GI obstruction/

obstacles, fistulae, relevant (small bowel) diverticulosis, motility disorder, cardiac pacemakers or other implanted electromedical devices, and age-specific contraindications.[2, 3]

MAGNETIC CAPSULE ENDOSCOPY

The U.S. Food and Drug Administration (FDA) approved a novel magnetically maneuvered CE system (NaviCam™; AnX Robotica, Inc.) in May 2020.[4] This system consists of a single-use ingestible capsule and magnet linked to a physician-operated console. The capsule contains a camera that wirelessly captures images of the desired anatomy. The console allows the operator to control the motion and direction of the capsule, ensuring visualization of the entire stomach. The system is non-invasive, does not require sedation, and has a procedural time of approximately 15 to 20 minutes. The capsule leaves the body in 24 hours on average but may take as long as two weeks. The device is contraindicated for use in patients with gastrointestinal obstruction, stenosis, fistula, or those with dysphagia. Other contraindications include patients with cardiac pacemakers or other implantable electronic medical devices as well as pregnant women, those <22 years of age, and those with a body mass index ≥38 kg/m^2.

REGULATORY STATUS

Table 1 summarizes some of the wireless CE devices with clearance by the FDA.

Code: NEZ

Table 1. Wireless Capsule Endoscopy Devices Cleared by the U.S. Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Pillcam SB 3 Capsule Endoscopy System, Pillcam Software 9.0e	Given Imaging Ltd.	8/27/2021	K211684	For visualization of the small bowel mucosa. It may be used in the visualization and monitoring of: lesions that may indicate Crohn's disease not detected by upper and lower endoscopy; lesions that may be a source of obscure bleeding not detected by upper and lower endoscopy; lesions that may be potential causes of iron deficiency anemia not detected by upper and lower endoscopy.
NaviCam Stomach Capsule System	AnX Robotica, Inc.	5/22/2020	K203192	For visualization of the stomach of adults (≥22 years) with a body mass index <38. The system can be used in clinics and hospitals, including emergency room settings.
CapsoCam Plus (SV-3)	CapsoVision Inc.	4/19/2019	K183192	For visualization of the small bowel mucosa in adults. It may be used as a tool in the detection of abnormalities of the small bowel.
Olympus Small Intestinal Capsule Endoscope System	Olympus Medical Systems Corp.	3/5/2019	K183053	For visualization of the small intestine mucosa. Intended for use in adults only.
MiroCam Capsule Endoscope System	IntroMedic Co. Ltd.	11/8/2018	K180732	May be used as a tool in the detection of abnormalities of the small bowel and this device is

Device	Manufacturer	Date Cleared	510(k) No.	Indication
				indicated for adults and children from 2 years of age.
Olympus Small Intestinal Capsule Endoscope System	Olympus Medical Systems Corp.	3/13/2018	K173459	May be used in the visualization and monitoring of lesions that may indicate Crohn's disease not detected by upper and lower endoscopy. - It may be used in the visualization and monitoring of lesions that may be a source of obscure bleeding (either overt or occult) not detected by upper and lower endoscopy. It may be used in the visualization and monitoring of lesions that may be potential causes of iron deficiency anemia (IDA) not detected by upper and lower endoscopy. The Red Color Detection Function is intended to mark frames of the video suspected of containing blood or red areas.
PillCam Patency System	Given Imaging Ltd.	3/8/2018	K180171	Intended to verify adequate patency of the gastrointestinal tract prior to administration of the PillCam video capsule in patients with known or suspected strictures.
MiroCam Capsule Endoscope System	IntroMedic Co. Ltd.	1/30/2018	K170438	For visualization of the small intestine mucosa.
PillCam SBC capsule endoscopy system PilCam Desktop Software 9.0	Given Imaging Ltd.	9/1/2017	K170210	For visualization of the small intestine mucosa.
RAPID Web	Given Imaging Ltd.	5/26/2017	K170839	Intended for visualization of the small bowel mucosa.
AdvanCE capsule endoscope delivery device	United States Endoscopy Group Inc.	3/10/2017	K163495	Intended for visualization of the small bowel mucosa.
Olympus Small Intestinal Capsule Endoscope System	Olympus Medical Systems Corp.	1/19/2017	K163069	Intended for visualization of the small bowel mucosa.
CapsoCam Plus (SV-3) Capsule Endoscope System	CapsoVision Inc	10/21/2016	K161773	Intended for visualization of the small bowel mucosa.
CapsoCam (SV-1)	CapsoVision Inc.	2/9/2016	K151635	For use in diagnosing disorders of the small bowel, esophagus, and colon.
PillCam COLON2	Given® Imaging	1/14/2016	K153466	Detection of colon polyps in patients after an incomplete colonoscopy and a complete evaluation of the colon was not technically possible, and for detection of colon polyps in patients with evidence of GI bleeding of lower GI origin with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy or moderate sedation in the event a clinically

Device	Manufacturer	Date Cleared	510(k) No.	Indication
				significant colon abnormality was identified on capsule endoscopy.
MiroCam Capsule Endoscope System	INTROMEDIC CO. LTD	3/17/2015	K143663	Intended for visualization of the small bowel mucosa.
Endocapsule software 10 and light	Olympus Medical Systems Corp.	2/8/2015	K142680	Intended for visualization of the small bowel mucosa.

GI: gastrointestinal.

EVIDENCE SUMMARY

STUDY SELECTION CRITERIA

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operator curve, area under the receiver operator curve, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

SUSPECTED SMALL BOWEL BLEEDING

The purpose of wireless capsule endoscopy (CE) for patients who have suspected small bowel bleeding is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

Systematic Reviews

Tables 2 and 3 summarize the characteristics and results of a systematic review (SR), which evaluated a number of case series that compared the diagnostic accuracy of CE with alternative procedures such as intraoperative endoscopy or mesenteric angiography.

Table 2. Characteristics of Systematic Reviews Evaluating Capsule Endoscopy for Iron-Deficient Anemia

Study	Dates	Trials	Participants	N (Range)	Design	QUADAS Assessment of Included Trials
Koulaouzidis (2012)[5]	2004-2011	24	Patients with iron-deficiency anemia who had SBCE and at least 1 lower and upper GI endoscopy prior to CE	1960 (35 to 652)	Observational	Low-to-moderate quality

CE: capsule endoscopy; GI: gastrointestinal; SBCE: small bowel capsule endoscopy.

Table 3. Results of Systematic Reviews Evaluating Capsule Endoscopy for Iron-Deficient Anemia

Study	Overall Diagnostic Yield[a]	Diagnostic Yield of Patients With IDA[b]	I^2, %	Diagnostic Yield, n (%)[c]
Koulaouzidis (2012)[5]				
Total N	1960	264		• Angioectasias: 293 (45.9) • Inflammatory lesions: 126 (19.7) • Polyp/mass lesions: 42 (6.6) • Not classified: 177 (27.7)
Pooled effect (95% CI), %	47 (42 to 52)	66.6 (61.0 to 72.3)	78.8	
p			<0.001	

CI: confidence interval; IDA: iron-deficient anemia.
[a] Per-patient analysis.
[b] From 4 studies (n=264 patients; 13.47% of total).
[c] Patients with positive Small Bowel Capsule Endoscopy findings.

Randomized Controlled Trials

A small randomized controlled trial (RCT) compared CE with mesenteric angiography in patients with acute melena or hematochezia. While CE had a higher diagnostic yield, secondary outcomes such as transfusion, hospitalization, and mortality did not differ significantly between groups. Tables 4 and 5 summarize the characteristics and results of selected RCTs.

Table 4. Characteristics of RCT Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Leung (2012)[6]	China	1	2005-2007	Consecutive adults with active overt obscure GI bleeding	30 randomized to CE	30 randomized to mesenteric angiography

CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial.

Table 5. Results of RCT Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Diagnostic Yield (95% CI), %[a]	Rebleeding Rates (95% CI), %	Hospitalization Rate, n (%)	Transfusion Rate, n (%)	Mean Follow-Up (SD), mo.
Leung (2012)[6]					
CE	53.3 (36.1 to 69.8)	16.7 (7.3 to 33.6)	5 (16.7)	3 (10)	48.5 (20.9)
Angiography	20 (9.5 to 37.3)	33.3 (19.2 to 51.2)	5 (16.7)	3 (10)	
Difference	33.3 (8.9 to 52.8)	16.7 (-5.3 to 36.8)			
p	0.016	0.23	1.0	1.0	

CI: confidence interval; CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial; SD: standard deviation.
[a] Percentage identified with a high probability of bleeding.

The purpose of the limitations tables (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 each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 6. Study Relevance Limitations of RCT Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Leung (2012)[6]	2. It is possible patients with moderate bleeding would not undergo angiography in a clinical setting 4. Patients with overt but nonmassive bleeding may not be ideal for CE or angiography		2. A criterion standard is lacking for evaluation of obscure GI bleeding		

CE: capsule endoscopy; GI: gastrointestinal; RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations of RCT Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Leung (2012)[6]					3. Study underpowered to detect significant difference in clinical outcome	

GI: gastrointestinal; RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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] 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.

Case Series

Tables 8 and 9 summarize the characteristics and results of selected case series.

Table 8. Characteristics of Case Series Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Country	Participants	Treatment Delivery	Follow-Up mo (Range)
Hartmann (2005)[7]	Germany	47 patients >18 y with obscure GI bleeding	Patients received CE and criterion standard, intraoperative endoscopy	NR
Pennazio (2004)[8]	Italy	100 patients ≥18 y with obscure GI bleeding	51 patients received CE and PE before or after the procedure	Mean: 18 (5 to 25)

CE: capsule endoscopy; GI: gastrointestinal; NR: not reported; PE: push enteroscopy.

Table 9. Results of Case Series Evaluating Capsule Endoscopy for Obscure GI Bleeding

Study	Treatment	Locating Bleeding With CE, %		Diagnostic Yield for Positive Lesions, %	PPV of CE, %
		Sensitivity	Specificity[a]		
Hartmann (2005)[7]	CE and intraoperative endoscopy	95	75	Both procedures: 76.6	95
Pennazio (2004)[8]	CE and PE	89	95	67 (95% CI, 54 to 80)	97

CE: capsule endoscopy; CI: confidence interval; NPV: negative predictive value; PE: push enteroscopy; PPV: positive predictive value.
[a] CE results confirmed by intraoperative endoscopy or other reference standards.

Section Summary: Suspected Small Bowel Bleeding

A small RCT compared CE with mesenteric angiography in patients with acute melena or

hematochezia. While CE had a higher diagnostic yield, secondary outcomes such as transfusion, hospitalization, and mortality did not differ significantly between groups. A large number of uncontrolled studies have evaluated the use of CE in the evaluation of patients with suspected small bowel bleeding. These studies have consistently reported that a substantial proportion of patients receive a definitive diagnosis following this test when there are few other diagnostic options. A meta-analysis of 24 studies estimated that the diagnostic yield in this patient population was approximately half of the included patients and was higher in patients with documented iron-deficiency anemia. Capsule endoscopy appears to locate the source of bleeding at least as well as other diagnostic methods and direct treatment to the source of bleeding.

ESTABLISHED CROHN'S DISEASE

The purpose of wireless CE for patients who have an established diagnosis of Crohn's disease (CD) is to inform management decisions based on disease status.

Systematic Reviews

Tamilarasan (2022) published a SR with meta-analysis to compare the diagnostic accuracy of panenteric capsule endoscopy (PCE) with endoscopic evaluation, intestinal ultrasound (IU) or magnetic resonance enterography (MRE) in patients with inflammatory bowel disease (IBD).[9] Fourteen studies were included (seven for CD and seven for Ulcerative Colitis [UC])). For CD, PCE had an increased diagnostic yield of 5% and 7% compared with MRE and colonoscopy, respectively. With a pooled odds ratio (OR) of 1.25 (95% CI, 0.85 to 1.86%) for the detection of CD. Panenteric capsule endoscopy had a diagnostic sensitivity for the detection of UC of 93.8% (95% CI, 87.6 to 97.0%) and a specificity of 69.8% (95% CI, 38.2 to 89.6%). The authors concluded that there remains a lack of standardization of PCE scoring systems and a lack of transmural assessment for diagnosing CD. In UC, PCE has an excellent diagnostic sensitivity and positive predictive value, limitations to its use include the lack of histologic assessment and poor specificity.

Kopylov (2017) published a SR of data evaluating the diagnostic yield (DY) of CE in detection and monitoring of small bowel for CD.[10] Reviewers included prospective studies comparing CE with MRE and/or small bowel contrast ultrasound (SICUS) in patients who had suspected and/or established CD. Studies were generally of good quality with low risk of bias. The DY of CE for detection of active SB CD was similar to that of MRE (10 studies, 400 patients, OR 1.17; 95% CI 0.83 to 1.67) and SICUS (5 studies, 142 patients, OR 0.88; 95% CI 0.51 to 1.53). The outcomes were similar for the subgroups of suspected versus established CD and adult versus pediatric patients. CE was superior to MRE for proximal SB CD (7 studies, 251 patients, OR 2.79; 95% CI 1.2 to 6.48). No significant difference between CE and SICUS was found.

Non-Randomized Studies

Calabrese (2022) completed a retrospective, matched cohort analysis to compare clinical outcomes between CE and standard of care (SOC), ileocolonoscopy/MRE in patients with suspected CD.[11] A total of 100 cases were included in the analysis (50 per arm, matched for demographics and clinical characteristics). Overall there were no significant differences in biologics and surgery in either group. The authors indicate that an analysis by disease location (L1-L4) resulted in less biologics and surgery in the L4 diagnosis only. No difference was found

between groups in flare occurrence and duration. The authors conclude that more extensive, prospective, multicentre, randomized studies are needed.

Kawano (2022) published a retrospective study to evaluate the safety and efficacy of CE and analyze patient characteristics, clinical course, characteristics of CE, and safety and efficacy of CE in newly diagnosed CD patients (n=32).[9] Patency Capsules (PC) were performed in 26 (81%) of patients. The total small intestine was observed in 93% of patients and there were two reported adverse events (unable to swallow the capsule and capsule retention). The authors point out that the capsule retention occurred in a patient that did not undergo PC. No abnormality was identified by ileocolonoscopy in 46% (15/32), and transition of small bowel lesions (TSL) was found in 35% (12/34) of the patients. The most common CE findings were erosions (n=23), followed by ulcers (n=21), and cobble stone appearance (n=9). Some limitations include retrospective design, small sample size, safety maybe misrepresented as those with prior diagnosed stenosis were likely not provided CE.

Elosua (2022) evaluated the therapeutic impact of CE in patients with established Crohn's CD in a retrospective, single-center study.[12] Therapeutic impact was defined as change in CD-related treatment recommended based on CE results. A total of 305 patients (n=432 procedures) with established CD who underwent a CE procedure between January 2008 and December 2019 were included. Of the included CE procedures, 87.5% were deemed conclusive. Mild inflammation was detected in 41.6% of patients and moderate-to-severe activity was detected in 21.9% of patients. Management changes guided by CE procedures occurred in 51.3% of procedures, with 46.1% of procedures leading to treatment escalation and 5.3% of procedures leading to de-escalation. Disease activity demonstrated by CE results was correlated with therapeutic changes. Mucosal healing assessed via CE was the only independent factor that predicted therapy de-escalation (OR, 6.86; 95% CI 1.42 to 33). The single-center group of clinicians limited heterogeneity. These results are limited by the retrospective design of the study.

Bruining (2020) reported results from the multicenter, prospective BLINK trial comparing the diagnostic accuracy of CE to ileocolonoscopy and/or MRE in patients with established CD.[13] The per-protocol analysis included 99 of 158 enrolled subjects with 16 patients tested by all three modalities. Major reasons for exclusion from analysis included patency failure or MRE stricture and major protocol violations. The reference standard was defined as the presence or absence of inflammation as designated by the modality-specific scoring system at prospective interpretation by expert central readers. In cases of discrepant findings for any bowel segment, all modalities were reviewed and resolved by a consensus panel consisting of three gastroenterologists. Overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 94% (95% CI 86% to 98%), 74% (95% CI 55% to 87%), 91% (95% CI 82% to 96%), and 83% (95% CI 64% to 94%) for CE compared to 100% (95% CI 95% to 100%), 22% (95% CI 10% to 41%), 77% (95% CI 68% to 85%), and 100% (95% CI 54% to 100%) for ileocolonoscopy and/or MRE. Sensitivity of CE was significantly higher compared to MRE for enteric inflammation in the proximal small bowel (97% vs. 71%, p=0.021) and similar in the terminal ileum and colon (p=0.500 to 0.625). Discrepant reads between the proximal small bowel, terminal ileum, and colon were 57%, 49%, and 81%, respectively. In the proximal small bowel, the majority consensus panel decision was agreement with CE.

Section Summary: Established Crohn's Disease

Two SRs compared CE with radiography, MRE or ultrasound for CD. One study found slightly

higher diagnostic yield compared to MRE and UI. A second SR A systematic review found a similar diagnostic yield with CE compared with radiography. A diagnostic accuracy study found a comparable sensitivity, higher specificity and PPV, and lower NPV with CD compared to ileocolonoscopy and/or MRE in patients with established CD. Differences may be attributed to high rates of discrepant reads between modalities, and high consensus panel agreement with CE results in cases of discrepancy. Randomized controlled trails are needed to further assess the impact of CE results on therapy management.

SUSPECTED CROHN'S DISEASE

The purpose of CE for patients with suspected CD is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

Systematic Reviews

Results from a meta-analysis by Choi (2017), which compared CE with various modalities for diagnosing CD, are summarized in Tables 10 and 11. The reference standards varied for the selected studies, so quantitative data were not synthesized for diagnostic accuracy. In the pooled analysis, in patients with suspected CD, the sensitivity of CE ranged from 89.6% to 92.0% and the specificity was 100%.

Table 10. Characteristics of Systematic Reviews Assessing the Diagnostic Yield of Capsule Endoscopy versus Other Modalities[a]

Study	Dates	Trials	Participants	N (Range)	Design
Choi (2017)[14]	2002-2013	24	Patients with suspected or established CD	NR	RCT, nonrandomized, and diagnostic accuracy studies

CD: Crohn's disease; CE: capsule endoscopy; NR: not reported; RCT: randomized controlled trial.
[a] Other modalities include small bowel follow-through, enteroclysis, computed tomography enterography, and magnetic resonance enterography.

Table 11. Results of Systematic Reviews Assessing the Diagnostic Yield of Capsule Endoscopy versus Other Modalities

Study	CE vs SBFT[a]	CE vs EC[b]	CE vs CTE[b]	CE vs MRE[b]
Choi (2017)[14]				
N	94			
Diagnostic yield, %	66 vs. 21.3	75.7 vs. 29.4	72.5 vs. 22.5	85.7 vs. 100
Weighted incremental yield (95% CI)	0.44 (0.29 to 0.59)	0.50 (0.21 to 0.79)	0.36 (0.18 to 0.90)	-0.16 (-0.63 to 0.32)
I^2, %	30	52	68	44

CE: capsule endoscopy; CI: confidence interval; CTE: computed tomography enterography; EC: enteroclysis; MRE: magnetic resonance enterography; SBFT: small bowel follow-through.
a From 4 studies (3 included in meta-analysis).
b From 2 studies.

Non Randomized Studies

Broderson (2023) a prospective blinded multicenter study, patients (n=99) with suspected CD were examined with CE and IC within two weeks.[15] The ileocolonic disease severity was assessed with the Simple Endoscopic Score for Crohn's Disease (SES-CD). CD was diagnosed in 30 patients with IC and CE. The mean SES-CD was 9.8 (CI 7.9 to 11.8) and 10.6 (CI 8.2 to 13.1), respectively (p=0.69). There was a substantial agreement (ICC 0.83, CI 0.68 to 0.92) and a strong correlation between SES-CD assessed with IC and CE (rs=0.78, p <0.001). A total of 55 bowel segments had ulcerations identified with both modalities (terminal

ileum 24, right colon 12, transverse colon eight, left colon eight and rectum three). Mean sub-scores for ulcer size, area of ulcerated surface and area of affected surface did not differ between modalities. The inter-modality agreement (κ) was 0.46, 0.34 and 0.43, respectively ($p<0.001$). The authors conclude that there is a strong correlation between IC and CE for the severity of ileocolonic CD and the agreement for SES-CD sub-scores is fair to moderate. The authors state that CE could be an alternative to IC for the assessment of endoscopic severity in selected patients with suspected CD.

Broderson (2022) published a prospective, blinded, multicenter study of the diagnostic accuracy, image quality, and patient experienced discomfort with CE, magnetic resonance enterocolonography (MREC) and ileocolonoscopy (IC) in patients with suspected CD.[16] A total of 153 patients were included in the study and IC, MREC, and CE was performed in 152, 151, 133 patients, respectively. Crohn's Disease was diagnosed with IC in 59 (39%) patients (terminal ileum (TI) 22, colon 20, TI and colon 17). The sensitivity and specificity for diagnosing ileocolonic CD with MREC was 67.9% (CI 53.7 to 80.1) and 76.3% (CI 65.2 to 85.3) (TI 76.9% and 85.6%; colon 27% and 93%) compared to 87.5% (CI 73.2 to 95.8) and 87.8% (CI 78.2 to 94.3) with CE (TI 96.6% and 87.5%; colon 75.0% and 93.0%). The sensitivity of CE was superior to that of MREC ($p = 0.02$). The patient experienced discomfort was equal with CE and MREC and significantly less than with IC.

Section Summary: Suspected Crohn's Disease

For patients with suspected CD who cannot be diagnosed by other modalities, CE can confirm the diagnosis in a substantial number of patients.

CELIAC DISEASE

Systematic Reviews

A meta-analysis by El-Matary (2009) compared the diagnostic performance of CE with a reference standard of duodenal biopsy.[17] The pooled analysis of three studies showed a sensitivity of 83% and a specificity of 98%. No major complications were reported. Another meta-analysis by Rokkas and Niv (2012) also compared the diagnostic performance of CE with biopsy, summarizing six studies (n=166).[18] The overall pooled sensitivity was 89%, and the specificity was 95%. Capsule endoscopy detected involvement of intestines beyond the duodenum; however, the clinical significance of detecting the extent of celiac disease is uncertain. Given the less than 90% sensitivity of CE for celiac disease, it does not appear to be an adequate alternative method of making an initial diagnosis when endoscopy with biopsy is possible, however, the authors conclude this method may be a reasonable alternative method of diagnosing CD.

Nonrandomized Studies

In a study by Kurien (2013), 62 patients with an equivocal diagnosis of celiac disease and 69 patients with confirmed celiac disease who were unresponsive to standard treatment were evaluated with CE.[19] Results were combined with human leukocyte antigen typing and response to gluten challenge, with the final diagnosis made by three expert physicians who received the information from all three sources. The main outcome was the increase in diagnostic yield after CE combined with the other tests. The diagnostic yield was greatest in cases with antibody-negative villous atrophy where a diagnosis of celiac disease was made in 9 (28%) of 32 patients. In 8 (12%) of the 69 nonresponsive celiac disease patients, CE

identified two cases of enteropathy-associated lymphoma, four type 1 refractory disease cases, one fibroepithelial polyp, and one case of ulcerative jejunitis. This study was limited by the small sample size and use of other tests in conjunction with CE to ascertain a final diagnosis.

Rondonotti (2007) published the results of a multi-center study in 43 consecutive patients with clinical symptoms suggesting celiac disease and positive serology in which CE was used to assess the severity and extent of mucosal changes.[20] CE was comparable to EGD for the diagnosis of celiac disease when there are overt villous changes. Capsule findings were evaluated for the presence of lesions compatible with celiac disease (scalloping of duodenal folds, fissures, flat mucosa, and mosaic appearance). Duodenal histology was normal in 11 and compatible with celiac disease in 32 of 43 patients studied. Using duodenal histology as the gold standard, the performance characteristics of capsule endoscopy for the diagnosis of celiac disease were: sensitivity 87.5 % (95 % confidence interval [CI]: 76.1 to 98.9 %), specificity 90.9 % (95 % CI: 81.0 to 100 %), positive predictive value 96.5 % (95 % CI: 90.1 to 100 %), negative predictive value 71.4 % (95 % CI: 55.8 to 87 %), positive and negative likelihood ratios 9.6 and 0.14, respectively. Eighteen patients had mucosal changes extending beyond the duodenum, involving the entire small bowel in three. These patients tended to have more severe symptoms, but the difference was not statistically significant. Interobserver agreement for the diagnosis of celiac disease by capsule endoscopy ranged between 79.2 and 94.4%; kappa values ranged between 0.56 and 0.87. The authors concluded that capsule endoscopy shows good sensitivity and excellent specificity for the detection of villous atrophy in patients with suspected celiac disease.

Capsule endoscopy in nonresponsive celiac disease

A study published by Barret (2012) evaluated the ability of CE to detect disease severity or complications compared to upper endoscopy or enteroscopy in refractory celiac disease.[21] In this study, nine patients with symptomatic celiac disease, 11 patients with refractory celiac disease type I (RCDI), 18 patients with refractory celiac disease type II (RCDII), and 45 patients without celiac disease underwent both CE and upper endoscopy or enteroscopy. A total of 47 CEs (10, 11, and 26 CEs in the symptomatic CD, RCDI, and RCDII groups, respectively) from the 38 celiac patients and 47 CEs from the 45 nonceliac patients were reviewed. Among celiac patients, CE was of acceptable quality in 96% of cases and was complete in 62% of cases. Concordance of CE with histology for villous atrophy was higher than for optic endoscopy (κ coefficient=0.45 vs. 0.24, $p<0.001$). In addition, extensive mucosal damage on CE was associated with low serum albumin ($p=0.003$) and the RCDII form ($p=0.02$). Three cases of overt lymphoma were detected by CE.

Atlas (2011) published the results of a comparative study of 42 patients with nonresponsive celiac disease matched by age and sex to 84 celiac disease-free controls, as well as retrospective evaluation in 30 patients with uncomplicated celiac disease.[22] Among nonresponsive cases, the overall sensitivity and specificity of CE for the detection of any degree of villous atrophy as graded by histology were 56% and 85%, respectively. Mucosal abnormalities were observed by CE in patients with both nonresponsive uncomplicated celiac disease and erosions/ulcerations of the gut were observed in 19% of nonresponsive celiac disease patients, 18% of controls, and 31% of patients with uncomplicated celiac disease ($p=0.35$). Importantly, two severe complications (ulcerative jejunitis and adenocarcinoma) were detected by CE in nonresponsive celiac disease patients.

Culliford (2005) published a case series evaluating 47 patients with complicated celiac disease.[23] Findings were consistent with celiac disease in 87%: atrophy (68%), fissuring (62%), and mosaic pattern (19%), extending to the ileum in 34%. Unexpected additional findings were observed in 60% of patients, most of which were ulcerations (45%), and also included cancer, polyps, submucosal mass, and ulcerated nodular mucosa.

Section Summary: Celiac Disease

Small bowel biopsy, celiac serologies, and human leukocyte antigen typing remain the standard tests for confirming celiac disease and have a higher sensitivity and specificity for this purpose. However, in cases where the diagnosis of celiac disease is equivocal, or when diagnosis with endoscopy with biopsy is not possible, there is evidence that CE can reveal morphologic changes in the small bowel consistent with celiac disease and studies of patients with unresponsive celiac disease undergoing CE have shown some yield of actionable diagnoses that have the potential to improve patient outcomes.

UNEXPLAINED CHRONIC ABDOMINAL PAIN

The purpose of wireless CE for patients who have unexplained chronic abdominal pain is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

Systematic Reviews

Xue (2015) reported on a systematic review of 21 studies (n=1520 patients) evaluating CE for unexplained chronic abdominal pain.[24] The pooled diagnostic yield was 20.9% (95% confidence interval [CI], 15.9% to 25.9%). The most commonly identified findings were inflammatory lesions (78.3%) and tumors (9.0%). Studies in the review were highly heterogeneous. Limitations in interpreting the findings included retrospective study designs, different durations of abdominal pain, and the use of different tests before CE.

Nonrandomized Studies

Wang (2022) published a retrospective study on patients (n=80) with chronic and recurrent abdominal pain who underwent CE for diagnostics. They reported abnormal findings in 54 patients (67.5%) including small intestinal erosion and congestion, small intestinal ulcers, small intestinal parasites, small intestinal vascular malformations, small intestinal polyps, small intestinal diverticulum, and small intestinal lymphangiectasia.[25] The authors reported that there were no significant side effects for up to one month after capsule ingestion and that the capsule was evacuated by all patients.

In a study not included in the systematic review, Yang (2014) reported on a case series evaluating 243 patients with CE for unexplained chronic abdominal pain.**[26]** The diagnostic yield of CE was 23.0%. Identified findings included 19 (7.8%) patients with CD, 15 (6.2%) with enteritis, 11 (4.5%) with idiopathic intestinal lymphangiectasia, 5 (2.1%) with uncinariasis, and 5 (2.1%) with abnormal transit time and other findings (eg, small bowel tumor, ascariasis, anaphylactoid purpura).

Section Summary: Unexplained Chronic Abdominal Pain

While CE diagnosed unexplained chronic abdominal pain in a proportion of patients reported in retrospective studies, the sequence and chronology of testing and treatment recommended before CE needs to be defined to determine whether CE has utility to diagnose the condition.

ULCERATIVE COLITIS

The purpose of wireless CE for patients who have ulcerative colitis is to inform management decisions based on disease status. No peer-reviewed systematic reviews or randomized controlled trials of wireless CE in ulcerative colitis have been published.

Nonrandomized studies

Several prospective observational studies evaluated the diagnostic accuracy of CE in patients with ulcerative colitis. Tables 12 and 13 summarize the characteristics and results of these studies.

Table 12. Characteristics of Observational Comparative Studies Assessing CE for UC

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Shi (2017)[27]	Single-center prospective observational	China	2014-2016	Patients 18-80 y with UC requiring colonoscopy	150 patients underwent CE-2 and colonoscopy	NR
San Juan-Acosta (2014)[28]	Single-blind prospective comparative	Spain	2010-2012	Patients 18-70 y with UC with flare in disease activity or due for CRC screening	23 underwent CE-1, 19 had CE-2; all followed by colonoscopy	NR
Oliva (2014)[29]	Prospective observational	Spain	2011-2012	Patients 6-18 y with a diagnosis at least 3 mo prior to enrollment	30 patients underwent CE-2, followed by colonoscopy	NR
Sung (2012)[30]	Prospective cohort	China and Singapore	2000-2008	Patients with suspected or known UC	100 patients underwent CE and same-day colonoscopy	NR

CE-1:first-generation capsule endoscopy CE-2:second-generation capsule endoscopy; CRC: colorectal cancer; NR: not reported; UC: ulcerative colitis.

Table 13. Results of Observational Comparative Studies Assessing CE for Ulcerative Colitis

Study	Active Colonic Inflammation, %		PPV, %	NPV, %	Correlation Between Colon CE and Colonoscopy	
	Sensitivity[a]	Specificity			Disease Severity	Extent of Inflammation
Shi (2017)[27]						
N	150	150	150		150	150
Mucosal inflammation (MES >0)	97			94-95		
M-to-S inflammation (MES >1)	94					
Postinflammatory polyps	100	91				
ICC (95% CI)					0.69 (0.46 to 0.81)[a]	0.64 (0.38 to 0.78)[b]
p					<0.001	<0.001
San Juan-Acosta (2014)[28]						
N	42	42	42		42	42

Study	Active Colonic Inflammation, %		PPV, %	NPV, %	Correlation Between Colon CE and Colonoscopy	
CE vs colonoscopy						
Disease activity	77.78	95.83	93.33	85.19		
Disease extent	68.75	96.15	91.67	83.33		
κ (95% CI)					0.79 (0.62 to 0.96)	0.71 (0.52 to 0.90)
Oliva (2014)[29]						
N	30	30	30			
% (95% CI)	96 (79 to 99)	100 (61 to 100)	100 (85 to 100)	85 (49 to 97)		
Sung (2012)[30]						
N	100	100	100			
% (95% CI)	89 (80 to 95)	75 (51 to 90)	93 (84 to 97)	65 (43 to 83)		

CE: capsule endoscopy; CI: confidence interval; ICC: intraclass correlation coefficient; MES: Mayo Endoscopic Subscore; M-to-S: moderate to severe; NPV: negative predictive value; PPV: positive predictive value.
[a] MES.
[b] Ulcerative Colitis Endoscopic Index of Severity.

In the study by San Juan-Acosta (2014), although the correspondence between the two methods was reasonably good, it is uncertain whether management changes based on one or the other test would result in similar or different patient outcomes.[28]

Oliva (2014) evaluated 30 patients with known ulcerative colitis with both CE and colonoscopy to assess disease activity.[29] The reference standard for disease activity was a Matts score greater than 6 as judged by colonoscopy. Although the two methods had a high concordance at this cutoff level of disease in this study, patient outcomes linked to these assessments of disease activity cannot be determined.

Section Summary: Ulcerative Colitis

Several diagnostic accuracy studies have compared CE with colonoscopy to assess disease activity in patients with ulcerative colitis. Two of the four studies were limited in their sample size (i.e., <50 patients) and thus data on diagnostic accuracy are limited. No RCTs assessing the clinical utility of wireless CE for ulcerative colitis were identified. Additional evidence is needed to determine the impact of CE on net health outcomes in patients with ulcerative colitis.

ESOPHAGEAL DISORDERS

The purpose of wireless CE for patients who have esophageal disorders is to inform management decisions based on disease status.

Systematic Reviews

Most studies have shown that CE has inferior diagnostic characteristics compared with traditional upper endoscopy for a variety of esophageal conditions. A meta-analysis by Guturu (2011) evaluated nine studies comparing CE with traditional endoscopy for detecting esophageal varices and calculated a sensitivity of 83% and specificity of 85%.[31] A meta-analysis by Bhardwaj (2009) assessed nine studies comparing CE with traditional endoscopy for detecting Barrett esophagus and reported a sensitivity of 77% and specificity of 86%.[32]

Because of the lower sensitivity and specificity, CE cannot substitute for traditional endoscopy nor can it be used to triage patients to endoscopy.

Section Summary: Esophageal Disorders

Other available modalities are superior to CE for monitoring esophageal disorders. The diagnostic characteristics of CE are inadequate to substitute for other modalities or to triage patients to other modalities.

HEREDITARY GASTROINTESTINAL POLYPOSIS SYNDROMES

The purpose of wireless CE for patients who have hereditary GI polyposis syndromes is to inform management decisions based on disease status. Patients with familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome (PJS) are genetically at high-risk of small bowel polyps and tumors.

Fukushi (2023) utilized SBCE to investigate the genotype-phonotype correlation of small-intestinal polyps in patients with FAP.[33] Patients (n=41) who underwent SBCE, Esophagogastroduodenoscopy (EGD), and adenomatous polyposis coli (APC) gene analysis were included in the study. More small-intestinal polyps were found in Spigelman stage III and IV groups than in the stage 0 group ($p<0.05$). The APC variant was negative for 6 patients (15%), and the sites associated with more than 5 small-intestinal polyps were codons 278, 1062, 1114, 1281, 1307, 1314, and 1504. The authors conclude that SBCE surveillance is potentially recommended for patients with pathogenic variants in the APC gene at codons 278 and 1062 to 1504 or with Spigelman stage III or higher.

Urquhart (2014) compared CE with MRE in 20 patients with PJS.[34] Capsule endoscopy identified more polyps 10 mm or larger (47 polyps) than MRE (14 polyps; p=.02). However, subsequent balloon enteroscopy in 12 patients showed a poor correlation of findings between techniques, with a 100% PPV of finding a polyp on balloon enteroscopy with MRE versus 60% for CE. A study by Brown (2006) in 19 patients showed a greater number of polyps identified with CE than with barium follow-through examinations.[35] Mata (2005) studied the role of CE in 24 patients with hereditary GI polyposis syndromes, including familial adenomatous polyposis (n=20) or PJS (n=4).[36] Compared with barium studies using small bowel enteroclysis, CE identified four additional patients with small bowel polyps, which were subsequently removed with endoscopic polypectomy. Although these studies were small, they demonstrated that CE can identify additional lesions compared with other diagnostic methods in persons with disease syndromes at high-risk for such lesions.

The lifetime risk of small bowel cancer in Lynch syndrome has been estimated at 5%. Although not extremely high, this risk is greatly increased compared with the general population. There are a few case series of the prevalence of neoplastic lesions in asymptomatic patients with Lynch syndrome. Haanstra (2015) evaluated 200 patients with Lynch syndrome who underwent CE.[37] Small bowel neoplasia was detected in the duodenum in two patients (one adenocarcinoma, one adenoma). These lesions would have been in the reach of a gastroduodenoscope. In a smaller study by Saurin (2010), 35 asymptomatic patients with Lynch syndrome underwent colon CE.[38] Small bowel neoplasms were diagnosed in three (8.6%) patients (one adenocarcinoma, two adenomas with low-grade dysplasia).

Section Summary: Hereditary Gastrointestinal Polyposis Syndromes

There is enough evidence that CE can identify additional lesions compared with other diagnostic methods in persons with hereditary polyposis syndrome including familial adenomatous polyposis and Peutz-Jeghers syndrome. Although studies have shown at least a low prevalence of small bowel neoplasms in Lynch syndrome, these data are insufficient to determine whether evaluation with CE would improve patient outcomes. Additional data on the prevalence and natural history of small bowel polyps in Lynch syndrome patients are necessary. At this time, surveillance of the small bowel is not generally recommended as a routine intervention for patients with Lynch syndrome.

PORTAL HYPERTENSIVE ENTEROPATHY

The purpose of wireless CE for patients who have portal hypertensive enteropathy is to inform management decisions based on disease status.

Systematic Reviews

Several systematic reviews relevant to wireless CE for portal hypertensive enteropathy, including a Cochrane review, have been published. Tables 14 and 15 summarize the characteristics and results of select systematic reviews.

Table 14. Characteristics of Systematic Reviews Assessing Capsule Endoscopy for Portal Hypertensive Enteropathy

Study	Dates	Trials	Participants	N (Range)	Design
McCarty (2017)[39]	2005-2015	17	Patients with portal hypertension	1328 (8 to 330)	NR
Colli (2014)[40]	2005-2014	16	Adults with cirrhosis	936 (NR)	Cohort

NR: not reported.

Table 15. Results of Systematic Reviews Assessing Capsule Endoscopy for Portal Hypertensive Enteropathy

Study	CE, %		Likelihood Ratios		Diagnostic Accuracy	
	Sensitivity	Specificity	Positive	Negative	CE	Medium-to-Large Varices
McCarty (2017)[39]						
N	1328	1328	1328			
PE (95% CI), %	83 (76 to 89)	85 (75 to 91)	5.4 (3.3 to 9.0)	0.20 (0.14 to 0.28)	90 (88 to 93)	92 (90 to 94)
Studies with low risk of bias, n						
PE (95% CI), %	80 (81 to 88)	86 (68 to 94)			85 (81 to 88)	92 (89 to 94)
Colli (2014)[40]						
N	936	936	936			
PE (95% CI), %	84.8 (77.3 to 90.2)	84.3 (73.1 to 91.4)	5.4 (3.1 to 9.5)	0.18 (0.12 to 0.27)		
Studies with low risk of bias, n	396	396	396			

Study	CE, %		Likelihood Ratios		Diagnostic Accuracy	
PE (95% CI), %	79.7 (73.1 to 85.0)	86.1 (64.5 to 95.5)	5.8 (2.1 to 16.1)	0.24 (0.18 to 0.31)		

CE: capsule endoscopy; CI: confidence interval; PE: pooled effect.

Section Summary: Portal Hypertensive Enteropathy

Capsule endoscopy has been used to diagnose portal hypertensive enteropathy. Systematic reviews of studies of diagnostic performance have reported limited sensitivity and specificity. Because neither the sensitivity nor the specificity was high for identifying esophageal varices, CE should not be used instead of esophagogastroduodenoscopy nor should it be used to triage patients to esophagogastroduodenoscopy. Based on these diagnostic characteristics, the test does not appear to have clinical utility.

ACUTE UPPER GASTROINTESTINAL TRACT BLEEDING

The purpose of wireless CE for patients who have acute upper GI tract bleeding is to inform management decisions based on disease status.

Randomized Controlled Trials

Sung (2016) reported on a prospective RCT to evaluate the use of CE in the emergency department for patients with suspected upper GI bleeding.[41] Capsule endoscopy was used to determine whether patients would be admitted to the hospital or sent home, versus an alternative strategy of admitting all patients. Eligible patients presented with signs and/or symptoms of acute upper GI bleeding but were without hemodynamic shock or conditions likely to preclude the use of the capsule endoscope. Seventy-one patients were randomized to CE in the emergency department (n=37), followed by monitoring for upper GI bleeding, or standard care (n=34), which included mandatory hospital admission. Seven CE patients with active bleeding or endoscopic findings were admitted, with the remainder discharged home. There were no deaths or morbid outcomes in either group, indicating that CE could result in equivalent patient outcomes with many patients safely avoiding emergency hospitalization.

Tables 16 and 17 summarize the characteristics and results of select RCTs.

Table 16. Characteristics of RCTs Assessing Capsule Endoscopy for Acute Gastrointestinal Tract Bleeding

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Sung (2016)[41]	China	NR	2013-2014	Patients presenting to ED with symptoms suggestive of UGIB	37 randomized to CE; admission determined by CE	34 randomized to SOC; admission determined by GBS
Gutkin (2013)[42]	U.S.	3	NR	Patients ≥18 y with history suggestive of acute UGIB ≤48 h prior to ED presentation	12 randomized to VCE prior to endoscopy	12 randomized to endoscopy

CE: capsule endoscopy; ED: emergency department; GBS: Glasgow Blatchford score; NR: not reported; RCT: randomized controlled trial; SOC: standard of care; UGIB: upper gastrointestinal bleeding; VCE: video capsule endoscopy.

Table 17. Results of RCTs Assessing Capsule Endoscopy for Acute Gastrointestinal Tract Bleeding

Study	Active Bleeding or Endoscopic Findings, n	Hospitalization, n	Mortality, n	GBS Score	Agreement Between CE and EGD
Sung (2016)[41]					
N	68	68	68	68	68
CE	• "Coffee ground" material: 2 • Peptic ulcer with Forrest Ib stigmata: 2 • Forrest IIa: 2 • Esophageal varix: 1	7	0	• 6 patients: 0 • 3 patients: 1 • 25 patients: ≥2	
SOC	• Peptic ulcer: 14 • Duodenal ulcer: 12 • Gastritis/duodenitis: 10 • Gastric or duodenal erosions: 5 • Mallory Weiss tear: 1	34	0	• No patients scored 0 • 7 patients: 1 • 27 patients: ≥2	
Gutkin (2013)[42]					
N	24				24
VCE	8 (67.7%) had positive findings confirmed by endoscopy; for these patients, average Rockall score was 3; average Blatchford score was 13				VCE data identical to EGD results (*P*=1.0)

CE: capsule endoscopy; EGD: esophagogastroduodenoscopy; GBS: Glasgow Blatchford score; RCT: randomized controlled trial; SOC: standard of care; VCE: video capsule endoscopy.

The purpose of the limitations tables (see Tables 18 and 19) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 18. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Sung (2016)[41]					
Gutkin (2013)[42]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 19. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Sung (2016)[41]						3. As a feasibility study, confidence intervals and p values were not reported
Gutkin (2013)[42]					2. Small sample size based on pilot/feasibility study	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Two 2013 studies with small cohorts of patients (range, 49 to 83 patients) have reported on the use of CE before upper endoscopy for acute GI bleeding, to triage and/or risk-stratify patients in the emergency department or hospital.[43, 44] These studies reported that CE provides useful information, such as identifying gross bleeding and inflammatory lesions in a substantial proportion of patients and in stratifying patients into high- or low-risk categories. However, the yield of CE in localizing the bleeding source was lower than for esophagogastroduodenoscopy, which is the standard initial evaluation for acute upper GI bleeding.

Section Summary: Acute Upper Gastrointestinal Tract Bleeding

Use of CE in the emergency department setting for suspected upper GI bleeding is based on efficiency (avoiding hospitalization, avoiding immediate endoscopy). Controlled studies are needed to assess further the impact of CE on health outcomes compared with standard management. Patients should be followed to their ultimate diagnosis to determine whether the use of CE versus other triage strategies or immediate endoscopy results in lower health care resource utilization.

COLON CANCER SCREENING

The purpose of wireless CE for patients who are being screened for colon cancer is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

Systematic Reviews

Several studies have assessed the accuracy of CE for detecting colonic lesions. Spada (2016) published a systematic review with meta-analysis of the diagnostic accuracy of CE for detecting colorectal polyps with stratified results for first- and second-generation capsules.[45] Across the 14 eligible studies, the indications for endoscopy included colorectal cancer screening (n=1261 [47%]), postpolypectomy surveillance or family history of colorectal cancer (n=636 [24%]), symptoms suggestive of cancer and/or fecal occult blood test positivity (n=619 [23%]), positive imaging tests (n=136 [5%]), or other indication (24 [1%]). There were no missed cancers (n=11) in the series using second-generation CE (per-patient sensitivity,

100%). In series using the first-generation CE, 6 of 26 proven cancers were missed on CE (per-patient sensitivity, 77%).

Kjolhede (2020) published a systematic review with meta-analysis of the diagnostic accuracy of CE compared to colonoscopy with stratified results for polyps of any size, polyps ≥ 6 mm, and polyps ≥ 10 mm.[46] Across analyzed patients in the 12 eligible studies, the indications for endoscopy included colorectal cancer screening or history of polyps or colorectal cancer (n=1200 [63.2%]), positive fecal immunochemical test (n=493 [26%]), first-degree relatives of patients with colorectal cancer (n=177 [9.3%]), or unspecified (n=28 [1.5%]). The rate of patients with an adequate bowel preparation ranged from 40% to 100%. The rates of complete CE transits ranged from 57% to 100%. The authors note that the relatively high rate of incomplete CE investigations limits the utility of CE in the colorectal cancer setting. All but one study was assessed to have a high risk of bias and applicability concerns for the reference standard.

Characteristics of the systematic reviews and their main findings are summarized in Tables 20 and 21, respectively.

Table 20. Characteristics of Systematic Reviews Assessing Capsule Endoscopy for Colon Cancer Screening

Study	Dates	Trials	N (Range)	Design	Outcome
Spada (2016)[45]	2006-2015	14	2681 (40 to 884)	Diagnostic accuracy studies	Per-patient sensitivity of CCE for different categories of polyp size and for cancer
Kjolhede (2020)[46]	2009-2020	12	2199 (20 to 884)	Diagnostic accuracy studies	Per-patient sensitivity of CCE for various polyp size thresholds

CCE: colon capsule endoscopy.

Table 21. Results of Systematic Reviews Assessing Capsule Endoscopy for Colon Cancer Screening

Random-Effects Model	Trials	N	Outcomes	Effect Size	95% CI	I^2, %
Spada (2016)[45]						
For ≥10 mm polyps	10	NR	Diagnostic accuracy for ≥10 mm polyps	Sens=80.0% Spec=96.2% PLR=18.6 NLR=0.22 DOR=90.4	66% to 90.3%; 94.0% to 97.6% 12.0 to 28.2 0.13 to 0.34 44 to 163	53.4 31.3
For ≥6 mm polyps	7	NR	Diagnostic accuracy for ≥6 mm polyps using 1st-generation CCE	Sens=58% Spec=85.7% PLR=3.7 NLR=0.51 DOR=7.4	44% to 70% 80.2% to 90.0%	65
For ≥6 mm polyps	6	NR	Diagnostic accuracy for ≥6 mm polyps using 2nd-generation CCE	Sens=86% Spec=88.1% PLR=7.9 NLR=0.16 DOR=50.5	82% to 89% 74.2% to 95.0% 3.7 to 16.1 0.12 to 0.21 20.3 to 107.0	0

Random-Effects Model	Trials	N	Outcomes	Effect Size	95% CI	I^2, %
For ≥10 mm polyps	3	NR	Diagnostic accuracy for ≥6 mm polyps using 1st-generation CCE	Sens=54% Spec=97.4% PLR=NR NLR=NR DOR=NR	29% to 77% 96.0% to 98.3%	76.2 0
For ≥10 mm polyps	6	NR	Diagnostic accuracy for ≥6 mm polyps using 2nd-generation CCE	Sens=88% Spec=95.3% PLR=NR NLR=NR DOR=NR	81% to 91% 91.5% to 97.5%	0 67
For ≥10 mm polyps	10	NR	Diagnostic accuracy for ≥10 mm polyps	Sens=80.0% Spec=96.2% PLR=18.6 NLR=0.22 DOR=90.4	66% to 90.3%; 94.0% to 97.6% 12.0 to 28.2 0.13 to 0.34 44 to 163	53.4 31.3
Kjolhede (2020)[46]						
For polyps of any size	4	338	Diagnostic accuracy for polyps of any size	Sens=85% Spec=85% PLR=NR NLR=NR DOR=30.5	73% to 92% 70% to 93% 16.2 to 57.2	NR
For polyps ≥6 mm	6	1324	Diagnostic accuracy for polyps ≥6 mm	Sens=87% Spec=88% PLR=NR NLR=NR DOR=51.1	83% to 90% 75% to 95% 19.8 to 131.8	NR
For polyps ≥10 mm	7	1577	Diagnostic accuracy for polyps ≥10 mm	Sens=87% Spec=95% PLR=NR NLR=NR DOR=136.0	82% to 90% 92% to 97% 70.6 to 262.1	NR

CCE: colon capsule endoscopy; CI: confidence interval; DOR: diagnostic odds ratio; NLR: negative likelihood ratio; NR: not reported; PLR: positive likelihood ratio; Sens: sensitivity; Spec: specificity.

Nonrandomized Studies

Other studies have evaluated the diagnostic characteristics of CE, using subsequently performed colonoscopy as the reference standard.[47-50] Of note, the Cash (2021) study randomized patients to colon CE or CT colonography followed by optical colonoscopy.[50] In the Saito (2015) study, of 66 evaluable patients, per-patient sensitivity for the detection of polyps was 94% (95% CI, 88.2% to 99.7%). In the Morgan (2016) study, for lesions 10 mm or larger, sensitivity of CE was 100% (95% CI, 56.1% to 100%), with a specificity of 93.0% (95% CI, 79.9% to 98.2%). For lesions 6 mm or larger, sensitivity was 93.3% (95% CI, 66.0% to 99.7%) and the specificity was 80.0% (95% CI, 62.5% to 90.9%). The Parodi (2018) study included 177 first-degree relatives of individuals with colorectal cancer and found, for lesions 6 mm or larger, a sensitivity of 91% (95% CI, 81% to 96%) and a specificity of 88% (95% CI, 81% to 93%).[49] In the Cash (2021) study, data from 286 patients revealed that the proportion of enrollees with any polyp 6 mm or larger confirmed by subsequent blinded optical colonoscopy was 31.6% for colon CE versus 8.6% for CT colonography.[50] The sensitivity and specificity of

colon CE for polyps 6 mm or larger was 79.2% and 96.3%, respectively, while that of CT colonography was 26.8% and 98.9%. For polyps 10 mm or larger, the sensitivity and specificity of colon CE was 85.7% and 98.2% compared with 50% and 99.1% for CT colonography. The authors concluded that colon CE should be considered comparable or superior to CT colonography as a screening test; however, neither test was as effective as optical colonoscopy.

Section Summary: Colon Cancer Screening

Studies of diagnostic characteristics alone are insufficient evidence to determine the efficacy of CE for colon cancer screening. Because diagnostic performance is worse than standard colonoscopy, CE would need to be performed more frequently than standard colonoscopy to have comparable efficacy. Without direct evidence of efficacy in a clinical trial of colon cancer screening using CE, modeling studies using established mathematical models of colon precursor incidence and progression to cancer could provide estimates of efficacy in preventing colon cancer mortality. Studies of CE in screening populations are necessary to determine the diagnostic characteristics of the test in this setting.

LOWER GASTROINTESTINAL TRACT BLEEDING AND MAJOR RISKS FOR COLONOSCOPY OR MODERATE SEDATION

The purpose of wireless CE for patients with evidence of GI bleeding of lower GI origin and major risks for colonoscopy or moderate sedation is to visualize the colon for the detection of polyps or other sources of lower GI bleeding and inform a decision to proceed to further treatment and testing.

Diagnostic Accuracy Studies

Several studies have evaluated the diagnostic characteristics of CE for the detection of colon polyps in patients with evidence of lower GI bleeding (eg, hematochezia, positive fecal occult blood test [FOBT]). Study characteristics and results are described in Table 22 and 23.

Table 22. Study Characteristics of Clinical Validity

Study	Study Population	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comments
Kobaek-Larsen (2017)[51]	FOBT-positive individuals participating in a CRC screening program in Denmark (N=253; median age, 64 y)	OC adjusted by any findings from all follow-up procedures; repeat colonoscopy was offered for suspected missed polyps	Polyps >9 mm within ±50% of CE measure	OC performed 1 day after CE	Investigators were blinded to both CE and OC; in the case of a second endoscopy, investigator was unblinded to CE findings	RS adjusted in 75 patients due to follow-up procedures; only 50% (126) had complete OC and CE

Study	Study Population	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comments
Rondonotti (2014)[52]	FOBT-positive individuals participating in a CRC screening program in Italy (N=54; age range, 50-69)	OC followed by colon segment re-inspection if double unblinding to CTC and CE results revealed a disparity	Polyps ≥6 mm	CTC and OC performed 15 days after CE	Initial blinding to CE and CTC results followed by double-unblinding and opportunity for re-inspection and adjustment of RS	4 patients excluded from analysis (consent withdrawal [2], endoscopist not blinded [2])
Eliakim (2009[53]	Individuals with known or suspected colonic disease in Israel; 21% of patients had hematochezia or positive FOBT (N=104; mean age, 49.8)	OC	Polyps ≥6 mm and ≥10 mm within +50% of CE measure	OC performed within 10 hours of CE	Investigators blinded to both OC and CE	6 patients excluded from analysis (did not complete bowel prep [2], withdrawal [1], could not ingest capsule [1], capsule retention [1], technical failure [1])

CE: capsule endoscopy; CRC: colorectal cancer; CTC: computed tomography colonography; FOBT: fecal occult blood test; OC: optical colonoscopy; RS: reference standard.

Table 23. Study Results of Clinical Validity

Study	N	CE Completion Rate, % (95% CI)	Sensitivity, % (95% CI)[1]	Specificity, % (95% CI)[1]	PLR; NLR	Adverse Events
Kobaek-Larsen (2017)[51]						None related to OC or CE.
All patients; CE >9mm	253	54 (48 to 60)	87 (83 to 91)	92 (89 to 95)	NR	
Complete CE and OC; CE >9 mm	126	---	97 (94 to 100)	90 (85 to 95)	NR	
All patients; OC > 9 mm	253	90 (86 to 94)	88 (84 to 92)	100 (100)	NR	
Complete CE and OC; OC > 9 mm	126	---	89 (84 to 94)	100 (100)	NR	
Rondonotti (2014)[52]						None related to OC or CE. 10 cases of mild abdominal pain and 2 cases of

Study	N	CE Completion Rate, % (95% CI)	Sensitivity, % (95% CI)[1]	Specificity, % (95% CI)[1]	PLR; NLR	Adverse Events
						significant pain during CTC.
CE ≥6 mm	50	100	88.2 (62.2 to 97.9)	87.8 (70.8 to 96.0)	3.75; 0.06	
CTC ≥6 mm	50	100	88.2 (62.2 to 97.9)	84.8 (67.3 to 94.3)	3.0; 0.07	
Eliakim (2009)[53]						1 capsule retention; 7 cases of mild-moderate headache, nausea, or vomiting related to CE bowel preparation.
CE ≥6 mm	98	NR	89 (70 to 97)	76 (72 to 78)	NR	
CE ≥10 mm	98	NR	88 (56 to 98)	89 (86 to 90)	NR	

CE: capsule endoscopy; CI: confidence interval; CTC: computed tomography colonography; NLR: negative likelihood ratio; NR: not reported; OC: optical colonoscopy; PLR: positive likelihood ratio.
1 Per-patient analysis.

Kobaek-Larsen (2017) reported on FOBT-positive individuals participating in a colorectal cancer screening program in Denmark.[51] The reference standard consisted of OC adjusted by any findings from all additional follow-up procedures, including repeat endoscopy due to suspected missed polyps unblinded to CE results in 53 patients, repeated OC due to inadequate bowel preparation in 8 patients, and follow-up CT colonography in 14 patients. The CE completion rate was significantly lower than optical colonoscopy (p<.001), with only 50% of patients (n=126) having complete optical colonoscopy and CE investigations.

Rondonotti (2014) reported on FOBT-positive individuals participating in a colorectal cancer screening program in Italy.[52] Unblinded colonoscopy, integrating optical colonoscopy, computed tomography colonography, and CE results, was used as the reference standard. Investigations were completed in all patients with a positive likelihood ratio and negative likelihood ratio of 3.75 and 0.06 for CE, respectively.

Eliakim (2009) conducted a prospective, multicenter study evaluating CE compared to colonoscopy in individuals with known or suspected colonic disease.[53] Twenty-one percent of patients had hematochezia or positive FOBT. The majority of patients were referred for optical colonoscopy due to a personal or family history of colorectal cancer or for colorectal cancer screening. Polyps of any size were detected in 44% of patients, with 53% identified as having adenomas. Overall colon cleanliness for CE was considered adequate in 78% of patients (95% CI, 68 to 86%).

Study relevance, design, and conduct limitations are described in Table 24 and 25.

Table 24. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kobaek-Larsen (2017)[51]	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation.		2. Adjusted and/or unblinded reference standard not uniformly applied to all patients.	1,3. Impact of findings on health outcomes not assessed. Predictive values not reported.	
Rondonotti (2014)[52]	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation.			1. Impact of findings on health outcomes not assessed.	
Eliakim (2009)[53]	4. Study did not specifically evaluate individuals with major risks for colonoscopy or moderate sedation; only 21% of subjects had evidence of lower gastrointestinal bleeding.			1,3. Impact of findings on health outcomes not assessed. Predictive values not reported.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 25. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kobaek-Larsen (2017)[51]	1. Selection not described.	1. In case of second endoscopy for suspected missed polyps, endoscopist not blinded to results of CE.			1,3. Unclear how many complete investigations included patients with comparison to adjusted and/or unblinded reference standard. High loss due to low CE completion rate.	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Rondonotti (2014)[52]	1. Selection not described.	1. Endoscopist was unblinded to results of CE and CTC in event polyps were missed prior to segment reinspection.	2. CTC and OC performed 15 days later.			
Eliakim (2009)[53]	1. Selection not described.			1. Not registered.		

CE: capsule endoscopy; CTC: computed tomography colonography; OC: optical colonoscopy.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Lower Gastrointestinal Tract Bleeding and Major Risks for Colonoscopy or Moderate Sedation

Studies evaluating the diagnostic characteristics of CE as a triage test have primarily involved colorectal cancer screening populations that have not specifically enrolled patients with major risks for optical colonoscopy or moderate sedation. The three studies identified are heterogeneous in the timing of delivery of the reference standard, in the definition and blinding of the reference standard, and in the significant polyp size threshold determining a positive test result. Only one small study reported positive and negative likelihood ratios. Per-patient sensitivity and specificity ranged from 88% to 97% and 76% to 92%, respectively, and was generally reported with wide CIs. While one study reported a higher sensitivity and specificity compared to optical colonoscopy versus the defined reference standard, a consistent reference standard was not applied to all patients and carried a low combined rate of complete optical colonoscopy and CE investigations (50%). No studies assessed the impact of study findings on specific health outcomes. Adherence to recommended follow-up diagnostic or therapeutic interventions in patients with major risks for colonoscopy or moderate sedation is unknown. Studies of CE in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting.

INCOMPLETE COLONOSCOPY

The purpose of wireless CE for patients with an incomplete colonoscopy after adequate preparation where a complete evaluation of the colon was not technically possible is to visualize the colon for the detection of polyps and inform a decision to proceed to further treatment and testing.

The comparator of interest is repeat optical colonoscopy. Repeat colonoscopy following a prior incomplete procedure may be modified with adjusted endoscopic techniques, pediatric instruments, abdominal pressure and position changes, water exchange and water immersion techniques, carbon dioxide insufflation, magnetic endoscope imaging, alternate sedation methods, anesthesia assistance, and management with more experienced physicians.[54]

Nonrandomized Studies

Havshoi (2022) published a prospective study comparing the quality of Colon Capsule Endoscopy (CCE), defined by completion rate (CR) and polyp detection rate (PDR), with that of CT colonography (CTC) and AA colonoscopy (AAC), respectively.[55] A total of 65 patients were included in the analysis (n=36 as an alternative to CTC and n=27 as an alternative to AAC). The PDR was 75% in CCE compared to 20% in CT colonography ($p < 0.001$) and 78% in CCE compared to 35% in AA colonoscopy ($p = 0.013$). The CCE completion rate was low in both groups: 44% compared to 96% in CTC ($p < 0.001$) and 33% compared to 100% in AAC ($p < 0.001$). The authors conclude The PDR of CCE was high, indicating an acceptable sensitivity in complete investigations, and that the CR of CCE on this indication is unacceptably low.

Additional prospective case series describing the diagnostic yield of CE following incomplete colonoscopy for various indications are summarized in Table 26. Study relevance, design, and conduct limitations are described in Table 27 and 28.

Table 26. Study Characteristics and Results

Study	Study Population	Indications for OC	Threshold for Significant Polyps	Timing of CE	Incremental CE Diagnostic Yield, n/N (%)	Complete Visualization of the Colon, n/N (%)	Comments
Hussey (2018)[56]	Patients aged ≥18 y who had an incomplete OC for reasons other than poor bowel preparation or suspected obstruction of the colonic lumen (N=50)	NR	> 6 mm or ≥ 3 polyps	Administered 90 min after IC	CE (any polyps): 19/50 (38) CE (significant polyps): 7/50 (14) CE + IC (any diagnosis): 37/50 (74)	CE: 38/50 (76) CE + IC: 42/50 (84)	CCE Findings (n): normal (13), polyps (19; 7/19 significant), inflammation (1), diverticular disease (1), angiodysplasia (1), cancer (1). 7 patients with significant polyps were referred for polypectomy, which detected 14 adenomas and hyperplastic polyps.
Baltes (2018)[57]	Patients aged ≥18 y who had an incomplete OC due to	CRC screening (22%), anemia (15%),	≥ 6 mm or ≥ 3 polyps	Protocol A: next day CE	CE (significant polyps): NR (24)	Protocol A: CE: 24/38 (63.3)	Per protocol analysis: 74/81 due to 7 exclusions for technical failure

Study	Study Population	Indications for OC	Threshold for Significant Polyps	Timing of CE	Incremental CE Diagnostic Yield, n/N (%)	Complete Visualization of the Colon, n/N (%)	Comments
	failure to reach the cecum or ileo-cecal anastomosis due to looping, bowel angulation, adhesions, and intolerance of sedation or inflammation (N=81)	hematochezia (15%), irregular stool (12%), abdominal pain (12%), colitis (5%), other reasons (12%)		(n=38) Protocol B: CE within 30 d (n=36)	CE + IC (significant polyps): 21/74 (28)	CE + IC: 34/38 (89.5) Protocol B: CE: 24/36 (66.7) CE + IC: 35/36 (97.2)	Adverse events: 1 capsule retention; 1 case of nausea and vomiting due to prep
Nogales (2017)[58]	Patients aged ≥18 y who had an incomplete OC when cecal intubation was not achieved despite adequate bowel preparation (N=96)	NR	>6 mm or > 3 polyps	Within 72 hours in 8 cases of suspected CRC. During the following week for all other patients.	CE (any diagnosis): 58/96 (60.4) CE (significant polyps): 25/96 (26)	CE: 69/96 (71.9) CE + IC: 89/96 (92.7)	CCE Findings (n): polyps (41; 25/41 significant), diverticula (11), colon cancer (2), angioectasia (2), solitary colonic ulcers (2). In 43/58 patients (44.8%) the new findings modified the therapeutic approach.
Negreanu (2013)[59]	Patients who are at risk for CRC who 1) refused (n=37) or failed prior OC (n=30), or 2) were unable to undergo OC because of anesthetic risk and co-	Abnormal transit (8), abdominal pain (4), anemia or overt bleeding (22), weight loss (1), average and high risk CRC	>6 mm or ≥ 3 polyps	NR	CE (relevant lesions): 23/67 (34) [95% CI, 21.6 to 44.1] CE (significant polyps): 15/67 (22)	CE: 51/67 (76.1)	Exclusions: technical failures (3) CCE Findings (n): polyps >6 mm (5), ≥3 polyps (10), multiple colonic angiomas (2), newly discovered Crohn's disease (1), radiation enteritis (1),

Study	Study Population	Indications for OC	Threshold for Significant Polyps	Timing of CE	Incremental CE Diagnostic Yield, n/N (%)	Complete Visualization of the Colon, n/N (%)	Comments
	morbidities (n=3) (N=70)	screening (29), abnormal imaging or tumor markers (6)					diverticulosis (17), ulcerative colitis and inflammatory pseudopolyps (1), <6 mm polyp (1). 17/23 patients with relevant lesions agreed to therapeutic interventions. 1 clinical failure (ulcerated rectal tumor) who refused OC following incomplete CE was reported. Adverse events: capsule impaction and retention (5)
Pioche (2012)[60]	Patients with an indication for OC per the recommendations of the French National Authority for Health, including symptoms or screening who had 1) colonoscopy failure due to difficult sigmoid loop or adhesions not related to stenosis or inadequate bowel cleansing	Abnormal transit (14), abdominal pain (22), anemia or overt bleeding (30), weight loss (2), CRC screening (39)	>5 mm or ≥ 3 polyps	NR	CE (significant polyps, screening): 12/39 (30.8) [95% CI, 22.1 to 39.5] CE (any lesions explaining symptoms): 16/68 (23.5) CE (significant polyps not explaining symptoms): 8/68 (11.8) CE (any significant	CE: 89/107 (83.2) [95% CI, 76.1 to 90.3]	CCE Findings (n): significant polyps (20), insignificant polyps (2), diverticulosis (6), telangiectasia (1), lesions explaining symptoms (16) Adverse events: capsule retention (6) Management: Screening group (12) (endoscopic treatments [6], follow-up [5], refusal [1]); Negative findings (9/64) (OC - normal findings or nonsignificant lesions [5], adenomas [1];

Study	Study Population	Indications for OC	Threshold for Significant Polyps	Timing of CE	Incremental CE Diagnostic Yield, n/N (%)	Complete Visualization of the Colon, n/N (%)	Comments
	(n=77) or 2) contraindications to OC with anesthesia due to cardiovascular or respiratory disease (n=30) (N=107)				diagnosis): 36/107 (33.6) [95% CI, 24.7 to 42.5]		CTC - normal findings [3]); Symptomatic group (24) (medical treatments [8], colectomy [1], endoscopic APC [1], follow-up [6], endoscopic treatments [7], refusal [1])

CCE: colon capsule endoscopy; CE: capsule endoscopy; CI: confidence interval; CRC: colorectal cancer; IC: incomplete colonoscopy; NR: not reported; OC: optical colonoscopy.

Table 27. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Hussey (2018)[56]	2,3. Original indications for OC not reported.		2. Not compared to a reference standard.	1,3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Baltes (2018)[57]	1. It is not clear whether detection of polyps was the primary goal of CE for symptomatic patients.		2. Not compared to a reference standard.	1,3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Nogales (2017)[58]	2,3. Original indications for OC not reported.		2. Not compared to a reference standard.	1,3. Impact of findings on health outcomes not assessed. Clinical validity outcomes	1. No follow-up with reference standard.

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
				cannot be assessed.	
Negreanu (2013)[59]	1,4. It is not clear whether detection of polyps was the primary goal of CE for symptomatic patients. Only a small subset of study patients reported IC.		2. Not compared to a reference standard.	1,3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.
Pioche (2012)[60]	1,4. It is not clear whether detection of polyps was the primary goal of CE for symptomatic patients. Only a subset of study patients reported IC.		2. Not compared to a reference standard.	1,3. Impact of findings on health outcomes not assessed. Clinical validity outcomes cannot be assessed.	1. No follow-up with reference standard.

CE: capsule endoscopy; IC: incomplete colonoscopy; OC: optical colonoscopy.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 28. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Hussey (2018)[56]	1. Selection not described.	1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.
Baltes (2018)[57]	1. Selection not described.	1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Nogales (2017)[58]		1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.
Negreanu (2013)[59]	1. Selection not described.	1. No comparison to reference standard.		1. Not registered.		2. Comparison to other tests not reported.
Pioche (2012)[60]	1. Selection not described.	1. No comparison to reference standard.	1. Timing of CE not described.	1. Not registered.		2. Comparison to other tests not reported.

CE: capsule endoscopy.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Incomplete Colonoscopy

No randomized controlled studies evaluating the diagnostic characteristics of CE compared to a reference standard for the detection of colon polyps in patients with an incomplete colonoscopy following adequate bowel preparation were identified. Case series describing the incremental diagnostic yield of CE varied in their reporting of original indications for OC and inclusion of symptomatic and/or screening patients. It is unclear whether the primary goal of CE was the detection of colon polyps in symptomatic patients, as these lesions were reported as not explaining symptoms in one study. Successful CE completion rates were low (range, 33% to 83.2%) with three out of five studies reporting full visualization of the colon for combined CE and IC in 84% to 97.2% of patients. Given the variable prevalence of significant and actionable findings for patients with mixed indications for colonoscopy, the diagnostic yield is insufficient to determine the clinical validity of the test. No studies assessed the impact of study findings on specific health outcomes. Information on adherence to recommended follow-up diagnostic or therapeutic interventions in patients with incomplete colonoscopies are limited, with several refusals and clinical failures reported. Studies of CE compared to standard management with repeat colonoscopy in the intended use population are necessary to determine the diagnostic characteristics of the test in the triage setting.

PATENCY CAPSULE

The purpose of the patency capsule is to inform the decision to proceed to CE by confirming adequate patency of the gastrointestinal tract in patients with known or suspected strictures.

Systematic Review

Wang (2021) published a systematic review with meta-analysis of the pooled rates, predictors, and temporal-trend of video capsule endoscopy (VCE) adverse events.[61] The review included data from 402 studies, including 108,079 VCE procedures. Most studies were observational (360 [89.55%]; including 156 prospective and 204 retrospective studies), forty-two (10.45%) studies were RCTs. Egger's test did not indicate the existence of obvious publication bias for retention rate (p=0.6063), incomplete examination rate of esophagus (p=0.7632), small bowel (p=0.1315), and colon (p=0.1393), however, the rate of stomach incomplete examination (p=0.0017), swallow disorder (p<0.0001), aspiration (p<0.0001), technical failure (p<0.0001), and procedural adverse events (p<0.0001) showed significant asymmetry. The authors found that a patency capsule reduced retention rate by 5.04% (95% CI − 8.75% to − 1.33%, p=0.0077). While these data suggest patency capsule before VCE in patients with a high-risk of retention may be useful to avoid retention, the authors note not all patients undergoing VCE should be offered a patency capsule since several complications have been reported, including small bowel obstruction and perforation.

Nonrandomized studies

Ukashi (2022) published a post-hoc analysis of two prospective cohort studies of adult patients with quiescent small-bowel CD that underwent PC between 2013 and 2020.[62] A total of 190 patients were included (47-failed PC, 143-passed PC, median follow-up 34.12 months) The primary composite-outcome was the need for intestinal surgery or endoscopic-dilation during follow-up with or without failed PC. Patients with a failed-PC had higher rates of the primary composite-outcome (21.3% vs. 1.4%, Hazard ratio [HR] 20.3, 95% confidence interval [CI] 4.4 to 93.7, p<0.001) and also secondary outcomes including intestinal-surgery (14.9% vs. 0.70%, p<0.001), endoscopic-dilation (14.9% vs. 0.70%, p<0.001), admissions (23.3% vs. 5.7%, p<0.001) and clinical-flares (43.9% vs. 27.7%,p=0.005) during follow-up compared with controls. The authors conclude that clinically stable CD patients with failed-PC have worse long-term clinical outcomes than those without, independently of CD phenotype.

A prospective, multicenter study of a patency capsule to preclude subsequent small bowel capsule endoscopy (SBCE) retention in 1096 patients with suspected or established small bowel stenosis was published by Nakamura (2021).[63] Patency was confirmed in 976 (89.1%) of the patients and capsule excretion occurred in 579 patients. Of the remaining 517 patients, patency was confirmed using imaging in 401 (77.5%). SBCE retention occurred in five (0.51%) of 963 patients who underwent SBCE. Non-confirmation of patency was associated with established Crohn's disease, stenosis, abdominal fullness, serum albumin levels <4.0 g/dL, and previous small bowel obstruction (adjusted odds ratios: 4.21, 2.60, 2.47, 2.12, and 2.00; 95% confidence intervals: 2.62 to 6.78, 1.62 to 4.17, 1.43 to 4.27, 1.32 to 3.40, and 1.15 to 3.47, respectively).

Spada (2007) reported findings for 27 patients, 24 with CD.[64] In this study, 25 (92.6%) patients retrieved the patency capsule in their stools. Six patients complained of abdominal pain, four of whom excreted a nonintact capsule, and hospitalization was required in one patient due to the occlusive syndrome.

Delvaux (2005) reported findings in 22 patients with suspected intestinal stricture, 15 of whom had CD.[65] In this study, at 30 hours after ingestion, the patency capsule was detected in 17 (72.3%) patients. In all patients in whom the capsule was blocked in the small intestine, the stenosis had been suspected on CT scan or small bowel follow-through. In three patients, the delay in the progression of the patency capsule led to the cancellation of CE. In three patients,

the patency capsule induced a symptomatic intestinal occlusion, which resolved spontaneously in one and required emergency surgery in two. The authors commented that the current technical development of the patency capsule limits its use in clinical practice, because it did not detect stenoses undiagnosed by CT or small bowel follow-through, and the start of dissolution at 40 hours after ingestion is too slow to prevent episodes of intestinal occlusion. They also commented that a careful interview eliciting the patient's history and symptoms remains the most useful indicator for suspicion of an intestinal stenosis.

Several studies have shown that patients who had an uncomplicated passage of the patency capsule subsequently underwent uncomplicated CE.[66-68] These patients often had significant findings on CE.[66, 67] However, it is difficult to determine whether CE findings in these patients improved their outcomes beyond any alternative testing regimen available. In one of these studies, three of 106 patients had severe adverse events, including one patient who required surgery.[66]

Section Summary: Patency Capsule

The use of the patency capsule has some associated risk. Published studies are small and do not provide comparative data on the incremental value of this capsule over standard clinical evaluation. In some series, the administration of the patency capsule has produced adverse events including symptoms requiring hospitalization and surgery.

MAGNETIC CAPSULE ENDOSCOPY FOR UNEXPLAINED UPPER ABDOMINAL COMPLAINTS

The purpose of magnetic CE for patients who have unexplained upper abdominal complaints is to confirm a diagnosis and inform a decision to proceed to appropriate treatment.

Diagnostic Accuracy Studies

Denzer (2015) prospectively evaluated a magnetically guided gastric capsule as compared to conventional gastroscopy in 189 patients with upper abdominal complaints (eg, upper abdominal pain and/or anemia) from two centers.[69] In this study, capsule gastroscopy was performed initially followed by conventional gastroscopy, with a maximum delay of one day but a minimum delay of four hours. For conventional gastroscopy, the examination was performed blinded initially. If results of the magnetic capsule and blinded gastroscopy differed, then a subsequent unblinded gastroscopy was performed. Biopsies were taken whenever appropriate. The combined endoscopic assessment (blinded and unblinded gastroscopy) including biopsy was used as the final gold standard. The primary outcome parameters were the accuracy and the sensitivity, specificity, and predictive values of magnetically guided capsule gastroscopy compared with the final gold standard with regard to major lesions on a per-patient and per-lesion basis. Overall, 23 major lesions were discovered in 21 patients. Capsule accuracy on a per-patient basis was 90.5% (95% CI, 85.4% to 94.3%) with a specificity of 94.1% (95% CI, 89.3% to 97.1%) and a sensitivity of 61.9% (95% CI, 38% to 82%). The PPV and NPV were 56.5% (95% CI, 34.5% to 76.8%) and 95.2% (95% CI, 90.7% to 97.9%), respectively. Similar results for these values were seen on a per-lesion basis. Of the other 168 patients, 94% had minor and mostly multiple lesions; the capsule made a correct diagnosis in 88.1% (95% CI, 82.2% to 92.6%). No complications of capsule or conventional gastroscopy were noted. Patient preference for capsule use for a future gastroscopy, if indicated, was 100%. In this first large study to evaluate magnetically guided capsule gastroscopy in patients with upper abdominal symptoms, the authors concluded that this

technique was feasible in practice and clearly preferred by patients; however, further studies are needed to define its role in the clinical setting (eg, as a filter test to stratify patients to undergo conventional gastroscopy or some other role). Of note, this non-US study reported a low sensitivity with a wide CI and provided an extremely limited discussion of the types of upper abdominal complaints experienced by enrolled patients. No discussion in terms of the severity and duration of the complaints, as well as prior testing and treatment was undertaken, which makes determination of the appropriate place in therapy for magnetic CE in patients with unexplained upper abdominal complaints difficult.

Liao (2016) evaluated the accuracy of magnetically controlled CE as compared with conventional gastroscopy in 350 patients with upper abdominal complaints in a prospective, multicenter, blinded comparison study conducted in China.[70] All patients underwent magnetic CE followed by conventional gastroscopy two hours later, without sedation. The primary outcome of the study was an evaluation of gastric focal lesions. Overall, with conventional gastroscopy as the gold standard, magnetic CE detected gastric focal lesions in the entire stomach with 90.4% sensitivity (95% CI, 84.7% to 96.1%), 94.7% specificity (95% CI, 91.9% to 97.5%), and 93.4% accuracy (95% CI, 90.83% to 96.02%). The PPV and NPV were 87.9% (95% CI, 81.7% to 94%) and 95.9% (95% CI, 93.4% to 98.4%), respectively. Similar sensitivity and specificity results were observed with magnetic CE as compared to conventional gastroscopy when detecting focal lesions in the upper or lower stomach specifically. No lesions of significance were missed by magnetic CE. Additionally, 335 (95.7%) patients preferred magnetic CE over conventional gastroscopy and only five patients reported an adverse event; the majority of these events were considered to be related to gastric preparation. The authors concluded that magnetic CE detects upper abdominal focal lesions with comparable accuracy to conventional gastroscopy and is a promising alternative for screening for gastric diseases; however, similar to the prior study, this non-US study provided no discussion of the types of upper abdominal complaints experienced by patients or prior tests or treatments undertaken.

The purpose of the limitations tables (Tables 29 and 30) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 29. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Denzer (2015)[69]	4. Study population non-U.S. (conducted in France)			1. Sensitivity is low with a wide confidence interval	
Liao (2016)[70]	4. Study population non-U.S. (conducted in China)		2. Conventional gastroscopy performed without sedation		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or

risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 30. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Denzer (2015)[69]	1. Selection of patients not clearly described	1. Final gold standard of conventional gastroscopy with biopsy was unblinded				
Liao (2016)[70]	1. Selection of patients not clearly described					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Magnetic Capsule Endoscopy for Unexplained Upper Abdominal Complaints

Studies evaluating the diagnostic characteristics of magnetic CE as compared to conventional gastroscopy in the target population have generally demonstrated similar accuracy, sensitivity, and specificity, with increases in patient preference and an acceptable safety profile with the magnetic CE approach. However, the sequence and chronology of testing and treatment recommended before magnetic CE needs to be defined to determine whether magnetic CE has utility to diagnose the condition. No RCTs assessing the clinical utility of magnetic CE for this indication were identified.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF GASTROENTEROLOGY

The American College of Gastroenterology (ACG) published colorectal cancer screening clinical guidelines in 2021.[71] They provide the following conditional recommendation (very low quality of evidence):consideration of the following screening tests for individuals unable or unwilling to undergo a colonoscopy or FIT [fecal immunochemical testing]: flexible sigmoidoscopy, multitarget stool DNA test, CT [computed tomography] colonography, or colon capsule [capsule endoscopy].

In 2023, ACG issued updated guidelines on the diagnosis and management of celiac disease.[72] The guideline does not mention the use of capsule endoscopy (CE) at any stage of the diagnosis or treatment in patients with celiac disease. These guidelines were updated from those of 2013, which stated that “capsule endoscopy (CE) not be used for initial diagnosis, except for patients with positive celiac-specific serology who are unwilling or unable to undergo

upper endoscopy with biopsy (strong recommendation, moderate level of evidence). Capsule endoscopy should be considered for the evaluation of small bowel mucosa in patients with complicated celiac disease (strong recommendation, moderate level of evidence)."[73]

In 2018, the ACG updated its guideline on the management of Crohn's disease in adults.[74] The guideline provides recommendations specific to video capsule endoscopy, which states, "Video capsule endoscopy (VCE) is a useful adjunct in the diagnosis of patients with small bowel Crohn's disease in patients in whom there is a high index of suspicion of disease. Patients with obstructive symptoms should have small bowel imaging and/or patency capsule evaluation before VCE to decrease risk of capsule retention." The guideline also states, "some studies have questioned the specificity of capsule endoscopy findings for CD, and to date there is no consensus as to exactly which capsule endoscopy findings constitute a diagnosis of CD."[74]

In 2015, the ACG issued a guideline on the diagnosis and management of small bowel bleeding (including using "small bowel bleeding" to replace "obscure GI [gastrointestinal] bleeding," which should be reserved for patients in whom a source of bleeding cannot be identified anywhere in the GI tract).[75] The guideline made the following statements related to video CE (Table 31).

Table 31. Recommendations on Diagnosis and Management of Small Bowel Bleeding

Recommendation	SOR	LOE
"… VCE should be considered as a first-line procedure for SB evaluation after upper and lower GI sources have been excluded, including second-look endoscopy when indicated"	Strong	Moderate
"VCE should be performed before deep enteroscopy to increase diagnostic yield. Initial deep enteroscopy can be considered in cases of massive hemorrhage or when VCE is contraindicated"	Strong	High

GI: gastrointestinal; LOE: level of evidence; SB: small bowel; SOR: strength of recommendation; VCE: video capsule endoscopy.

AMERICAN SOCIETY OF GASTROINTESTINAL ENDOSCOPY

In 2017, the American Society of Gastrointestinal Endoscopy released guidelines for the use of endoscopy in the management of suspected small bowel bleeding.[76] These guidelines made the following recommendations on capsule endoscopy (Table 32).

Table 32. Recommendations on Use of Endoscopy to Manage Suspected Small Bowel Bleeding

Recommendation	QOE
We suggest VCE as the initial test for patients with overt or occult small-bowel bleeding. Positive VCE results should be followed with push enteroscopy if within reach or DAE."	Moderate
"We suggest DAE or push enteroscopy if VCE is unavailable or nondiagnostic in patients with overt small bowel bleeding."	Moderate

DAE: device-assisted enteroscopy; QOE: quality of evidence; VCE: video capsule endoscopy.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE

In 2017, the American Gastroenterological Association Institute issued guidelines on the use of CE.[77] Table 33 summarizes the most relevant recommendations (not all recommendations are included).

Table 33. AGA 2017 Capsule Endoscopy Recommendations

Stmt No.	Recommendation	Grade	QOE
Recommendations Supporting the Use of CE			
1	For suspected CD, with negative ileocolonoscopy and imaging studies (CE of small bowel)	Strong	Very low
2	For CD and clinical features unexplained by ileocolonoscopy or imaging studies	Strong	Very low
3	For CD, when assessment of small-bowel mucosal healing (beyond reach of ileocolonoscopy) is needed	Conditional	Very low
4	For suspected small-bowel recurrence of CD after colectomy, undiagnosed by ileocolonoscopy or imaging studies	Strong	Very low
7	For celiac disease with unexplained symptoms despite treatment and appropriate investigations	Strong	Very low (efficacy) Low (safety)
8	For documented overt GI bleeding (excluding hematemesis) and negative findings on high-quality EGD and colonoscopy	Strong	Very low
9	For overt, obscure bleeding episode, as soon as possible	Strong	Very low
10	With prior negative CE with repeated obscure bleeding, repeated studies (endoscopy, colonoscopy and/or CE)	Strong	Very low
11	For suspected obscure bleeding and unexplained mild chronic iron-deficiency anemia, in selected cases	Strong	Very low
12	For polyposis syndromes, which require small bowel studies, for ongoing surveillance	Conditional	Very low (efficacy) Low (safety)
Recommendations Against Use of CE			
5	For diagnosing CD when chronic abdominal pain or diarrhea are only symptoms, and with no evidence of biomarkers associated with CD	Conditional	Low
6	For diagnosing celiac disease	Strong	Very low (efficacy) Low (safety)
13	For routine substitution of colonoscopy	Strong	Very low
14	For IBD, as substitute for colonoscopy to assess extent and severity of disease	Strong	Very low (efficacy) Low (safety)

AGA: American Gastroenterology Association; CD: Crohn's disease; CE: capsule endoscopy; EGD: esophagogastroduodenoscopy; GI: gastrointestinal; IBD: inflammatory bowel disease; QOE: quality of evidence; Stmt: statement.

The AGA institute issued updated practice guidelines (2022) on the management of refreactory celiac disease.[78] The guidelines recommend to perform small bowel imaging with CE and computed tomography or magnetic resonance enterography to exclude enteropathy-associated T-cell lymphoma and ulcerative jejunoileitis at initial diagnosis of type 2 refractory celiac disease.

U.S. MULTI-SOCIETY TASK FORCE

The U.S. Multi-Society Task Force (2021) issued recommendations for colorectal cancer screening with representation from the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy.[79, 80] Capsule endoscopy every five years received a tier 3 ranking with the following recommendation: "We suggest that capsule colonoscopy (if available) is an appropriate

screening test when patients decline colonoscopy, FIT, FIT-fecal DNA, CT colonography, and flexible sigmoidoscopy (weak recommendation, low-quality evidence)."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) published its most recent recommendations for colorectal cancer screening in 2021.[81] Colorectal cancer screening was recommended starting at age 50 years and continuing until age 75 years (A recommendation) and in adults aged 45 to 49 years (B recommendation). The USPSTF recommendation for screening for colorectal cancer does not include serum tests, urine tests, or CE for colorectal cancer screening because of the limited available evidence on these tests and because other effective tests are available.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Colorectal Guidelines (v.2.2023) state the following regarding capsule endoscopy:[82]

- Familial Adenomatous Polyposis: High level evidence to support routine small bowel screening distal to the duodenum is lacking. However, may consider small bowel visualization (e.g. capsule endoscopy), especially if advanced duodenal polyposis.
- Peutz- Jeghers Syndrome: Small bowel visualization (video capsule endoscopy or CT/MRI enterography) every 2-3 years. Shorter intervals may be indicated based on polyp size, number, and pathology.

The NCCN Guidelines for Small Bowel Adenocarcinoma (v.1.2023) state the following regarding capsule endoscopy:[83]

- Consider when radiographic imaging and other forms of endoscopy fail to reveal a suspected primary lesion. This is not the preferred primary method for diagnostic workup due to inability to obtain tissue for diagnosis. Contraindicated where small bowel obstruction or strictures exist.
- Routine capsule endoscopy is not indicated for surveillance.

SUMMARY

WIRELESS CAPSULE ENDOSCOPY

Suspected small bowel bleeding

For individuals with recurrent, obscure gastro-intestinal bleeding who have suspected small bowel bleeding, there is enough evidence to show that wireless capsule endoscopy (CE) can locate the source of bleeding at least as well as other diagnostic methods and direct treatment to the source of bleeding when prior upper and lower gastrointestinal (GI) endoscopic studies are inconclusive. Clinical guidelines based on research recommend CE for selected individuals who have suspected small bowel bleeding. Therefore, wireless capsule endoscopy (CE) may be considered medically necessary for individuals with recurrent, obscure gastro-intestinal bleeding who have suspected small bowel bleeding when prior upper and lower gastrointestinal (GI) endoscopic studies are inconclusive. In all

other situations, there is not enough research to show that CE improves health outcomes for people with suspected small bowel bleeding and is therefore considered investigational.

Crohn's disease (CD)

For individuals who have suspected small bowel Crohn's disease (CD) who receive wireless capsule endoscopy (CE), there is enough evidence to show that diagnostic yields are as good as or better than other diagnostic options, and these data are likely to improve health outcomes by identifying some cases of CD and directing specific treatment. Clinical guidelines based on research recommend CE for individuals who have suspected small bowel CD in these cases. Therefore, wireless capsule endoscopy (CE) may be considered medically necessary for the initial diagnosis of suspected Crohn's disease when clinical signs of Crohn's disease are present and there is not evidence of disease on conventional diagnostic tests.

For individuals who have an established diagnosis of Crohn's disease (CD) and there are unexpected change(s) in the course of disease or response to treatment who receive wireless capsule endoscopy (CE), there is evidence that the diagnostic yields are as good as or better than other diagnostic options. Clinical guidelines based on research recommend CE for individuals who have suspected small bowel CD in certain scenarios. Therefore, CE may be considered medically necessary in individuals who have an established diagnosis of CD and there are unexpected change(s) in the course of disease or response to treatment.

In all other situations, there is not enough research to show that CE improves health outcomes for people with suspected or established Crohn's disease and is therefore considered investigational.

Hereditary GI polyposis syndromes

There is enough evidence that wireless capsule endoscopy (CE) can identify additional lesions compared with other diagnostic methods in individuals with hereditary GI polyposis syndromes including familial adenomatous polyposis and Peutz-Jeghers syndrome. Clinical guidelines based on research recommend CE in patients with hereditary GI polyposis syndromes. Therefore, wireless CE may be considered medically necessary in individuals with hereditary GI polyposis syndromes including familial adenomatous polyposis and Peutz-Jeghers syndrome.

Celiac disease

Small bowel biopsy, celiac serologies, and human leukocyte antigen typing remain the standard tests for confirming celiac disease. However, in cases where the diagnosis of celiac disease is equivocal, there is enough evidence that wireless capsule endoscopy (CE) can reveal morphologic changes in the small bowel consistent with celiac disease and studies of patients with unresponsive celiac disease undergoing CE have shown some yield of actionable diagnoses that have the potential to improve patient outcomes. Clinical guidelines based on research recommend CE for patients with celiac disease in certain scenarios. Therefore, CE may be considered medically necessary in individuals with clinical evidence of celiac disease and positive celiac-specific serology who are unable to undergo upper endoscopy with biopsy and for re-evaluation of individuals with celiac disease who remain symptomatic despite treatment. In all other situations, there is not enough research to show

that CE improves health outcomes for people with celiac disease and is therefore considered investigational.

Esophageal disorders

There is not enough research to show that evaluation of the esophagus with wireless capsule endoscopy (CE) improves health outcomes for individuals with gastroesophageal reflux or other esophageal pathologies. Clinical guidelines based on research do not recommend evaluation of the esophagus with CE in patients with gastroesophageal reflux or other esophageal pathologies. Therefore, wireless capsule endoscopy is considered investigational for these patients.

GI diseases and conditions when policy criteria are not met

There is not enough research to show that wireless capsule endoscopy (CE) improves health outcomes for the evaluation of GI diseases and conditions when policy criteria are not met, including but not limited to: irritable bowel syndrome, hereditary *non*polyposis syndromes (including but not limited to Lynch syndrome), small bowel neoplasm, portal hypertensive enteropathy, lower GI tract bleeding, incomplete colonoscopy, and unexplained chronic abdominal pain. Clinical guidelines based on research generally do not recommend CE for patients with these conditions. Therefore, CE is considered investigational for the evaluation of GI diseases and conditions when policy criteria are not met.

Colon Cancer Screening

There is not enough research to show that wireless capsule endoscopy (CE) improves health outcomes when used to screen for colon cancer and there is evidence that the diagnostic performance of CE is worse than standard colonoscopy. Clinical guidelines based on research either recommend against the use of CE for colon cancer screening or provide a weak recommendation based on low-quality evidence. Therefore, CE is considered investigational for colon cancer screening.

Acute Upper Gastrointestinal Bleeding

There is not enough research to show that wireless capsule endoscopy (CE) improves health outcomes for individuals who have acute upper GI tract bleeding. Clinical guidelines based on research do not recommend CE for acute upper GI tract bleeding. Therefore, CE is considered investigational for acute upper GI tract bleeding.

Patency Capsule for Patients with Bowel Stricture

There is not enough research to show that the use of patency capsules prior to wireless capsule endoscopy improves net health outcomes for patients. While the available studies have reported that endoscopy following a successful patency capsule test results in high rates of success with low rates of adverse events, the patency capsule is also associated with adverse events including small bowel obstruction and perforation. Because of the lack of comparative data to other diagnostic strategies, it is not possible to determine whether the use of the patency capsule improves the net health outcome. Therefore, the use of patency capsules is considered investigational.

Magnetic Capsule Endoscopy for Patients with Suspected Gastrointestinal Disorders

There is not enough research to show that magnetic capsule endoscopy improves health outcomes for any indication. No clinical guidelines based on research recommend magnetic capsule endoscopy for any indication. Therefore, magnetic capsule endoscopy is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report
	91110	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy) esophagus through ileum, with interpretation and report
	91111	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), esophagus, with interpretation and report
	91113	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), colon, with interpretation and report
	91299	Unlisted diagnostic gastroenterology procedure
HCPCS	None	

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